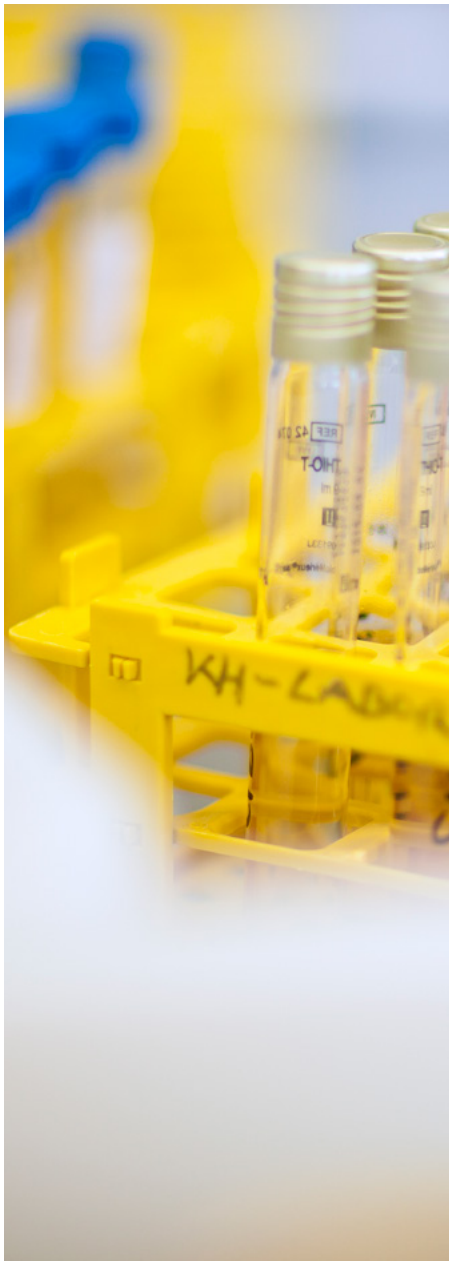
MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

Research Report 2015



Contents

Foreword

Dear readers,

it is a great pleasure for me to present the first research report of the Medical University of Innsbruck (MUI), detailing our research activities in 2013–2014.

Since its inception as an independent University in 2004, MUI in collaboration with the Tiroler Krankenanstalten (TILAK GmbH, now Tirol Kliniken) has made a deep commitment to fostering research innovation and excellence with the aim of creating knowledge to advance health.

In the past years MUI has continued to built on its established research strengths namely genetics, epigenetics and genomics, as well as infectology, immunology and organ/tissue replacement, neurosciences and oncology. With almost € 70 million external research funding (2013/2014), including three FWF funded doctoral programmes (HOROS, SPIN, MCBO), two special research programmes (SFB-021 "Cell Proliferation and Cell Death in Tumors" and SFB-F44 "Cell Signaling in chronic CNS disorders"), 30 EU Projects and the K1 Project Oncotyrol, the K Project VASCage and two Christian Doppler labs (approved in 2014), the MUI also has earned a well-deserved reputation among physicians and scientists as a place where faculty and students can pursue creative and novel ideas in a collaborative and supportive environment.

The current research report was created as part of a project of the Knowledge Transfer Centre West (WTZ). This common project of the western Austrian Universities and associates (Leopold Franzens University, Innsbruck; Paris Lodron University, Salzburg; Mozarteum, Salzburg; Johannes Kepler University, Linz; Universität für künstlerische und industrielle Gestaltung, Linz) is financed by the Federal Ministry of Science, Research and Economy (BMWFW). Two of the primary intentions of the knowledge centre are to simplify the search for university based cooperation partners and to facilitate the rapid launching of projects. The project resulted in the realisation of a research report and competence map.

The following pages present the profiles and results for each of the MUI's clinical departments and institutes and underline the discoveries and advances which have come about thanks to the enormous effort of our scientists.

I would like to take this opportunity to thank all the scientists for their contribution and their continuing efforts in the name of our University.
Furthermore I would like to thank all the people involved in putting this report together and hope that you will enjoy reading our first research report.

Univ.-Prof.in Dr.in Christine Bandtlow
Vice Rector for Research and International Relations

Medical Theoretical Research Units

Medical Biochemistry

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Keywords

Cell cycle, cell proliferation, signal transduction, ribosom, phospho-dynamics

Research Focus

- Cell Cycle & Proliferation (Ludger Hengst)
- Signal Transduction & Proliferation (Wolfgang Doppler)
- Phospho-Dynamics (Peter Gruber)
- Ribosomal Proteins (Wolfgang Piendl)
- Eco- & Nutritional Biochemistry (F. Überall)

General Facts

Research in the Division of Medical Biochemistry is focused on signalling pathways regulating cell proliferation, apoptosis and differentiation in mammalian tissues with special reference to malignant cells. In addition, RNA-protein interactions are investigated with a focus on protein translation and ribosome function.

Research

Cell Cycle and Proliferation
Ludger Hengst

Precisely coordinated cell division and differentiation processes are essential for growth, development and integrity of multicellular organisms. Before cells commit to divide, they are exposed to a flood of diverse and sometimes conflicting signals aimed to regulate cell growth, differentiation, cell proliferation or cell fate. Multiple external as well as internal signals can impinge on the central cell cycle control machinery in order to promote or block cell proliferation. All signals need to be properly processed and integrated to maintain body and organ homeostasis. Incorrect signal interpretation, processing or integration can lead to hypo- or hyperproliferative disorders, including diseases like cancer or anaemia.

The decision to continue proliferation or to exit from the cell cycle into quiescence is usually made during a specific window of the eukaryotic cell division cycle. The cell cycle can be subdivided into four phases. DNA replication during S-phase is separated by gap phases G1 and G2 from the segregation of the duplicated DNA and other cellular components in M-phase (mitosis and cytokinesis). Cells can decide to withdraw from proliferation or to commit to another round of cell division until they progress over the restriction point, a specific point in G1 phase (Fig. 1). Progression over the restriction point renders the cell cycle mitogen independent and committed to another round of cell division.

We investigate molecular mechanisms that link diverse signalling networks to the central cell cycle control machinery. At the core of this machinery is a conserved family of protein kinases, called cyclin-dependent kinases (CDKs). CDKs become activated by binding of a positive regulatory subunit, the cyclin. Sequential activation and inactivation of specific CDK complexes is required for cell cycle progression. p21 (CDK-interacting protein, Cip1) p27 (Kinase inhibitory protein, Kip1) and p57 (Kip2) constitute one out of two families of CDK inhibitors (CKI) that bind to CDKs and control their activity. Their expression, localisation and modifications play a central role in regulating CDK kinase activity especially in G1-phase and the decision between proliferation and cell cycle exit. In addition to their canonical function in CDK kinase regulation, they can also exert CDK-independent functions. For example, the CDK inhibitor p27 can regulate cell motility and cell migration, linking this tumour suppressor protein not only to hyperproliferation but also to cancer metastasis.

Among others, we identified the CDK inhibitor protein p27Kip1. Its activity, localisation or stability can be regulated by diverse mitogen signalling pathways. We investigate how these pathways control Cip/Kip family protein expression, localization, modification, activity or function and study their physiological roles in normal cells and cancer cells.
p27 regulates cell cycle progression over the restriction point. Abundant p27 binds and inactivates CDKs and can prevent cell proliferation. The CDK inhibitor protein becomes unstable upon cyclin / CDK2 activation, as cells traverse the restriction point and progress towards S-phase. A positive feedback loop couples p27 ubiquitin-dependent degradation to CDK activation (Fig. 2). The molecular mechanism that can initiate this feedback loop in presence of

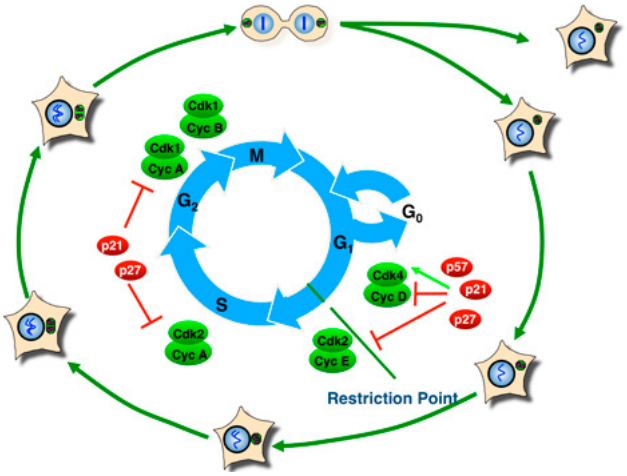

Fig. 1: Overview of the mammalian cell cycle. Cent-ral CDK/cyclin complexes are indicated next to the cell cycle position when they are active and the Cip/Kip CDK inhibitors are shown next to CDK/Cyclin complexes, which they bind. The green arrow indicates that p21 and p27 are not only inhibitors but also acti-vators of cyclin D / CDKs.

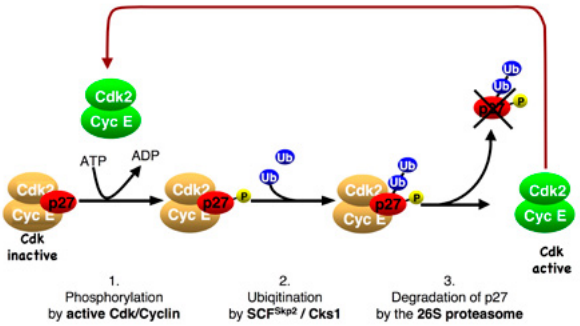

Fig. 2: A feedback loop controls CDK2 activation at the restriction point. Active CDK2 triggers the degradation of its own inhibitor p27, promoting the switch-like activation of CDK2 kinase at the restriction point.

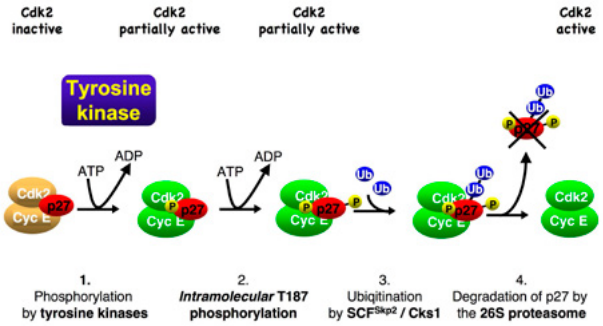

Fig. 3: Oncogenic tyrosine kinases like JAK2, Src or BCR-Abl can phosphorylate p27. This leads to the activation of bound CDK2. The activated CDK2 can phosphorylate the bound inhibitor p27, leading to its degradation and strong CDK activation.

abundant CDK inhibitors and thus inactive CDKs has long remained a puzzle.
We observed that oncogenic tyrosine kinases including BCR-Abl, Src or JAK2 can activate p27-bound CDKs by directly phosphorylating the inhibitor. This tyrosine phosphorylation ejects an inhibitory helix of p27 from the catalytic cleft of the CDK and permits the p27-bound CDK complex to bind ATP and to phosphorylate substrates. Among these substrates is p27 itself. Phosphorylation of p27 by the bound CDK generates a phosphodegron which can initiate the ubiquitin-proteasomal degradation of the CDK inhibitor (Fig. 3). Using this mechanism, that can be abused by diverse oncogenic tyrosine kinases, mitogen signals can inactivate and destabilise the inhibitor p27 and thereby promote CDK activation and cell cycle progression. Additional mechanisms include translational control or involve regulation by the ubiquitin proteasome system.

Ongoing Research:

Regulation of cell cycle progression through G1 phase by tyrosine kinases, translational control in and of the cell cycle; temporal and spatial regulation of Cdk-inhibitory proteins during cell cycle progression and in apoptosis, regulation of ubiquitin ligase activity in G1, molecular mechanism of statin-induced cell cycle arrest, cell cycle control by erythorpoietin and its receptor EpoR. Mouse knock-in models of cancer development.

Major Achievements:

We discovered a novel mechanism that triggers p27 degradation, CDK activation and cell cycle progression and identified different oncogenic tyrosine kinases including Src, BCR-Abl or JAK2, which induce p27 tyrosine phosphorylation. We identified novel mechanism that control the localisation of p27. Recently, we elucidated the molecular mechanisms that induces p27 stabilisation in the presence of statins. This involves the selective degradation of the ubiquitin ligase subunit Skp2 and results from inhibition of protein geranylgeranylation.
We also identified novel p27 mRNA binding proteins that regulate the IRES- and Cap-dependent translation of p27 and investigated the role of p27 in apoptosis.

Current Research Projects:

Function and regulation of CDK-inhibitory proteins.
Role of translational control for the decision between cell proliferation and withdrawal from the cell cycle.
Regulation of cytokine receptor signalling.

STAT1 in Cancer

Wolfgang Doppler

Strengthening a productive anti-tumor immune response as well as suppressing tumor-promoting activities of immune cells represent important therapeutic options in cancer treatment. For the rational design of appropriate strategies to achieve these goals, a more refined knowledge of the mechanisms regulating the recruitment, differentiation, expansion and function of tumor-infiltrating immune cells is mandatory. In this context, we investigate the role of a key mediator of the action of interferons on cells of the innate and acquired immune system, the signal transducer and activator of transcription 1 (STAT1). It acts as a transcription factor to induce the expression of genes required for antigen processing, maturation and recruitment of immune effector cells, and of genes required for the antiviral defense. STAT1 also co-operates with the cellular machinery regulating proliferation and apoptosis.
In cancer, STAT1 has been shown to fulfill opposite roles in either promoting or impeding tumor development, depending on the stage of tumor development and the particular type of tumor: As a mediator of the interferon-dependent anti-tumor immune response, STAT1 prevents or restricts the development of spontaneously formed tumors. However, particularly at later stages of tumor development, where the anti-tumor immune response is blunted by the tumor and immune cells are frequently subverted to facilitate the growth and survival of the tumor, STAT1 can contribute to tumor-promoting effects.

Ongoing Research:

We are investigating the role of STAT1 in the infiltration, differentiation and biological function of tumor-infiltrating immune cells. Our focus is on HER2-positive breast cancer. We are particularly interested on changes in the composition and function of tumor infiltrating immune cells upon treatment by chemotherapeutic agents, which act on the tumor epithelium but also influence the anti-tumor immune response.

Major Achievements:

We could demonstrate anti-tumor as well as tumor promoting properties of STAT1 in spontaneously growing mammary tumors. They are promoted by two different subsets of immune cells, namely CD8+ T cells and tumor associated macrophages (TAMs). CD8+ T cells contribute to the antineoplastic activity of chemotherapeutic agents, i.e. doxorubicin and lapatinib, and

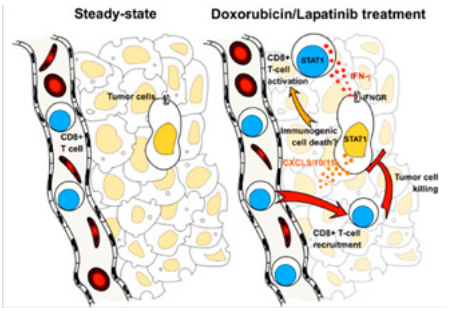

Fig. 4: Proposed role of STAT1, IFN-gamma and the CXCR3 – binding chemokines CXCL9, CXCL10 and CXCL11 in the anti-tumor activity of doxo-rubicin and lapatinib.

this is critically dependent on STAT1. By this means, STAT1 serves in the anti-tumor response. STAT1 was also shown to be required for the regeneration of the B-cell compartment after doxorubicin induced bone-marrow toxicity by promoting the development of early B-cell precursors in the bone marrow. It is thereby important for the recovery of the B-cell lineage after treatment with this anti-cancer drug. On the other hand, STAT1 is positively influencing the infiltration of mammary tumors with TAMs by transcriptionally inducing the expression of the macrophage growth factor CSF1. We could show that intense local proliferation of fully differentiated macrophages rather then low-pace recruitment of blood-borne precursors drives the accumulation of TAMs, which themselves are promoting tumor growth. The tumor promoting effect of STAT1 via influencing differentiation and infiltration of TAMs was supported by the results of a retrospective study. There we could show an association of STAT1 mRNA levels with macrophage infiltration and bad prognosis in breast cancer.

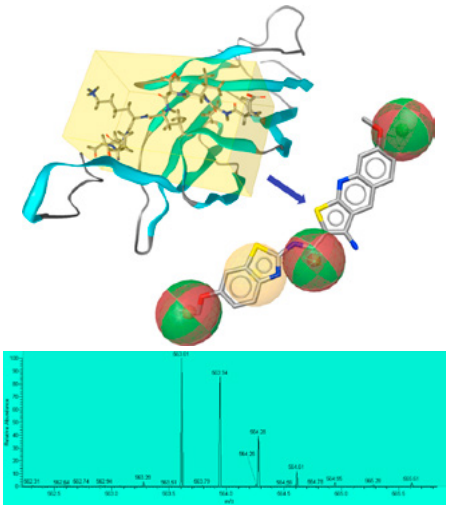

Fig. 5: X-ray structure of the C2-like domain of PKCepsilon. The protein backbone is illustrated as cartoon, while the protein segment EAVSLKPT (RACK2 binding domain on PKCepsilon and isozyme specific inhibitory peptide) is highlighted in the yellow box. The pharmacophore model is aligned with the structure of a novel small molecule inhibitor. RACK2 (receptor for activated C kinase 2) represents a protein that by binding to PKCepsilon defines its final sorting in the cell. By using inhibitory peptides or similarily structured other small molecules, the trans-location and thus the function of PKCepsilon is inhibited. These tools are employed for the identification of novel PKCepsilon substrates by quantitative phosphoproteomics.

Current Research Projects:
We are exploring the mechanisms by which STAT1 contributes to the chemotherapy-induced anti-tumor immune response. In particular, we are investigating the role of the STAT1 target genes CXCL9, CXCL10 and CXCL11 in the recruitment and differentiation of CD8+ T cells.

Phospho-Dynamics
Peter Gruber

PKC is a family of serine/threonine specific protein kinases. The different PKC isozymes play important roles in diverse signal transduction pathways. PKCepsilon has been reported to be enriched at the growth cones of extending neurites in differentiating neural cells, to participate in nerve growth factor signaling as well as in transmitter release and to participate in cell death and survival. Since so far only very few substrates of PKCepsilon have been identified with reasonable certainty, the identification of PKC-downstream targets represents the next major area of research in this field. Since PKCepsilon is an important sensitizing kinase in the CNS and an attractive drug target for treatment of several diseases, especially against pain (hyperalgesia), addiction and anxiety disorders, the discovery of additional drug targets through identification of PKCepsilon substrates and the elucidation of signaling pathways involved, might help to find novel points of attack for therapeutic intervention and to manifest the importance of PKCepsilon in the nervous system.

Major Achievements:
- Generation of novel PKCepsilon/RACK2 interaction inhibitors
- (Patent application: 'Novel inhibitors of Protein Kinase C epsilon signaling')
- Identification of novel PKCepsilon substrates

Future Goals:
- Identification of novel PKCepsilon substrates and elucidation of signaling pathways involved
- Further improvement of the potency of PKCepsilon/RACK2 protein-protein interaction inhibitors

Ribosomal Proteins
Wolfgang Piendl

Interaction of Ribosomal Proteins with rRNA and mRNA

We are investigating ribosomal protein L1 from different (hyper)thermophilic archaea and bacteria. They exhibit a 10 to 100 fold higher affinity to their specific binding sites on rRNA and mRNA compared to that of their mesophilic counterparts. This

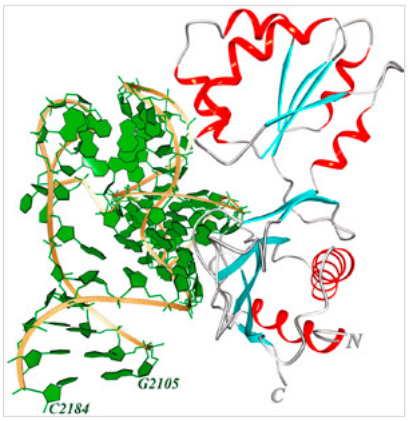

Fig. 6: Ribosomal protein L1 from the archaeon Sulf-olobus acidocaldarius in complex with 23S rRNA

stronger protein-RNA interaction might substantially contribute to the thermal tolerance of ribosomes in thermophilic organisms. Our investigations are focusing on the identification and characterization of those structural features of RNA-binding proteins that modulate the affinity for their specific RNA binding site. In this context we determined the crystal structures of L1-rRNA and L1-mRNA complexes at high resolution (in collaboration with our Russian partners).

Function of Ribosomal Protein L1

L1 is a two-domain protein with N and C termini located in domain I. In close collaboration with a Russian group we succeeded in constructing a truncation mutant of L1 representing domain I by deletion of the central part of L1 (= domain II). We could demonstrate that domain I alone is sufficient for specific RNA binding, whereas domain II stabilizes the L1-23S rRNA complex.

Major Achievements:

Solution of the structure of the L1 protuberance in the ribosome (with the Russian collaborator); see Fig. 6.

Construction of a truncated mutant of ribosomal protein L1 and elucidation of its role in RNA binding

Control of ribosomal protein synthesis in mesophilic and thermophilic archaea

As bacteria and eukarya, archaea have to coordinate the synthesis of about 60 ribosomal proteins with each other and with three rRNAs. Research is focusing on the MvaL1 operon (encoding ribosomal proteins L1, L10 and L12) and on the MvaL3 operon (encoding 5 ribosomal proteins) from mesophilic and thermophilic Methanococcus species. As in bacteria, regulation of the operons takes place at the level of translation. The regulator protein MvaL1, and

MvaL4, respectively, binds preferentially to its binding site on the 23S rRNA, and, when in excess, binds with lower affinity to its regulatory binding site on its mRNA (in the case of MvaL1 a structural mimic of the 23S rRNA binding site) and thus inhibits translation of all cistrons of the operon.

Future Goals:

To define the translational step at which archaeal L1 inhibits its own synthesis

To study the mechanism of MvaL4-mediated autoregulation of its operon in Archaea

VOC Bioactivity Assessment
Johanna M. Gostner

So far, cellular reactions to single volatile organic compounds (VOCs) have been investigated in detail only sparsely, due to the difficulties in the modelling of realistic exposure scenarios *in vitro*. In cooperation with Bioenergy2020+, a novel exposure incubator system has been developed that enables long-term exposures to VOCs over a broad concentration range. Exposures of air-liquid interphase cultures of lung cell models were realized with formaldehyde. Although results cannot be extrapolated directly to *in vivo*, this *in vitro* approach can contribute to risk-benefit assessments. Furthermore, when investigating other VOCs, tryptophan breakdown via enzyme indoleamine 2,3-dioxygenase is frequently affected.

Major Achievements:

- For the first time, a long term treatment of cells to gaseous formaldehyde was realised
- Kif6 as potential target in A549 cells identified

Future Goals:

- Investigating formaldehyde as endogenous signalling molecule
- Exploring tryptophan-kynurenine pathway activation by VOC

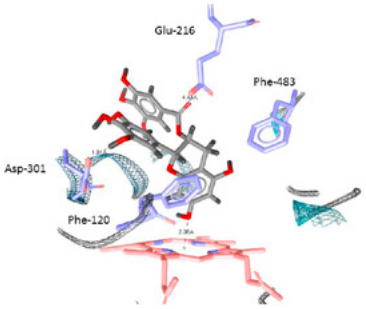

Fig. 7: shows green tea polyphenol (-) Epigallocatechin-3-gallate in the active site cavity of the human drug metabolizing enzyme Cytochrome P450 2D6. The genetic algorithm GOLD was used for docking the flexible non-generic (-) EGCG in the binding site of CYP2D6.

- Extent research on bioactivities of essential oil contained VOC

Eco- and Nutrional Biochemistry & Nutrigenomics
Florian Überall

- Risk/benefit assessment of the impact of natural products on cells through the use of cellular model systems
- Identification of gene expression signatures and genome wide pathway and network analysis
- Cellular detox systems:
  Phase I: Cytochrome P450 isoenzymes (Johannes Hochleitner);
  Phase II: Keap1/Nrf2 signalling (Martina Naschberger) and a detailed understanding of cellular redox regulated pathways
- Development of new kitchen appliances for healthier cooking (cooperation with PHILIPS Austria GmbH) and of a small-scale bio-sensor (cooperation with CTR) (all + Maria Lerchbaumer)

Risk/benefit assessment of natural products – such as volatile organic compounds and phytochemicals – is an integral part of bio-medicine and in the development of potential therapeutics. Therefore, we have developed suitable and reliable cellular models to achieve a deep understanding of the impact of natural products on cell biology, with a primary focus on redox-regulated pathways. The identification of gene expression signatures and genome wide pathway and network analysis is at the core of our analyses. Thereby, our specific focus tackles the cell's own detoxification systems. In this regard, Phase I detoxification, regulated via cytochrome P450 isoenzymes is investigated in depth, as well as Phase II, orchestrated by the Keap1/Nrf2 signalling pathway. We strive to translate the findings of our research into applications of use for society and in this context we have taken part in the development of new kitchen appliances for healthier cooking as part of a fruitful cooperation with PHILIPS Austria GmbH. This project was initiated in 2013. Within this framework, the advancements thus obtained have been extrapolated into the development of a small-scale biosensor in accordance with CTR.

Selected Publications

CDK4 T172 Phosphorylation Is Central in a CDK7-Dependent Bidirectional CDK4/CDK2 Interplay Mediated by p21 Phosphorylation at the Restriction Point. Bisteau X, Paternot S, Colleoni B, Ecker K, Coulonval K, De Groote P, Declercq W, Hengst L, Roger PP.
PLOS GENETICS. 2013; 9(5); e1003546.

The p27-Skp2 axis mediates glucocorticoid-induced cell cycle arrest in T-lymphoma cells. Kullmann MK, Grubbauer C, Goetsch K, Jaekel H, Podmirseg SR, Trockenbacher A, Ploner C, Cato ACB, Weiss C, Kofler R, Hengst L.
CELL CYCLE. 2013; 12(16); 2625-2635.

Statin-induced depletion of geranylgeranyl pyrophosphate inhibits cell proliferation by a novel pathway of Skp2 degradation. Vosper J, Masuccio A, Kullmann M, Ploner C, Geley S, Hengst L.
ONCOTARGET. PubMed: 25605247

Lapatinib and doxorubicin enhance the Stat1-dependent antitumor immune response. Hannesdottir L, Tymoszuk P, Parajuli N, Wasmer M-H, Philipp S, Daschil N, Datta S, Koller J-B, Tripp CH, Stoitzner P, Mueller-Holzner E, Wiegers GJ, Sexl V, Villunger A, Doppler W. EUROPEAN JOURNAL OF IMMUNOLOGY. 2013; 43(10); 2718-2729.

In situ proliferation contributes to accumulation of tumor-associated macrophages in spontaneous mammary tumors. Tymoszuk P, Evens H, Marzola V, Wachowicz K, Wasmer M-H, Datta S, Mueller-Holzner E, Fiegl H, Boeck G, van Rooijen N, Theurl I, Doppler W. EUROPEAN JOURNAL OF IMMUNOLOGY. 2014; 44(8); 2247-2262.

Replenishment of the B cell compartment after doxorubicin-induced hematopoietic toxicity is facilitated by STAT1. Datta S, Parajuli N, Tymoszuk P, Ottina E, Parson W, Sgonc R, Villunger A, Doppler W. JOURNAL OF LEUKOCYTE BIOLOGY. 2014; 95(6); 853-866.

High STAT1 mRNA levels but not its tyrosine phosphorylation are associated with macrophage infiltration and bad prognosis in breast cancer. Tymoszuk P, Charoentong P, Hackl H, Spilka R, Mueller-Holzner E, Trajanoski Z, Obrist P, Revillion F, Peyrat JP, Fiegl H, Doppler W. BMC CANCER. 2014; 14(S); 257.

Thienoquinolines as Novel Disruptors of the PKC epsilon/RACK2 Protein-Protein Interaction. Rechfeld F, Gruber P, Kirchmair J, Boehler M, Hauser N, Hechenberger G, Garczarczyk D, Lapa GB, Preobrazhenskaya MN, Goekjian P, Langer T, Hofmann J. JOURNAL OF MEDICINAL CHEMISTRY. 2014; 57(8); 3235-3246.

Pathway-focused bioassays and transcriptome analysis contribute to a better activity monitoring of complex herbal remedies. Klein A, Wrulich OA, Jenny M, Gruber P, Becker K, Fuchs D, Gostner JM, Ueberall F. BMC GENOMICS. 2013; 14(S); 133.

Immunoregulatory Impact of Food Antioxidants. Gostner J, Ciardi C, Becker K, Fuchs D, Sucher R. CURRENT PHARMACEUTICAL DESIGN. 2014; 20(6); 840-849.

Selected Funding

- EPO-Can – Gaining Sag on the Epotein's Sage. L. Hengst. EU-Projekt – EU-FP7. 157,930.40€
- Funktion der p27 Tyrosin Phosp horylierung durch BCR-Abl, JAK2 und FLT3 in der Tumorentstehung – FWF Einzelprojekt P 24031. L. Hengst. 342,412.00€
- DK MCBO Teilprojekt. Molecular Mecanism of the statin-induced cell cycle arrest. L. Hengst. FWF. 118,135€
- Protein Kinase C Epsilon-induced phosphoproteome P. Gruber. FWF Einzelprojekt P 25491. 267,177.75€
- Volatile Öle. Herta Firmberg Programm. Johanna Gostner. FWF. T 703. 223,500€
- PHYTORAF I: Isolation, quantification and bioactivity assessment of plant allelochemicals, F. Überall, FFG 834251, bmvit cluster "Intelligent technologies" 135,000€.
- VocOnCell: Design, realization and validation of a novel incubator system to expose cell cultures to volatile compounds, F. Überall, FFG 834169, bridge project. 475,000€.
- TRENDS IN NUTRITION: Implementation of novel food processing technologies for healthy nutrition, F. Überall, FFG 840590 headquarter project of PHILIPS Austria. 679,300€
- ABIOTIC STRESS IN EXTREMOPHILES: Characterization of abiotic stress factors of cyanobacteria – isolation of active principles, Mit M. Ganzera, LFU. F. Überall, FWF Einzelprojekt P 24168. 171,003€.

Collaborations

- Joyce M Slingerland, University of Miami, USA
- R. W. Kriwacki, St. Jude Hosp. of Sick Children, Memphis, USA
- Hartmut Halfter, Universität Münster, Germany
- Pierre Roger, Bruxelles, Belgium
- Stephen J. Elledge, Harvard, Boston, USA
- Joan Conaway, Stowers Institute Kansas City, USA
- Drorit Neumann, Tel Aviv University, Israel
- Terrance Lappin, Queens University Belfast, UK
- Elizabeth M Jaffee, Johns Hopkins, Baltimore, USA
- Johannes Kirchmair, University of Hamburg, Germany
- Gennady Lapa, Gause Institute of New Antibiotics, Moscow
- Johann Hofmann (senior advisor)
- Prof. Dr. M. Garber, Institute of Protein Research, Russian Academy of Sciences, Pushchino, Moscow Region, Russia
- Ulrich-Merzenich G., "Omics"-technologies in phytomedicine, Universitätsklinikum Bonn, Germany
- Moscat J., Protein kinase C signaling, Genome Research Institute Cincinnati, USA
- Tonissen K., Eskitis Inst. for Drug Discovery, Griffith Univ., AUS
- Schwarzentruber P., Pyrosequencing & microbiome, Microstech, Olten, CH

Neurobiochemistry

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Keywords

Neuroscience, neuronal growth, central nervous system, brain, cytoskeletal changes

Research Focus

- Characterization of myelin-associated neurite growth inhibitors and their cognate receptors in the central nervous system.
- Signal transduction of neurite growth inhibitors in the brain with special emphasis on effects on cytoskeletal changes in neuronal growth cones.

Research

Neurobiochemistry
Christine Bandtlow

This laboratory is primarily interested in delineating the physiological functions of reticulon proteins (RTN) and their signaling molecules in the nervous system. Related to their association with the ER, RTN proteins have been suggested to play a role in the regulation of intracellular trafficking of proteins involved in exo- and endocytosis, but their precise cellular functions remain unknown. Although many RTN isoforms show distinct expression patterns in the CNS and PNS – both in the developing and mature nervous system – RTN4-A/Nogo, is the only RTN member with a defined function in the adult brain. Nogo-A was originally identified as a myelin-derived inhibitor of neurite outgrowth and has been implicated as a major factor preventing neuronal regeneration and compensatory sprouting in the adult CNS. Over the past few years, considerable progress has been made in our understanding of the structure-function relationship of Nogo-A, its axonal receptors, and the intracellular signaling cascades mediating inhibition of axon outgrowth. However its physiological significance as an intracellular protein of neurons is unknown.

Recent studies in our lab highlight novel functions of RTN-4A/Nogo-A and other RTN isoforms as important intracellular regulators of axonal and dendritic morphogenesis *in vitro* and *in vivo*. Present aims are to unravel the molecular mechanisms that mediate these effects and to analyse proteins that specifically interact with neuronally expressed RTN proteins. In addition, we use several knock-out mouse model systems to explore and define the role of the Nogo receptor components p75NTR and NgR in normal and diseased brains.

Major Achievements:
- Identification of RyR2 as a novel interaction partner of RTN1 in neurons
- Identification of VersicanV0/V1 as a specific NgR2 ligand that controls epidermal innervation

Future Goals:
Characterization of the physiological function of RTN protein interactions in neurons

Purine-mediated Neuroprotection
Gabriele Baier-Bitterlich

In order to improve the functional recovery and clinical outcome after a stroke, a major focus of current stroke research is the development of new neuroprotective and neuroregenerative strategies that aim to rescue the stroke-affected, but still viable tissue (penumbra, see Fig. 2). The rapid degradation of cellular ATP during hypoxia/ischemia results in the production and release of purine nucleosides. Growing evidence suggests that purine nucleosides might act as trophic factors in hypoxic rain.

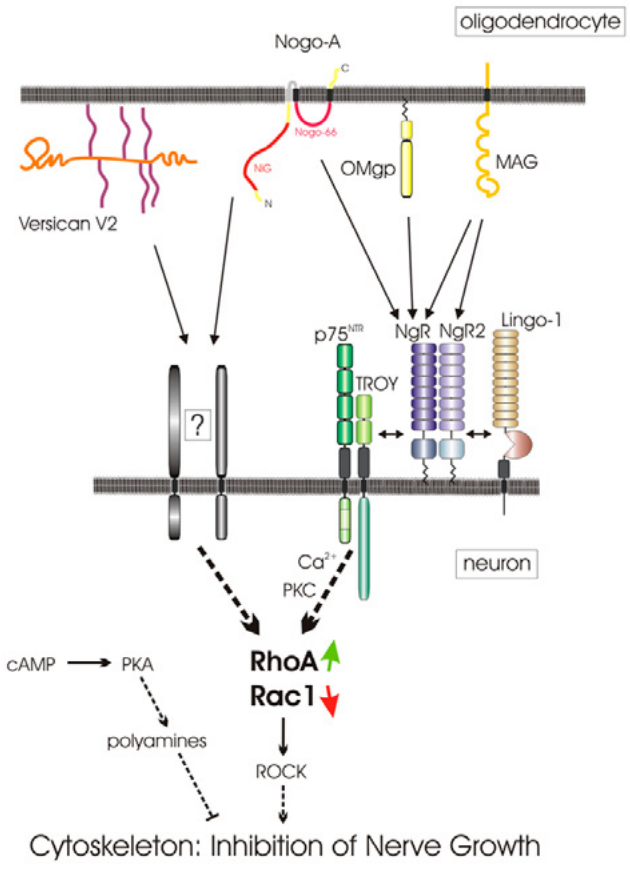

Fig. 1: Signalling by Nogo

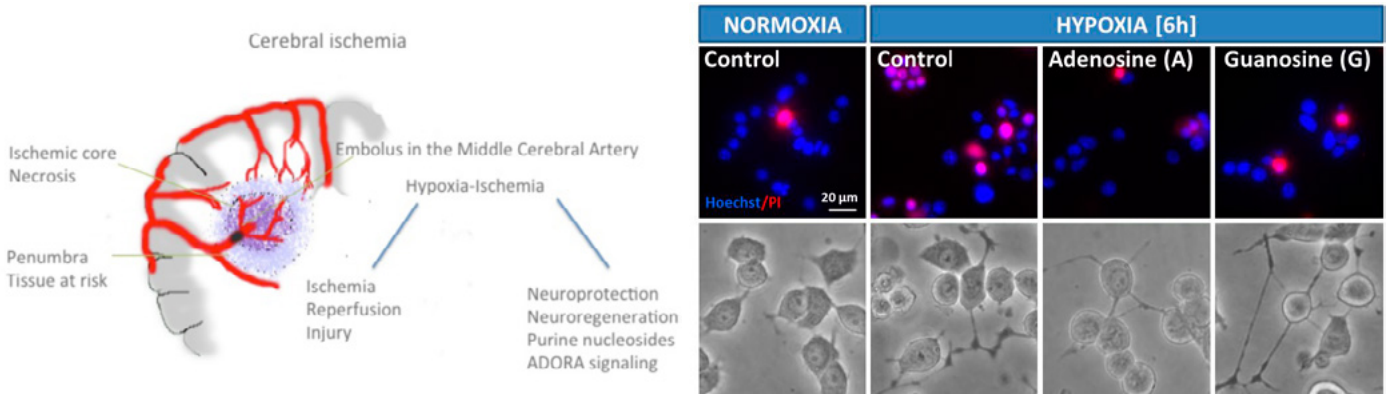

Fig. 2: Even a short blockade of oxygen flow in brain results in a rapid decline of cellular ATP and a subsequent loss of neuronal function and viability. Tissue in the ischemic core is beyond therapeutic rescue, however the penumbral tissue is affected by ischemia but still viable and therefore the key target for neuroprotective interventions. In response to hypoxia/ischemia purine nucleosides are produced and released from cells, and growing evidence suggests that they might act as trophic and neuroprotective factors in the central- and peripheral nervous systems. (Thauerer et al, 2012, 2014). Cell death and neurite formation (Hoechst (blue) and Propidium iodide staining (red)).

Therefore, purine nucleoside/adenosine receptors and their signaling pathways are a key focus of neuroprotective strategies. Previous results in our laboratory demonstrated the positive impact of purine nucleosides on viability and neurite outgrowth (see microscopy picture in Fig. 2) in hypoxic neuronal PC12 cells and primary rat cerebellar granule neurons. We could further show that activation of p42/p44 mitogen-activated kinases (alias ERK1/2), hypoxia-inducible transcription factor-1 (HIF1-alpha) and protein kinase C-related kinase (PKN1) are crucial for purine nucleoside-mediated regeneration and/or survival of neurons. These findings resulted in further funding to investigate the MAPK/HIF1-alpha (B. Thauerer, T421-B18, TWF) and PKN1 (G. Baier-Bitterlich, P26002-B24) signaling cascades in purine nucleosid-mediated neuroprotection.

Biooptics/Microscopy
Martin Offterdinger

The MUI Biooptics/microscopy facility, implemented in 2009 at the Division of Neurobiochemistry, provides university-wide access to advanced equipment, training, education and expertise in light microscopy to all scientists on campus. We currently offer assisted access to several research microscopes and image processing software.

Presently, we are harboring two laser scanning confocal microscopes (Leica SP5, Zeiss, LSM510 Meta) and a multifunctional microscope (Till, iMIC) for live cell imaging, which is equipped for TIRF, spinning disk, and FRAP. Moreover, we are harboring two wide-field microscopes. Access to an integrated stereology microscope/software system for neuron tracing (Neurolucida) is offered in collaboration with the Institute of Pharmacology.

In collaboration with the Leopold-Franzens-University Innsbruck a gated STED super-resolution microscope was purchased co-funded by the BMWF, which is operational since beginning of 2014. As a second superresolution technique, STORM was evaluated on the iMIC and will soon be officially offered. Both gSTED and STORM are able to resolve small structures clearly below Abbe's diffraction limit (250 to 300 nm).

Software support is offered from basic user training to complex calculations. We currently support Fiji, CellProfiler and MATLAB. A server-based deconvolution software package (Huygens Professional) enabling the improvement of the resolution of light microscopic images, including widefield, laser scanning confocal, spinning disk and also gSTED superresolution images is successfully running already for several years. Challenging interactive 3D image analyses are done using Imaris.

Microscopy-related teaching is offered in several PhD programmes and prior to independent usage of any microscope all users receive an instrument-specific training.
For all scientific equipment within the core facility biooptics (microscopes), an improved on-line booking system has been established in 2012 in order to ensure easy and fair access to all users.

Selected Publications

Direct association of the reticulon protein RTN1A with the ryanodine receptor 2 in neurons.
Kaya L, Meissner B, Riedl MC, Muik M, Schwarzer C, Ferraguti F, Sarg B, Lindner H, Schweigreiter R, Knaus H-G, Romanin C, Bandtlow CE. BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH. 2013; 1833: p. 1421–1433.

Nogo-A couples with Apg-1 through interaction and co-ordinate expression under hypoxic and oxidative stress.
Kern F, Stanika RI, Sarg B, Offterdinger M, Hess D, Obermair GJ, Lindner H, Bandtlow CE, Hengst L, Schweigreiter R.
BIOCHEMICAL JOURNAL. 2013; 455: p. 217–227.

Peripheral nerve regeneration and NGF-dependent neurite outgrowth of adult sensory neurons converge on STAT3 phosphorylation downstream of neuropoietic cytokine receptor gp130.
Quarta S, Baeumer BE, Scherbakov N, Andratsch M, Rose-John S, Dechant G, Bandtlow CE, Kress M.
J Neurosci. 2014 Sep 24;34(39):13222-33.

Loss of Nogo receptor homolog NgR2 alters spine morphology of CA1 neurons and emotionality in adult mice.
Borrie SC, Sartori SB, Lehmann J, Sah A, Singewald N, Bandtlow CE. Front Behav Neurosci. 2014 May 15;8:175.

Nogo receptor homolog NgR2 expressed in sensory DRG neurons controls epidermal innervation by interaction with Versican.
Bäumer BE, Kurz A, Borrie SC, Sickinger S, Dours-Zimmermann MT, Zimmermann DR, Bandtlow CE.
J Neurosci. 2014 Jan 29;34(5):1633-46.

Modulation of phenylalanine and tyrosine concentrations by ischemia and guanosine in neuronal PC12 cells.
Thauerer B, Geisler S, Fuchs D, Baier-Bitterlich G.
PTERIDINES. 2013; 24: p. 245–250.

Selected Funding

- FWF, W1206: Doctoral College "Signal processing in neurons", Bandtlow Christine E
- FWF, P26002-B24: "Analyse der Rolle der PRK1 in der Neuroprotektion", Baier-Bitterlich Gabriele
- FWF, T421-B18: "Mechanismus der HIF-1alpha Aktivierung", Thauerer Bettina

Collaborations

- Paul Lingor, Univ. Göttingen, Germany
- Dieter Zimmermann, Univ. Zurich, Switzerland
- Michail Sitkovsky, Dana-Farber Cancer Institute, Boston, USA

Core Facilities

- Leica SP5 laser scanning confocal microscope
- Till, iMIC-microscope, multifunctional microscope for live cell imaging (TIRF, spinning disk, FRAP)
- SP8 gSTED microscope
- Zeiss LSM510Meta laser scanning confocal microscope
- two widefield microscopes
- Neurolucida (in collaboration with the Institute of Pharmacology)

Clinical Biochemistry

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https://www.i-med.ac.at/imcbc/clinbiochemfolder/clinbiochem.html

Keywords

Protein Analysis, PTM Identification, Mass Spectrometry, Phospho-proteomics, Proteome-wide Quantification, Capillary Electrophoresis, HPLC, Method Development, Epigenetics, Protein Microanalysis Facility

Research Focus

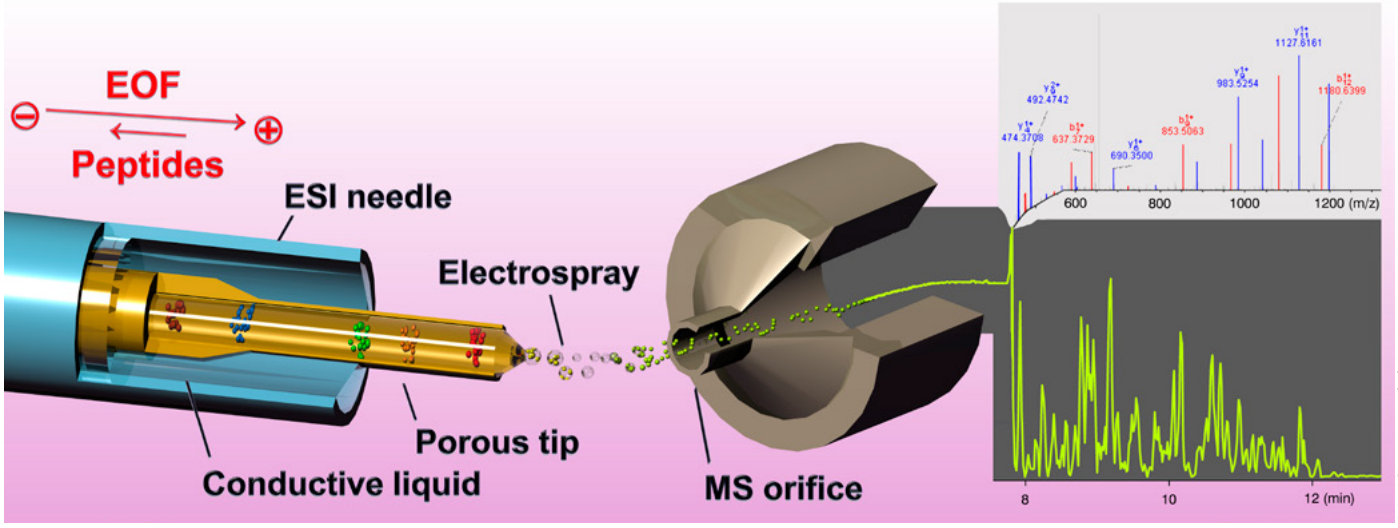
- Development of multidimensional LC/CE-MS-based methods
- PTM identification of various nuclear and extracellular proteins
- Identification of novel phospho-histone binding proteins
- Identification of histone-modification patterns at the nucleosomal level
- Method development for top-down and middle-down proteomics using ETD- and HCD-fragmentation
- Development of targeted protein absolute quantification methods

General Facts

Our lab focuses on the development of high-resolution methods for the separation and identification of post-translationally modified proteins in order to investigate their biological significance. A set of separation methods based on capillary electrophoresis (CE), reversed-phase chromatography, hydrophilic interaction liquid chromatography (HILIC) and mass spectrometry (MS) was introduced in our lab. Now, as a result of a continuous development program over many years, our group offers a wide range of analytical methods and services to support the work of other research scientists in the University (see Protein Micro-Analysis Facility). Our main technologies are: LC/CE-ESI-MS, HPLC (e.g. RPC, HILIC, IEC, GPC), Capillary electrophoresis, Phospho-proteomics, Chromatin immune-precipitation, Co-immunoprecipitation and proteome-wide quantification (e.g. SILAC, iTRAQ, TMT, Dimethyl labeling).

Research

At present, we have two main research interests. The first focuses on the evaluation of capillary electrophoresis-mass spectrometry (CE-MS) as an alternative proteomics tool for nanoLC-MS. Up to now, LC-MS is the commonly used technique for the analysis of complex protein mixtures in proteomics. The use of CE as a complementary separation method to reversed-phase HPLC has not yet become fully accepted as an alternative. One of the reasons is the on-line interfacing of CE with MS that allows stable electrospray processes without compromising the quality of separation or the detection sensitivity. A recently published concept of a sheathless interface based on a separation capillary with a porous tip acting as nanospray emitter combines low flow characteristics of CE with an integrated ESI source, as a promising alternative to nanoLC-ESI-MS. We recently published the successful application of CE-MS for the analysis of moderately complex mixtures consisting of distinctly acetylated, phosphorylated, methylated and deamidated proteins as well as of microsequence variants differing only slightly in mass and charge. Our present aim is to evaluate the suitability of CE-MS for its use in identification and quantification of deamidation related products. Deamidation of asparaginyl



© Anal Chem 2011; 83(19):7297–305

Fig. 1: The design of a sheathless interface for coupling capillary electrophoresis to mass spectrometry (Faserl et al. 2011: Anal. Chem. 83(19): 7297–305).

residues is one of the most frequent modifications in peptides and proteins, and in the majority of cases is a non-enzymatic reaction that takes place under physiological conditions *in vitro* in the course of isolation or storage, and *in vivo* during development and/or aging of cells. This posttranslational modification reaction often follows a complex mechanism, producing a mixture of aspartyl, succinimidyl and isoaspartyl forms, with L-isoaspartyl dominating. Due to its biochemical importance, various analytical techniques for the characterization of deamidated peptides have been described, however it is still a challenging task to distinguish between isoAsp, Asp and Asn residues. Isoaspartyl residues can significantly affect protein structure and typically alter biological activity and function of peptides and proteins.

Our second interest is directed to quantitative proteomics, which is a powerful approach used for both discovery and targeted proteomic analyses to understand global proteomic dynamics in a cell, tissue or organism. Most quantitative proteomic analyses entail the isotopic labeling of proteins or peptides, which can then be differentiated by mass spectrometry. Relative quantitation methods (SILAC, ICAT, ICPL and isobaric tags) are used to compare protein or peptide abundance between samples. Recently, we performed quantitative proteome analyses using metabolically labelled yeast proteins. Samples were analyzed by CE- and LC-ESI-MS and the characteristic features of the two approaches and the number of identified and quantified peptides and proteins were compared. Moreover, the two MS data sets were mined for post-translationally modified peptides, e.g. acetylated, phosphorylated, deamidated and oxidized forms.

Protein Micro-Analysis Facility
ao. Univ.-Prof. Dr. Herbert Lindner

The Protein Micro-Analysis Facility is established within the Division of Clinical Biochemistry and is dedicated to provide investigators with equipment, expertise and custom services for the detection, characterization and quantification of proteins and peptides on a recharge basis. The facility maintains a suite of state of the art instrumentation including:

- Q Exactive Plus (Thermo Fisher Scientific) hybrid FT mass spectrometer LTQ Orbitrap XL ETD (Thermo Fisher Scientific)
- LTQ VELOS mass spectrometer (Thermo Fisher Scientific)

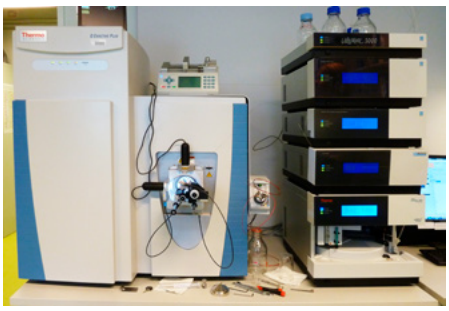

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Fig. 2: Nano-LC-MS system consisting of a Q Exactive™ Hybrid Quadrupole-Orbitrap Mass Spectrometer (Thermo Scientific™) and a nano-LC gradient system UltiMate 3000 (Dionex).

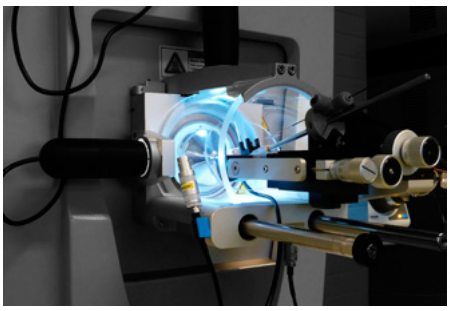
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Fig. 3: Nanospray Flex™ ion source (Thermo Scientific™).

- MALDI TOF/TOF 4800 plus analyzer (AB Sciex)
- Procise 492 protein sequencer (Applied Biosystems)
- Nano-LC gradient systems UltiMate 3000 (Dionex)
- Probot microfraction collector (LC-Packings) for on-line MALDI target preparations
- Various capillary electrophoresis and HPLC Systems
- Solar M6 dual Zeeman spectrometer (Thermo Fisher Scientific) for trace element analysis

<u>Provided Services:</u>

- Comprehensive protein identification of simple and complex protein digests from gel bands, immunoprecipitations (IP), and whole-cell/secreted/tissue digests by mass spectrometry
- Molecular mass determination of intact proteins or peptides
- Localization and quantification of post-translational modifications (phosphorylation, acetylation, methylation, etc.)
- Mass spectrometry supported determination of protein complex structure by identification of chemical cross-linked peptides
- Enrichment of phosphopeptides by Immobilized Metal Affinity Chromatography (IMAC, etc.)
- Quantitative Proteomics using isotope labeling strategies (e.g. SILAC, iTRAQ, TMT, etc.)
- Lable free Quantification
- Separation technologies including analytical and semi-preparative liquid chromatography (e.g. ion exchange, reverse-phase, normal phase) and capillary electrophoresis
- Quantitative amino acid analysis
- Quantitative elemental analysis using atomic absorption spectrometry (AAS)
- Capillary electrophoresis-electrospray ionization-mass spectrometry (CESI-MS)

Selected Publications

Comparing and combining capillary electrophoresis electrospray ionization mass spectrometry and nano-liquid chromatography electrospray ionization mass spectrometry for the characterization of post-translationally modified histones. Sarg B, Faserl K, Kremser L, Halfinger B, Sebastiano R, Lindner HH.
MOL CELL PROTEOMICS. 2013; 12(9): p. 2640–56.

Histone H5-chromatin interactions in situ are strongly modulated by H5 C-terminal phosphorylation. Kostova NN, Srebreva L, Markov DV, Sarg B, Lindner HH, Rundquist I.
CYTOMETRY A. 2013; 83: p. 273–9.

MALDI-MS tissue imaging identification of biliverdin reductase B overexpression in prostate cancer. Pallua JD, Schaefer G, Seifarth C, Becker M, Meding S, Rauser S, Walch A, Handler M, Netzer M, Popovscaia M, Osl M, Baumgartner C, Lindner H, Kremser L, Sarg B, Bartsch G, Huck CW, Bonn GK, Klocker H.
J PROTEOMICS. 2013; 91: p. 500–14.

Characterization of the Link between Ornithine, Arginine, Polyamine and Siderophore Metabolism in Aspergillus fumigatus. Beckmann N, Schafferer L, Schrettl M, Binder U, Talasz H, Lindner H, Haas H. PLOS ONE. 2013; 18;8(6):e67426.

Quantitative proteomics using ultralow flow capillary electrophoresis-mass spectrometry. Faserl K, Kremser L, Müller M, Teis D, Lindner HH. ANAL CHEM. 2015 May 5;87(9):4633-40.

Selected Funding

- Coupling capillary electrophoresis to mass spectrometry for protein and proteome analysis; Industrial Project with AB SCIEX
- Investigation of in-vivo O-Glycosylation of the low abundance marker NT-proBNP by Affinity Proteomics Methods and Mass Spectrometry in blood plasma from patients with severe heart failure
- Industrial Project with Roche Diagnostics GmbH Penzberg, Germany
- Determination of changes in histone acetylation and methylation of Histone H4 in peripheral blood mononuclear cells isolated from human panic disorder patients prior to – during – and following – therapy; SFBF44 “Cell signaling in chronic CNS disorders”

Collaborations

- Reinhard Dallinger, Institute of Zoology, LFU, Innsbruck, Austria
- Peter Ladurner, Institute of Zoology, LFU, Innsbruck, Austria
- Nicolas Singewald, Institute of Pharmacy, LFU, Innsbruck, A
- Margarethe Geiger, Depart. of Vascular Biology and Thrombosis Research Centre of Physiology and Pharmacology, Vienna, A
- J. Ausio, University of Victoria, Victoria, Canada
- M. Freitas, Ohio State Univ. Medical Center, Columbus, USA
- N. Guzman, Princeton Biochemicals Inc., New Jersey, USA
- Pedro Suau, Universitat Autonoma de Barcelona, Spain
- S. Krylov, Department of Chemistry and Centre for Research on Biomolecular Interactions, York University, Toronto, Canada
- D.D. Chen, Department of Chemistry, University of British Columbia, Vancouver Canada
- R. Cole, Johns Hopkins University School of Medicine, Balitimore, USA

Core Facilities

Protein Micro-Analysis Facility:
protein.analysis.iftz@i-med.ac.at
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Keywords

Structural biology, biochemistry, molecular biology, clinical chemistry, protein purification, high pressure liquid chromatography, bioethics

Research Focus

- Structural biology of disease proteins with a special focus on neurofibromatosis type-1, an inherited disease with relatively high incidence but poorly understood pathogenic mechanisms.
- The biochemistry and clinical chemistry of pteridine and tryptophan metabolism. Pteridines are structurally related to the vitamins folic acid and riboflavin but, in contrast to these, can be formed in the mammalian body.
- Ethical, cultural and social issues concerning the use of innovative technologies in biomedicine.

General Facts

We are performing basic research on biomolecular systems that can impact on human health and disease. Our research areas include pteridine and lipid metabolism as well as intracellular signal transduction and its regulation, particularly in the context of small guanine nucleotide binding (G) proteins.

Another focus is gaining an understanding of novel biotechnologies in the context of biomedicine and how they create and at the same time serve emerging markets as well as to explore their ethical, social and cultural dimensions. Research and teaching in this field has led to numerous cooperations (see below) and the participation in the building of a local interinstitutional platform of expertise on ethics in the context of health and medicine.

Our methods spectrum includes biochemical techniques such as FPLC/HPLC for preparative protein purification and analysis, eukaryotic cell culture, various biophysical as well as bioanalytical methods and biomolecular X-ray crystallography.

We consider teaching a major responsibility in the education of young scientists and contribute to the respective activities for students of the Medical as well as the Leopold-Franzens University Innsbruck.

Research

Structural Biology and Mechanisms of the Neurofibromatosis Type 1 Protein
Klaus Scheffzek

We aim to understand the disease mechanism of neurofibromatosis type-1 (NF1), a genetic disease with relatively high incidence. NF1 patients have an increased risk of developing tumours, show a variety of developmental defects and frequently have learning disabilities. The tumour suppressor gene NF1 encodes the giant protein neurofibromin (320 kDa) and is not functional in NF1 patients due to genetic alterations. Our long term vision is to define the functional spectrum of neurofibromin in as much detail as possible. Our research activities currently include determining the structure of full length neurofibromin as well as the definition of its interaction partners (collaborations with Frank McCormick, UCSF, and Lukas A. Huber, Innsbruck). In addition, we explore the mechanism of neurofibromin-mediated repression of MHCII protein expression (collaboration with Andreas von Deimling, Heidelberg).
A major activity in the reporting period comprised the implementation and finalization of our biomolecular crystallography platform that includes a robot based crystallization screening laboratory (ArtRobbins/DunnLab, Rigaku) with automated imaging system and an X-ray generator (Microstar, Bruker).

Neuropsychoimmunology
Dietmar Fuchs

Mood changes and depression are common in patients suffering from inflammatory disorders like virus infections, autoimmune syndromes, malignant tumour diseases and also in the overweight, but the pathogenesis of symptoms is still unclear. Several of our recent studies showed associations between neuropsychiatric deviations in patients and increased neopterin

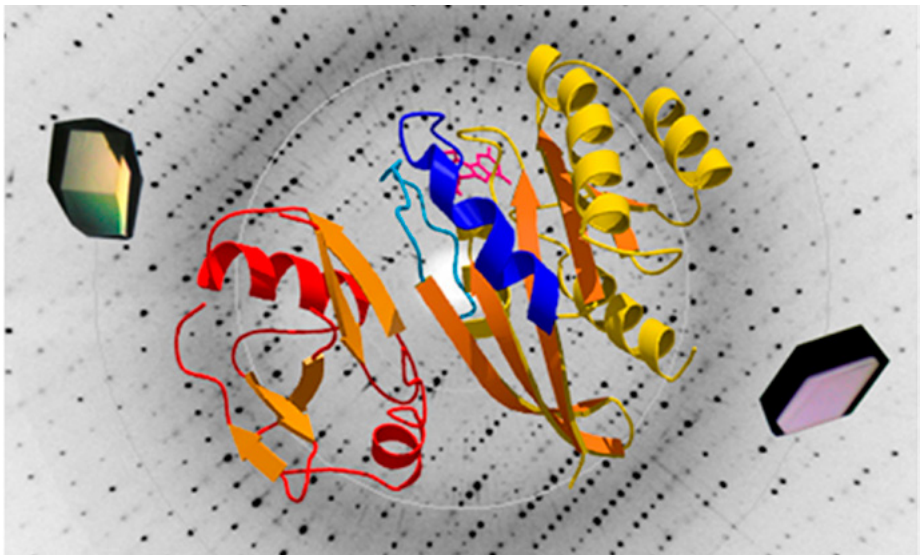

Fig. 1: Since our move to the CCB building we have been implementing a now running platform dedicated to biomolecular sample production, crystallization and structure determination.

concentrations and tryptophan breakdown (Kyn/Trp) in the blood. Our most recent work sheds more light on this observation and its relevance for neuropsychoimmunology. We have also observed higher blood phenylalanine levels and higher phenylalanine to tyrosine ratios in such patients and also in healthy elderly individuals. Especially in combination with the measurement of Kyn/Trp, Phe/Tyr determinations can support treatment decisions as to whether serotonergic or noradrenergic/adrenergic/dopaminergic treatment options are more likely to be useful in the individual patient. Clinical and *in vitro* studies utilizing the model of freshly isolated peripheral blood mononuclear cells (PBMC) were performed, and in the years 2013/14 more than 50 papers derived from multiple collaborations worldwide have been published by the group. The reference given below refers to a review article in which the general concept behind our research activities is described and from which detailed references can be extracted (Capuron *et al.*, Curr Pharm Des 2014;20:6048–57).

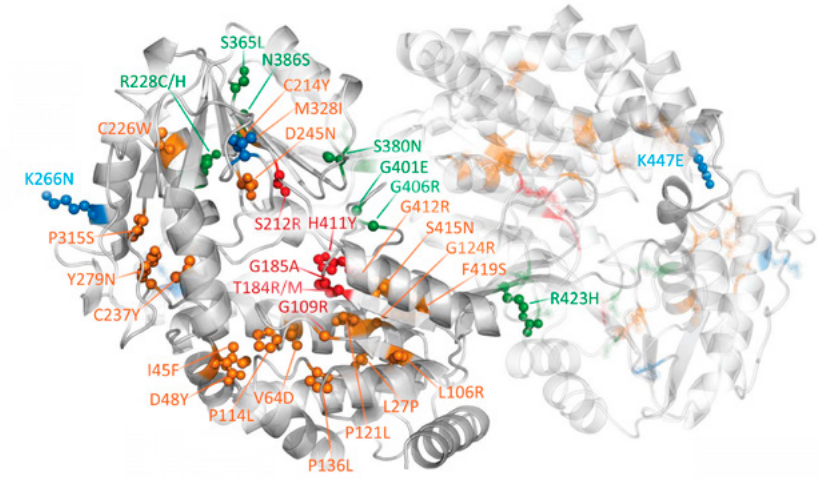

Fig. 2: Position of Sjögren-Larsson syndrome causing amino acid changes in the fatty aldheyde dehydrogenase structure.

Alkylglycerol Monooxygenase, a Novel Ether-Lipid Cleaving Enzyme

Katrin Watschinger, Gabriele Werner-Felmayer, Georg Golderer and Ernst R. Werner

Building on the 30 years plus focus on pteridine research in the institute, we are currently focusing on ether lipid metabolism. The central enzyme for the degradation of these compounds, alkylglycerol monooxygenase, is dependent on the cofactor tetrahydrobiopterin. Tetrahydrobiopterin, a compound structurally related to the vitamins folic acid and riboflavin, is synthesized in the animal body, and is required for five specific, crucial hydroxylation reactions. In addition to alkylglycerol monooxygenase these include the conversion of phenylalanine to tyrosine, the first essential step in the degradation of the essential amino acid phenylalanine, the biosynthesis of the neurotransmitters dopamine, epinephrine and serotonin as well as the biosynthesis of the versatile messenger molecule nitric oxide.

The alkylglycerol monooxygenase reaction was first described in 1964, along with the subsequent conversion of its fatty aldehyde product to the corresponding fatty acid by fatty aldehyde dehydrogenase. It took until 2010 when we managed to assign a sequence to the very labile integral membrane protein alkylglycerol monooxygenase, which could not be purified so far. We then explored the biochemistry of the enzyme by site directed mutagenesis screens. We now proceed to the manipulation of the expression of this enzyme in cultured cells and in model organisms in order to study its physiological role. Fatty aldehyde dehydrogenase, the subsequent enzyme in ether lipid metabolism, causes a rare inherited disease when its function is lost, the Sjögren Larrson Syndrome. This is a severe disease characterized by developmental delays and a skin phenotype called ichtyosis. Although humans have more than a dozen different aldehyde dehydrogenases, they cannot compensate for a deficiency in fatty aldehyde dehydrogenase. We characterized by biochemical and structural methods the human fatty aldehyde dehydrogenase and found that a special additional structural feature of this enzyme, a gatekeeper helix, is responsible for its specificity to fatty aldehydes.

Bioethics

Gabriele Werner-Felmayer

Based upon interdisciplinary dialogues with colleagues from philosophy, social and political science, medical law, economics and health management, we focus on epistemology and culture in biomedicine as well as its ethical dimensions. Special emphasis is placed upon the concepts of hope and promise in genomics, medically assisted reproduction and stem cell research. Current projects deal with international regulation of assisted reproductive technologies, with third party cross-border reproductive care, with unintended traumatization of patients in the context of medicalised reproduction, and with prevailing determinist views in the dynamic field of genetics/genomics that are particularly powerful in marketing personal genetic/genomic services. PhD projects deal with the ethics of reprogenetics in developing countries and with the definition of “race” in pharmacogenomics.

Selected Publications

Functional MHC Class II Is Upregulated in Neurofibromin-Deficient Schwann Cells. Reuss DE, Mucha J, Holtkamp N, Mueller U, Berlien H-P, Mautner VF, Ehemann V, Platten M, Scheffzek K, von Deimling A. JOURNAL OF INVESTIGATIVE DERMATOLOGY. 2013; 133: p. 1372–1375.

Activated Immune System and Inflammation in Healthy Ageing: Relevance for Tryptophan and Neopterin Metabolism. Capuron L, Geisler S, Kurz K, Leblhuber F, Sperner-Unterweger B, Fuchs D. CURRENT PHARMACEUTICAL DESIGN. 2014; 20: p. 6048–6057.

A gatekeeper helix determines the substrate specificity of Sjogren-Larsson Syndrome enzyme fatty aldehyde dehydrogenase. Keller MA, Zander U, Fuchs JE, Kreutz C, Watschinger K, Mueller T, Golderer G, Liedl KR, Ralser M, Krauetler B, Werner ER, Marquez JA. NATURE COMMUNICATIONS. 2014; 5: p. 4439.

Genetics as Social Practice – Transdisciplinary Views on Science and Culture. Prainsack B, Schicktanz S, G Werner-Felmayer. ISBN 978-1-4094-5549-3; Ashgate, Farnham (UK); January 2014. http://www.ashgate.com/isbn/9781409455493.

Selected Funding

- Structural basis for the modulation of dendritic spine density by the interaction of neurofibromin and the AAA-ATPase p97/vcp, FWF, MCBO graduate school, Klaus Scheffzek
- Characterization of immunomodulatory effects of nanoparticles *in vitro*, Austrian Science Fund (FWF), Dietmar Fuchs
- Role of alkyglycerol monooxygenase and tetrahydrobiopterin biosynthesis in adipocyte function. Autonomous Province of Bolzano/Bozen–South Tyrol (Division for the Promotion of Education, Universities and Research), Katrin Watschinger

Collaborations

- Lucile Capuron, University of Bordeaux, France
- Keith Channon, Jonathan Hodgkin, University of Oxford, United Kingdom
- Frank McCormick, San Francisco, USA
- Andreas von Deimling, Heidlerberg, Germany
- Magnus Gisslen, Lars Hagberg, Östra University Hospital, Gothenburg, Sweden
- Harald Mangge, Eva Reininghaus, Medizinische Universität Graz, Austria
- Teo T Postolache, University of Baltimore, MD, USA
- Richard W Price, Institut of Neurology, San Francisco General Hospital, UCSF, USA
- Markus Ralser, University of Cambridge, United Kingdom

The bioethics branch collaborates with colleagues from numerous institutions at local, national and international levels (King’s College London, University Medicine Goettingen). It is the Austrian partner of the International Network of the UNESCO Chair in Bioethics (Haifa).

Cell Biology

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Research Focus/Keywords

- Signal Transduction and Proteomics
- Cell Differentiation
- Membrane Traffic and Signaling

General Facts

We study molecular mechanisms that control the organization and function of living cells. To address these fundamental questions, we use a combination of genetic model systems, state-of the-art microscopy and quantitative proteomics. Our division provides an international and dynamic research environment for Master & PhD students as well as PostDocs. We have numerous national and international collaborations with academic partners and biotech companies. We are embedded the international PhD program MCBO (Molecular Cell Biology and Oncology). We participate in and coordinate several EU projects.

Research

Three research groups are currently active at the division of Cell biology:

Signal Transduction and Proteomics
Lukas Huber Lab

We would like to understand how specific cell fate decisions are made by using a pool of very similar kinases within MAPK signalling pathways. We are especially interested in the role of scaffold proteins in organizing signal transduction complexes and study the spatial and temporal resolution of signaling mechanisms as well as their cytoplasmic effectors and target genes. The aim of our research is to understand the physiological function of scaffold complexes in MAPK signaling at the molecular level in cells and at the level of the entire organism.

<u>The LAMTOR complex – At the crossroad between signal transduction and endosomal biogenesis</u>

Over the last two decades we and others could show that the LAMTOR complex (late endosomal/lysosomal adaptor, MAPK and MTOR activator) is strictly recruited to the membrane of late endocytic compartments, from where it actively influences MAPK, mTORC signaling and endosomal trafficking. The complex is involved in several biological processes including immunity, early embryogenesis, tissue homeostasis, cellular proliferation and migration. We use complementary molecular and cellular biology methods, stretching from proteomics, to live and confocal microscopy, electron microscopy, and structural biology, in order to functionally characterize the LAMTOR complex at the molecular and cellular levels. In addition, we use model organisms such as yeast and knockout mice to determine the biological roles of the complex *in vivo*, at the organism level.

As a result of an interaction proteomics screen using TAP-MS (Tandem Affinity Purification, coupled to Mass Spectrometry) we have identified several proteins interacting with the LAMTOR complex. The core interactome includes all members of the LAMTOR complex, the RAG GTPases (that mediate the translocation of mTORC1 to endosomes/lysosomes), and SLC38A9 (a previously uncharacterized member of the solute carrier family 38, that we recently identified as an integral component of the amino acid-sensing machinery that controls the activation of mTORC1 (Rebsamen *et al.*, Nature 2015). We are currently analysing this comprehensive interactome data functionally with a special focus on the interplay between signaling and endosomal biogenesis (Fig. 1).

<u>The LAMTOR complex: disease models</u>

The use of animal models led to great progresses in understanding the role of the endosomal adaptor Lamtor2 in endosomal/lysosomal trafficking. In a first approach LAMTOR2 knockout mice were generated, but severe defects during embryogenesis resulted in no viable offspring (Teis *et al.*, J Cell Biol. 2006). During this time, four patients, all siblings, suffering from a primary immunodeficiency syndrome, due to a hypomorph LAMTOR2 allele, were identified and demanded for further investigations of the immune functions LAMTOR2 (Bohn *et al.*, Nat Med. 2007).

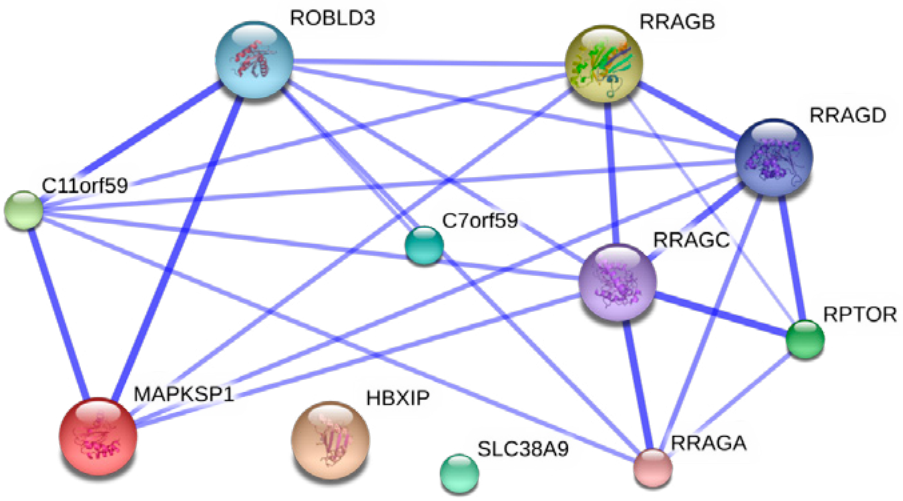

Fig. 1: Core interactome of the LAMTOR complex.

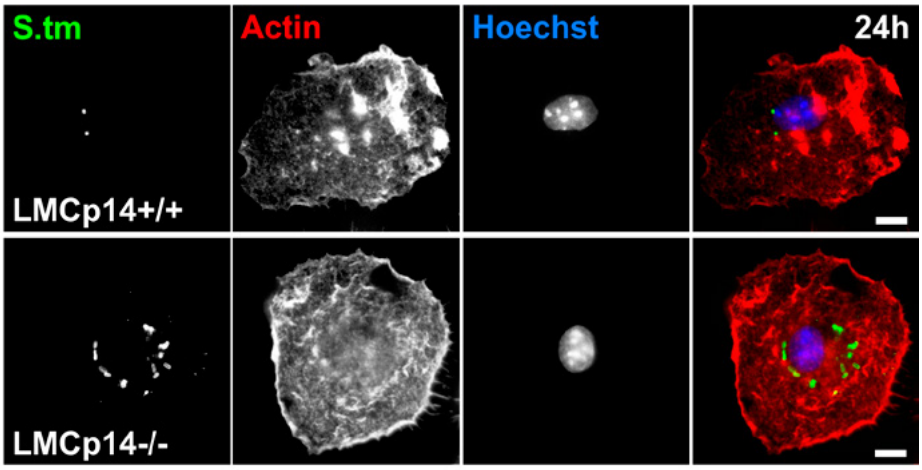

Fig. 2: Primary LAMTOR2+/+ and LAMTOR2-/- macrophages infected with Salmonella (green). After 24 h an increased bacteria load in LAMTOR2-/- macrophages was observed. Actin (red) and Hoechst (blue). Scale bars: 10 mm (Taub et. al., 2012).

Therefore, we have established conditional knockout mouse models to investigate the role of LAMTOR2 in antigen presenting cells including macrophages and dendritic cells (DCs). The correct uptake and processing of pathogens and antigen presentation in the context of the immune response is strictly regulated by the endosomal/lysosomal system. Using a mouse model where Lamtor2 was specifically depleted in macrophages, key players in the immune system, we have been able to demonstrate that LAMTOR2 is a host defense factor against pathogens (Fig. 2) (Taub *et al.* J Cell Sci. 2012) and our findings correlate with the previously described immunodeficiency syndrome. We are currently following this line of results combining the mouse genetic approach with a proteomic approach aimed at deepening our understanding of the Lamtor2 interaction partners and downstream targets involved in phagolysosomal maturation underlying an efficient antimicrobial response.

DCs are initiators of adaptive immunity and unlike macrophages also able to prime naïve T cells. Investigation of a DC specific knockout mouse revealed a crucial role of LAMTOR2 for DC homeostasis. While soon after birth the epidermal Langerhans cell (LC) network is dispersed due to increased apoptosis and a proliferation defect (Sparber *et al.*, 2014), the aging animals suffer from a massive expansion of conventional (cDCs) and plasmacytoid DCs (pDCs) cumulating in a myeloid proliferation syndrome (MPD) (Fig. 3). As cellular mechanism causing those phenotypes a deregulation of late endosomal LAMTOR complex dependent MAPKinase and mTORC1 signaling were identified. Loss of LCs was related to a decreased signaling, while cDC and pDC expansion was caused by boosted mTORC1 activation (Scheffler *et al.*, 2014).

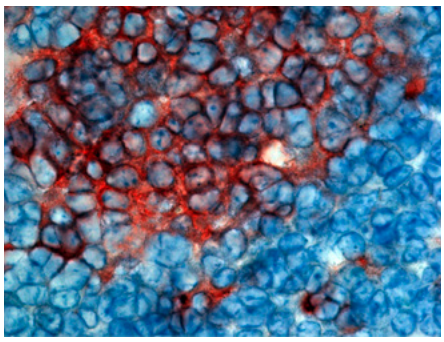

Fig. 3: Dendritic cell infiltrate in a spleen section of a DC specific LAMTOR2 knockout mouse model at the age of three months. red: CD11c, blue: hematoxylin.

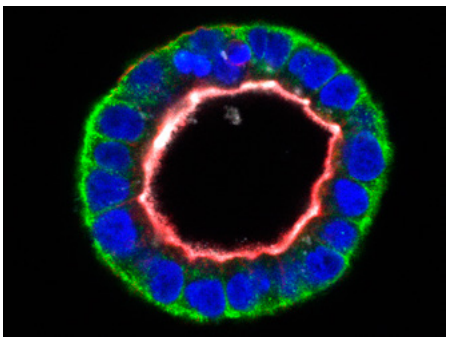

Fig. 4: Polarized epithelial CaCo2 cyst showing basolateral proteins (green), apical proteins (white and red) and nuclei (blue).

Microvillus inclusion disease – intracellular trafficking and epithelial polarity

Microvillus inclusion disease is an autosomal recessive enteropathy characterized by intractable diarrhea setting on within the first few weeks of life. The hallmarks of MVID are a lack of microvilli on the surface of villous enterocytes, occurrence of intracellular vacuoles lined by microvilli (microvillus inclusions), and the cytoplasmic accumulation of periodic acid-Schiff (PAS)-positive vesicles in enterocytes.
Together with our collaborators from the Department of Pediatrics I, MUI, and the Division of Histology and Embryology, MUI, we were the first to identify mutations in MYO5B, encoding the unconventional type Vb myosin motor protein, in a first cohort of nine MVID patients (Mueller *et al.*, Nature Genetics 2008). In a follow-up study, we described further 15 novel nonsense and missense mutations in MYO5B in 11 unrelated MVID patients (Ruemmele *et al.*, Human Mutation 2010).
Further investigations have focused on the role of Myosin Vb and its interplay with Rab Small GTPases in the establishment of correct epithelial polarity by making use of a CaCo2 RNAi cell model (Thoeni *et al.*, Traffic 2014).
Recently, we have identified novel mutations in the STX3 gene, causing a variant form of MVID in patients negative for mutations in MYO5B (Wiegerinck *et al.*, Gastroenterology 2014). Syntaxin 3 is an apical t-SNARE protein pivotal for polarized apical exocytosis and secretion in epithelial cells.
By using a CaCo2 cell model for epithelial/enterocyte polarity and state of the art genome-editing technologies we focus on the intracellular cascade and the proteins involved, which ensure correct polarized intracellular traffic in order to maintain proper epithelial polarity (Fig. 4).

Cell Differentiation
Ilja Vietor Lab

The interplay between cell proliferation and differentiation controls not only development but also regeneration and therefore its regulatory mechanisms are of interest as therapeutic targets. Based on our studies we predict that the transcriptional co-repressor TPA inducible sequence 7 (TIS7) is one of the players affecting the cellular regeneration events. TIS7 inducible by the mitogen TPA or growth factors is differentially expressed

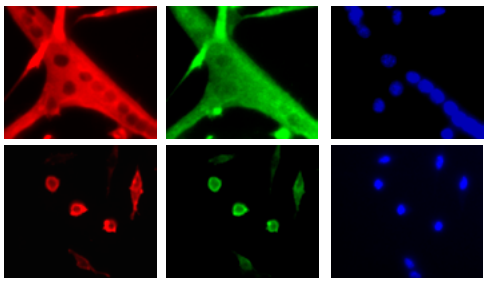

Fig. 5: Muscle satellite cells grown under differentiation conditions. Immunofluorescence microscopy images depict: MF20-differentiated myoblasts marker protein (red), pICln-TIS7-interacting methylosome subunit protein (green), and DAPI (blue).

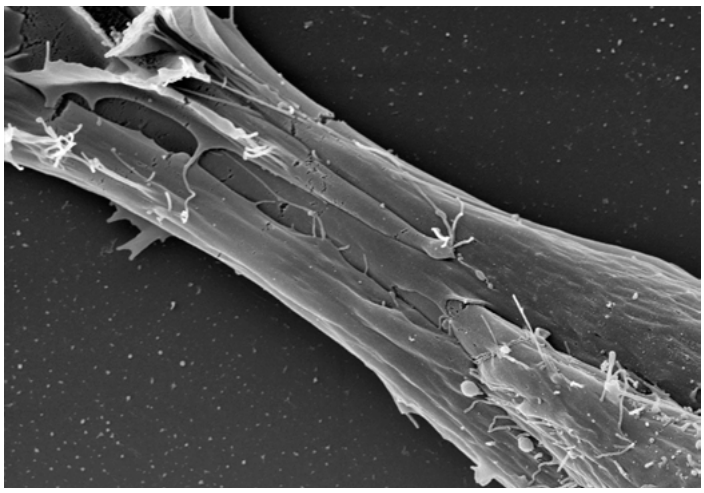

Fig. 6: Fused TIS7 wt skeletal muscle cells grown under differentiation conditions in culture. Raster electron scanning micrograph.

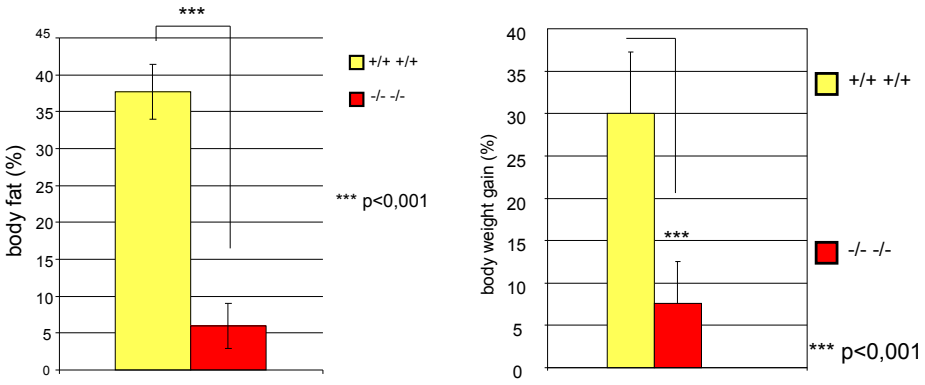

Fig. 8: Left: TIS7 SKMc15 double knockout mice are significantly leaner. 6 months old male mice; n= 6. Chow diet. Right: TIS7 SKMc15 double knockout mice gain significantly less weight upon feeding with high fat diet. 11 weeks male mice; n= 11; 3 weeks high fat diet.

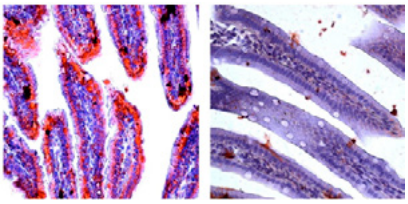

Fig. 7: Lack of fat vacuoles in the jejunum of TIS7 SKMc15 double knockout mice (right). Oil red oil staining; magnification 40x.

in various polarized cell types. We have shown that TIS7 represses transcription in an HDAC-dependent manner. In the TIS7-regulated downstream target genes we have identified a common regulatory motif, a so-called transcription factor "module". TIS7 expression increases during the process of tissue regeneration following a challenge like muscle crush damage or intestinal resection. Our previous studies have shown that in TIS7 knockout mice the differentiation and fusion potential of myoblasts is impaired.

The interplay between cell proliferation and differentiation controls not only development but also regeneration. Regulation of these two mechanisms is of interest because they represent possible therapeutic targets. Based on our studies, we predict that the transcriptional co-regulator TPA-inducible sequence 7 (TIS7) is one of the players affecting cellular regeneration events. TIS7, induced by the mitogen TPA or growth factors, is differentially expressed in several different polarized cell types. We have shown that TIS7 interacts with the SIN3 complex and regulates transcription in an HDAC-dependent manner. In the promoter region of TIS7-regulated downstream target genes we have identified a common regulatory motif C/EBPalpha-Sp1 transcription factor "module". Furthermore, TIS7 has the ability to inhibit the Wnt signaling in an HDAC-dependent manner. TIS7 expression increases during the process of tissue regeneration following a challenge like muscle crush damage or intestinal resection. Our previous studies have shown that in TIS7 knockout mice the expression of myogenic regulatory proteins is deregulated and the differentiation and fusion potential of muscle satellite cells is impaired.

Major Achievements:

The group of our collaborators around Prof. Chris Karp at the Cincinnati College of Medicine, USA, using TIS7 knockout mice generated in our lab as a specific experimental animal model, identified TIS7 to be the main modifier of the severity of the lung disease in cystic fibrosis. This lung disease is the major cause of morbidity and mortality in cystic fibrosis, an autosomal recessive disease caused by mutations in CFTR. In cystic fibrosis, chronic infection and dysregulated neutrophilic inflammation lead to progressive airway destruction. Neutrophils, but not macrophages, from TIS7-deficient mice showed blunted effector function. In vivo, TIS7 deficiency caused delayed bacterial clearance from the airway, but also less inflammation and disease. In humans, TIS7 polymorphisms were significantly associated with variation in neutrophil effector function. These data indicated that TIS7 modulates the pathogenesis of cystic fibrosis lung disease through the regulation of neutrophil effector function. These findings were published as a mutual collaboration in the journal Nature.

A second member of a novel gene family, SKMc15, is a protein which shares with TIS7 high homology at the amino acid level. Therefore, our laboratory generated SKMc15 single as well as TIS7

SKMc15 double knockout mice and now concentrates on the identification of the functional role of both genes and their protein products. Interestingly, the TIS7 SKMc15 double knockout mice have a prominent phenotype: they are significantly smaller and leaner and, most importantly, they are resistant against weight gain upon feeding with the high fat-diet. We are currently searching for the mechanism responsible for this phenotype on the molecular level.

Future Goals:

- Identification of molecular mechanisms responsible for the smaller body size and the lack of body fat deposits in TIS7 SKMc15 double knockout mice. The long term goal of this project is to be able to design strategies for intervention with possible signaling pathways.
- Identification of TIS7-interacting proteins and analyses of their biological role. In this project we will concentrate on further characterization of interactions between TIS7 protein complex components, mainly on their *in vivo* interactions within the living cell. The main focus will be on regulatory mechanisms by which TIS7 modulates gene expression of muscle-specific genes during myogenesis.
- Identification and detailed analysis of epigenetic mechanisms of transcriptional regulation affected by TIS7.

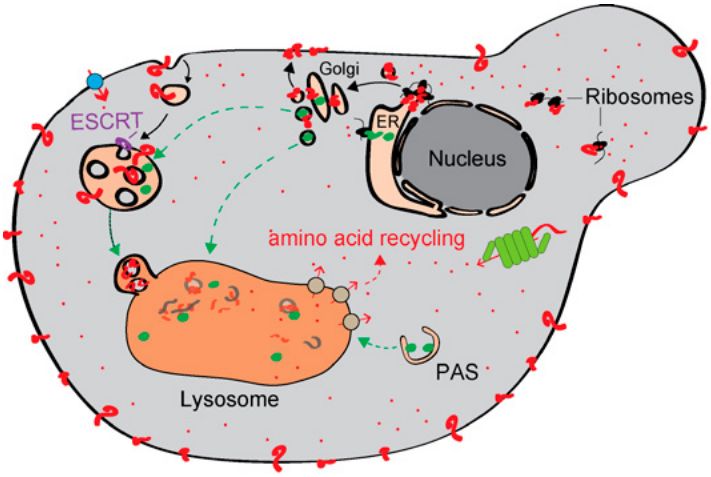

Fig. 9: Schematic representation of the MVB Pathway.

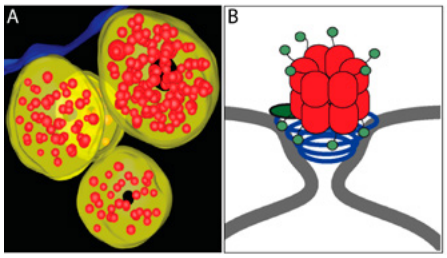

Fig. 10: (A) 3D-Modeling of cryo-fixed cells. MVBs (yellow), Intralumenal MVB vesicles (ILVs) (red), vacuole (blue). (B) Model of ESCRT-III and Vps4 during ILV neck constriction.

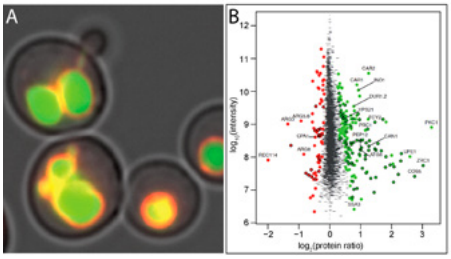

Fig. 11: (A) Fluorescence microscopy of living yeast, vacuole (red), GFP-CPS (green). (B) Graphical representation of quantitive proteomics.

Membrane Traffic and Signaling
David Teis Lab

Cell growth and survival requires the selective degradation of cellular components. Failure in cellular degradation systems result in severe defects in cell homeostasis, which in turn can cause in a wide variety of diseases ranging from cancer to neurodegeneration. We are particularly interested in the molecular mechanisms required for the selective degradation of integral membrane proteins. A key step for the selective degradation of membrane proteins occurs on endosomes, where the endosomal complexes required for transport (ESCRTs) bind to and sort ubiquitinated membrane proteins via the multivesicular body (MVB) pathway into the lumen of lysosomes for degradation (Fig. 9). This process requires a membrane remodeling reaction that buds intraluminal MVB vesicles (ILVs) away from the cytoplasm and into the lumen of MVBs (Fig. 10 A). Topologically similar ESCRT dependent membrane budding reaction are required in distinct cellular processes, including membrane scission at the end of cytokinesis, release of budding HIV from host cells, micro-vesicle formation at the plasma membrane, plasma membrane repair, quality control of nuclear pore complex assembly and nuclear envelop reformation and sealing.

Just how the ESCRT machinery catalyzes these membrane remodeling reactions is unclear.
One key question in our lab is how the ESCRT machinery sculpts membranes and how ESCRT mediated membrane remodeling and scission is coordinated with cargo sorting (Fig. 10 B).

Furthermore we would like to understand how the ESCRT dependent degradation of membrane proteins contributes to cell growth and survival, particularly given the key role of ESCRTs during developmental and disease.

To address these questions we use yeast as the best suited model system combining genetics with quantitative proteomics, biochemical methods and different imaging approaches (Fig. 11 A, B).

Selected Publications

The coordinated action of the MVB pathway and autophagy ensures cell survival during starvation. Müller M, Schmidt O, Angelova M, Faserl K, Weys S, Kremser L, Pfaffenwimmer T, Dalik T, Kraft C, Trajanoski Z, Lindner H, Teis D. ELIFE. 2015, Apr 22;4:e07736.

SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1. Rebsamen M, Pochini L, Stasyk T, de Araujo ME, Galluccio M, Kandasamy RK, Snijder B, Fauster A, Rudashevskaya EL, Bruckner M, Scorzoni S, Filipek PA, Huber KV, Bigenzahn JW, Heinz LX, Kraft C, Bennett KL, Indiveri C, Huber LA. NATURE. 2015 Mar 26;519(7544):477–81.

LAMTOR2 regulates dendritic cell homeostasis through FLT3-dependent mTOR signalling. Scheffler JM, Sparber F, Tripp CH, Herrmann C, Humenberger A, Blitz J, Romani N, Stoitzner P, Huber LA. Nat Commun. 2014 Oct 22;5:5138.

The late endosomal p14-MP1 (LAMTOR2/3) complex regulates focal adhesion dynamics during cell migration. Schiefermeier N, Scheffler JM, de Araujo ME, Stasyk T, Yordanov T, Ebner HL, Offterdinger M, Munck S, Hess MW, Wickström SA, Lange A, Wunderlich W, Fässler R, Teis D, Huber LA.
J Cell Biol. 2014 May 26;205(4):525–40.

Coordinated binding of Vps4 to ESCRT-III drives membrane neck constriction during MVB vesicle formation. Adell MA, Vogel GF, Pakdel M, Müller M, Lindner H, Hess MW, Teis D.
J Cell Biol. 2014 Apr 14;205(1):33–49.

Selected Funding

- FWF: Special research program SFB021 (LAH, DT)
- PhD Program MCBO (LAH, DT)
- START-Prize (DT)
- P18531-B12 (TV)
- P22350-B12 (IV)
- P26682-B21 (LAH)
- EU: FP7 Optatio (LAH)
- HFSP Career Development Award (DT)

Genomics and RNomics

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Keywords

Non-coding RNAs; RNPs, ribosomal RNA, RNA sequencing (RNAseq), ribosome, translation

Research Focus

In cells from all organisms two different types of RNA molecules are found: messenger RNAs (mRNAs), and the so-called "non-protein-coding RNAs" (ncRNAs). Many known ncRNAs, such as microRNAs, are involved in the regulation of gene expression. Our group focuses on the identification and functional characterization of regulatory non-coding RNAs in various model organisms. In particular, we are interested in the identification of ncRNAs regulating neural development and in the identification of ncRNAs involved in human diseases.

General Facts

Our group works on the identification and function of regulatory non-coding RNAs (ncRNAs) in various model organisms for which we have coined the term "Experimental RNomics". In particular, we are interested in ncRNAs involved in neurological diseases. Therefore, we have characterized the small ncRNA transcriptome, involved in the differentiation of mouse embryonic stem (ES) cells into neural cells, by generating specialized ribonucleo-protein particle (RNP)-derived cDNA libraries. By high-throughput sequencing and transcriptional profiling we identified hundreds of novel ncRNAs that are involved in ES cell differentiation. Based on these findings, we have generated a custom microarray chip that covers 1500 novel neuro-specific ncRNAs. By this approach, we have analysed the differential expression of ncRNAs in mouse models for neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Epilepsy.
A second research focus is the regulation of ribosomal translation by natural and non-natural modifications introduced into functionally important regions of the ribosome as well as those incorporated into the coding sequences of the mRNAs.

Major Achievements:
- Coordination GEN-AU Programme: ncRNAs: from identification to functional characterization
- Member of the 7th framework EU: SysKid
- PhD program participant: SPIN: signal processing in neurons
- Member of SFB program: Cell signaling in chronic CNS disorders
- Member of the 7th framework EU: ncRNAPain

Core Facilities:
- High-throughput sequencing: Genome Seq Core
- Expression profiling: Affymetrix Core Facility

Research

Role of ncRNAs in Neurodevelopmental Disorders

Alexander Hüttenhofer

Small non-protein-coding RNAs (ncRNAs) play important roles in the regulation of gene expression and have been implicated in a number of diseases of the central nervous system (CNS). miRNAs represent a well characterized class of small ncRNAs for which numerous commercial tools (e.g. qPCR panels, micro arrays) have been developed in order to screen for their differential expression in human patients as well as animal disease models. Indeed, by these approaches several miRNAs have been implicated in the etiology of neurological diseases. In addition to miRNAs there also exists a large number of short ncRNA species (sized about 18 – 200 nt), which are either poorly characterized or that belong to other known classes of ncRNAs (i.e. snRNAs, snoRNAs, or piRNAs) for which no

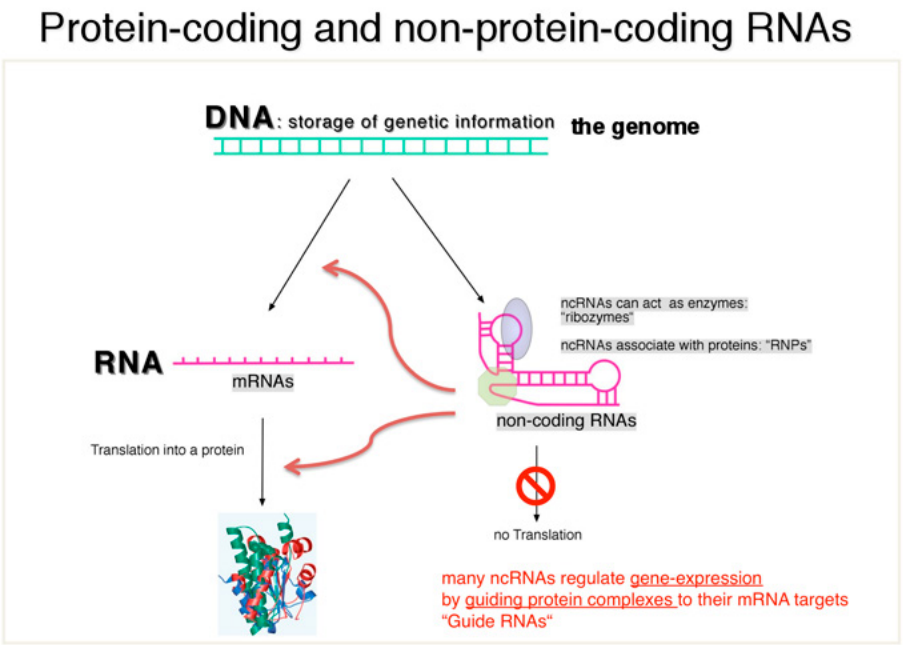

Fig. 1: Two classes of RNA species are transcribed from genomes of all organisms: messenger RNAs (mRNAs) and non-coding RNAs (ncRNAs); ncRNAs are not translated into proteins and many of them are able to regulate gene expression by regulating transcription or translation of mRNAs and thus act a genetic switches.

high-throughput tools have been developed to perform expression profiling. Thus in this project, which is part of the SFB-F44 "Cell signaling in chronic CNS disorders", we have developed an unbiased and comprehensive microarray platform to profile the expression of thousands of these novel ncRNA species from mouse brain tissues. To date we have applied this customized microarray, designated as neuro-ncRNA chip, to selected mouse models for LTCC activity and CNS disorders e.g. Alzheimer's disease and Multiple-system atrophy. Thereby we discovered more than 100 novel ncRNA candidates whose expression was found to be de-regulated in comparison to wild type controls. In the Alzheimer mouse model, we identified two snoRNAs, whose expression was deregulated prior to amyloid plaque formation. Interestingly, the presence of snoRNAs could be detected in cerebral spine fluid samples in humans, thus potentially serving as early diagnostic makers for Alzheimer's disease. In addition, we could show the applicability of our customized microarray to human post-mortem brain tissue of Alzheimer's disease patients and healthy individuals; Through the expression profiling of post mortem human brain samples from Alzheimer's disease patients and their comparison with healthy controls we were able to identify 51 differentially expressed ncRNAs in Alzheimer's disease and could also show that 60% of the ncRNAs that are present on our customized microarray exhibit expression signals above background in human tissue. In addition, we focused on the biochemical characterization of the novel ncRNA candidates using *in situ* hybridization in order to define the cellular as well as subcellular localization patterns of ncRNAs.

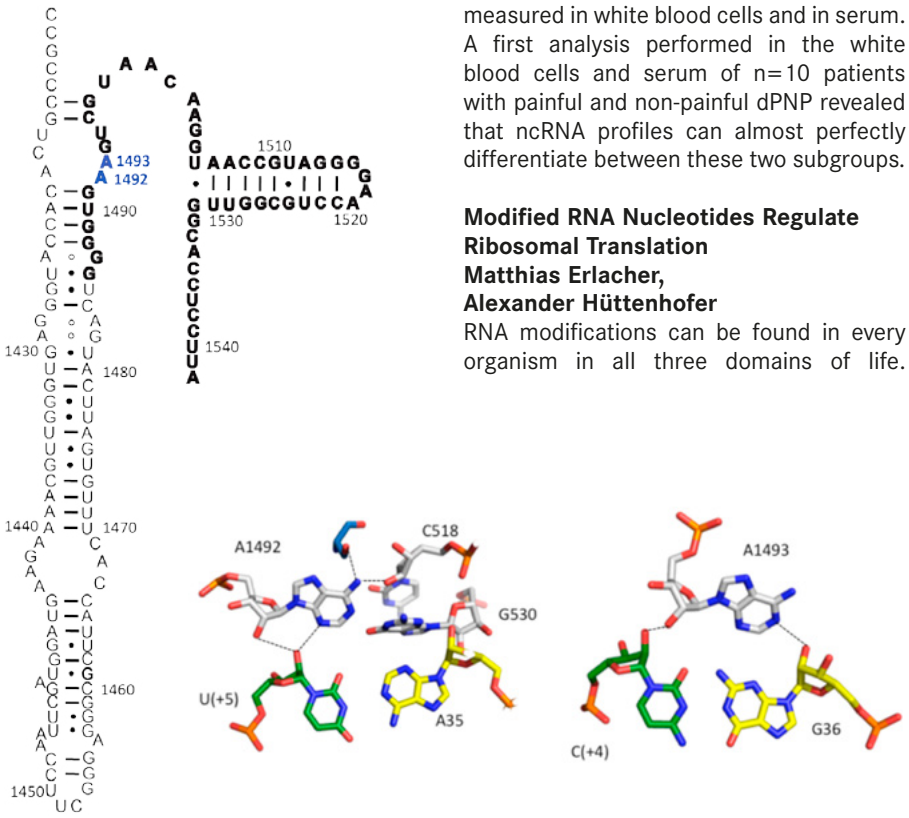

Fig. 2: Non-natural modifications can be site-specifically incorporated into the 16S rRNA, to determine their impact on decoding.

Identification of ncRNA Patterns as Biomarkers for Pain and Inter-Individual Variations

Alexander Hüttenhofer

This project is part of the EU Project "ncRNAPain" and aims to identify pain predisposing ncRNA patterns and to apply them as biomarkers for pain and inter-individual variation. This aim will be achieved by identifying altered expression patterns of ncRNAs/miRs in painful vs. non-painful diabetic neuropathies (dPNP), in complex regional pain syndrome (CRPS) after trauma vs. patients after trauma without CRPS and in addition in painful and non-painful nerve lesions (NL). An initial quality check showed that ncRNAs levels can be robustly measured in white blood cells and in serum. A first analysis performed in the white blood cells and serum of n=10 patients with painful and non-painful dPNP revealed that ncRNA profiles can almost perfectly differentiate between these two subgroups.

Modified RNA Nucleotides Regulate Ribosomal Translation

Matthias Erlacher,
Alexander Hüttenhofer

RNA modifications can be found in every organism in all three domains of life. Although more than 100 different types have been identified, mRNAs were thought to be only rarely modified.

Whereas N6-methyladenosine (m^6A) was described already 4 decades ago and shown to be the most abundant modification in eukaryotic mRNAs, the presence of 5-methylcytosine (m^5C) and pseudouridine (Ψ) in this class of RNA was only identified recently. The influence of any of these modifications on ribosomal translation is largely unknown and has been mainly a matter of speculation. Employing a cell free translation system, we systematically investigate the effects of single modified mRNA residues on the fidelity and efficiency of translation.

Modifications of the Ribosomal Decoding Site and their Impact on Translation

Matthias Erlacher

Ribosomal decoding is an essential process in every living cell. During protein synthesis the 30S ribosomal subunit needs to accomplish binding and accurate decoding of mRNAs. Through mutational studies and the analysis of high-resolution crystal structures nucleotides G530, A1492 and A1493 of the 16S ribosomal RNA have come into focus as important elements for the decoding process. In order to biochemically investigate decoding in greater detail we applied an *in vitro* reconstitution approach. This approach allowed us to exchange or eliminate single chemical groups on A1492 and A1493 and to test their impact on translational efficiency and fidelity.

Selected Publications

Generation of a neuro-specific microarray reveals novel differential expressed noncoding RNAs in mouse models for neurodegenerative diseases. Gstir R, Schafferer S, Scheiderler M, Misslinger M, Griehl M, Dachil N, Humpel C, Obermair GJ, Schmuckermair C, Striessnig J, Flucher BE, Hüttenhofer A.
RNA. 2014; 20 (12): p. 1929–1943.

Micro RNAs in nociceptive circuits as predictors of future clinical applications. Kress M, Hüttenhofer A, Landry M, Kuner R, Favereaux A, Greenberg D, Bednarik J, Heppenstall P, Kronenberg F, Malcangio M, Rittner H, Uçeyler N, Trajanoski Z, Mouritzen P, Birklein F, Sommer C, Soreq H.
Front Mol Neurosci. 2013; 6: S 33.

Selected Funding

SFB F44-11 – Cell signaling in chronic CNS disorders, FWF
7th framework EU: SysKid
7th framework EU: ncRNAPain

Collaborations

- Joerg Vogel, MPI, Berlin, Germany
- Ralph Bock, MPI Potsdam, Germany
- Jürgen Brosius, University of Münster, Germany
- Yuuchi Soeno, Nippon University, Tokyo, Japan
- Norbert Polacek, University of Bern

Core Facilities

- Genome Seq Core
- Affymetrix core facility

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Keywords

Chromatin and epigenetics, histone modifying enzymes, ATP-dependent chromatin remodeling, RNA methylation, filamentous fungi, iron metabolism, fungal infection, siderophores, lipocalins, antimicrobial proteins, innate immunity and allergy

Research Focus

Physiology, gene regulation and secondary metabolism in filamentous fungi

- Iron metabolism in filamentous fungi: links to human disease
- Functions of histone modifying enzymes in gene regulation, fungal physiology and as targets for novel antifungal substances
- Structure, mechanism of action and applicability of antimicrobial peptides/proteins secreted by filamentous fungi

Lipocalins and their involvement in innate immunity and allergy

Epigenetics and epitranscriptomics:

- Biological roles of ATP-dependent chromatin remodeling enzymes
- RNA methylation and its impact on gene expression regulation
- Posttranslational acetylation of regulatory non-histone proteins

General Facts

The Division of Molecular Biology is home to six independent research groups, whose scientific interests range from the investigation of diverse aspects of filamentous fungi physiology and metabolism, to the study of secretory lipocalins, to research into the nature and significance of chromatin remodeling mechanisms.
A common long-term goal of all groups is to explore the relationship of the diverse processes mentioned above with diagnostics and treatment of human disease. In this regard, the groups of Hubertus Haas, Gerald Brosch/Stefan Grässle, and Florentine Marx-Ladurner strive to elucidate pathogenicity determinants and potential drug targets of filamentous fungi. Moreover, they examine the regulatory mechanisms of secondary metabolites (e.g. penicillin), secretory proteins and components, such as antimicrobial proteins and iron-chelating siderophores, both of which have potential in antifungal therapy and diagnosis. The Redl group investigates the mechanism of action of lipocalins, which are secretory scavenger proteins. Thus, lipocalins are important components of the innate immune system, yet they might also be involved in allergic reactions. The Lusser group conducts studies of fundamental gene regulatory mechanisms involving the remodeling of chromatin structure as well as posttranscriptional modification of RNAs. One particular focus is on understanding chromatin changes in the context of neurodegenerative diseases and behavioral disorders. Finally, the Loidl group investigates histone modifying enzymes, in particular the role of acetylation of regulatory non-histone proteins.
Together, the researchers make use of a wide array of experimental model systems including filamentous fungi (*Aspergillus*, *Penicillium*, *Achremonium*), the fruit fly *Drosophila melanogaster*, and mammalian models such as different cell lines as well as knock-out mice.
The participation of members of the division in several intra- and extramural network activities such as the FWF-funded PhD programs "HOROS" and "MCBO", the special research network SFB "Cell signaling in chronic CNS disorder" as well as the EU-FP7 Marie Curie International Training Network "Nucleosome4D", the Infect-ERA network "AspMetNet" and the D-A-CH network on iron sensing in filamentous fungi attests to the high standard of research quality.
Staff of the Division of Molecular Biology also contribute substantially to the curricular teaching activities at the MUI. Notably, the division chair Peter Loidl is Vice Rector for Academic Affairs at the university. He also took a leading role in the establishment of the two new study directions in Molecular Medicine (Bachelor and Master studies). Alexandra Lusser is coordinator, Hubertus Haas is deputy coordinator of the PhD Program "Regulation of Gene Expression" and Bernhard Redl is coordinator of the Molecular Medicine Master program. Beyond that, all group leaders are teaching lectures, seminars and practical courses in the curricula of human medicine, dental medicine, molecular medicine (bachelor and master) and of the PhD curriculum. In addition, most group leaders are involved in the teaching of Biology students at the Leopold Franzens University Innsbruck.

Research

Physiology, Gene Regulation and Secondary Metabolism in Filamentous Fungi

Gerald Brosch, Stefan Graessle, Hubertus Haas, Florentine Marx-Ladurner

Fungi affect the life of mankind in positive and negative ways. On the one hand, fungi are major players in saprobic decomposition, they mutually interact with plants (mycorrhiza), serve as food source (mushrooms) or in food production (e.g. bread, cheese, alcohol), and produce widely used primary (e.g. citric acid) and secondary metabolites (e.g. penicillin). On the other hand, some fungi are pathogens of plants (e.g. *Fusarium spp.*) and animals (e.g. *Aspergillus fumigatus*), or spoil food by contamination or toxin production (e.g. aflatoxin). Therefore, fungi impact ecology, biotechnology, medicine, agriculture and

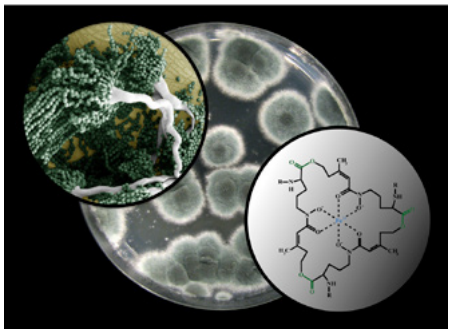

Fig. 1: Cover Figure of Natural Product Reports 31(10). "Fungal siderophore metabolism with a focus on Aspergillus fumigatus". Haas H. 2014.

food industry. The best-studied fungal organism is *Saccharomyces cerevisiae*. In several respects, however, the physiology of this unicellular organism is not comparable to that of the more complex filamentous fungi (e.g. iron metabolism, light regulation, secondary metabolism). Three research groups in the Division of Molecular Biology address different aspects of filamentous fungal physiology ranging from iron metabolism and its significance for pathogenesis (Haas), to chromatin-linked mechanisms of gene expression control (Brosch/Graessle) and the nature and mechanisms of action of antimicrobial proteins produced by filamentous fungi (Marx-Ladurner).

Iron Metabolism in Filamentous Fungi: Links to Human Disease

Hubertus Haas

Our central research goal is to characterize the fungal metabolism and to exploit this knowledge for both improvement of antifungal therapy and diagnosis of fungal infections as well as improvement of the biotechnological potential of fungi. Current research focus is the iron/siderophore metabolism of *Aspergilli*. *A. fumigatus* is a typical saprobic filamentous ascomycete but also the most common airborne fungal pathogen of humans. It causes allergic and invasive disease depending on the immune status of the patient. Unsatisfying diagnostic and therapeutic possibilities are reflected in a high mortality rate. *A. fumigatus* and its low-pathogenic relative *Aspergillus nidulans* produce extracellular siderophores (triacetylfusarinine C) for iron acquisition and intracellular siderophores (ferricrocin) for storage and distribution of iron. Siderophore biosynthesis is regulated by two transcription factors, SreA and HapX. Siderophores are central components of the fungal metabolism as they affect germination, sexual and asexual reproduction, oxidative stress resistance and virulence. Lack of siderophore biosynthesis renders *A. fumigatus* apathogenic. Consequently, the siderophore system represents a novel attractive target for improvement of antifungal therapy and diagnosis of fungal infections.

Additional research topics include light regulation, nitrogen metabolism, noncoding RNAs, secondary metabolism (e.g. cephalosporin biosynthesis by *Achremonium chrysogenum*) and improvement of molecular tools for the manipulation of fungi.

<u>Major Achievements:</u>

Identification and characterization of fungal iron-regulatory and iron-sensing mechanisms. Characterization of fungal iron uptake and storage, particularly the siderophore system.

Regulatory and structural links of iron homeostatic mechanims and other metabolic pathways, e.g. pH regulation, ergosterol biosynthesis, hypoxia adaptation.

First-time *in vivo* PET-imaging of fungal infections using ^{68}Gallium-labelled siderophores

<u>Future Goals:</u>

Detailed characterization of the iron homeostasis-maintaining mechanisms of filamentous fungi (in particular of *Aspergilli*) and applied medical and biotechnological exploitation of the knowledge gained.

Functions of Histone Modifying Enzymes in Gene Regulation and Fungal Physiology

Gerald Brosch and Stefan Graessle

In addition to distinct regulatory sequences in gene promoters, the readout of genetic information in eukaryotes is significantly controlled at the chromatin level. In addition to ATP-dependent chromatin remodeling and the methylation of DNA on distinct cytidines, covalent posttranslational modifications of histones have profound structural and functional consequences for the transcription program of a cell. The main research focus of the lab lies on elucidating the functional impact of histone acetylation and histone/protein arginine methylation on fungal physiology. We are particularly interested in studying to what extent histone modifying activities are involved in fungal pathogenicity as well as to investigate their role in the regulation of secondary metabolite production.

To this end, we have generated *Aspergillus* strains with individual or pairwise deletions of all protein arginine methyltransferase (PRMT) genes and of the class I histone deacetylases (HDACs) RpdA and HosA. Using these tools along with specifically engineered transgenes, we study their impact on viability and metabolism of the fungus. Moreover, we perform proteomic and transcriptomic analyses to (i) characterize novel substrates and (ii) to investigate the contribution of HDACs and PRMTs to the regulation of secondary metabolism as well as of stress response genes.

<u>Major Achievements:</u>

Identification of a novel PRMT (RmtD) in filamentous fungi, which differs from other PRMTs in that it does not accept canonical substrates (histones, RNPs) but instead methylates three as yet unknown proteins.

Identification and functional characterization of two fungal-specific protein domains

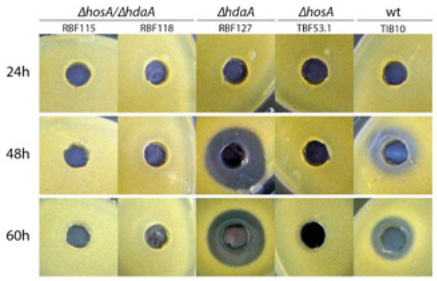

Fig. 2: Production of penicillin (PN) in different Aspergillus HDAC-mutants. A bacterial growth inhibition assay plate with Kocuria rhizophila as indicator organism was used to quantify PN in the medium of wild type (wt), ΔhdaA, ΔhosA, and two double mutant strains after 24h, 48h, and 60h of growth. The relative sizes of bacterial growth inhibition zones correspond to relative accumulation of PN in the culture medium of the fungus. Whereas the class 2 HDAC HdaA has a repressing effect, the class 1 enzyme HosA seems to be crucial for the production of PN in Aspergillus nidulans.

in the HDAC RpdA, which are essential for the viability of *Aspergillus* and thus might serve as targets for future antifungal therapy.

Identification of the HDAC HosA as a major regulator of secondary metabolites in filamentous fungi.

<u>Future Goals:</u>

Characterization of RmtD substrates and elucidation of the biological role of RmtD. Development of antifungal strategies targeting the fungal-specific domains of RpdA. Elucidation of novel HosA-regulated small bioactive molecules of *Aspergillus.*

Structure, Mechanism of Action and Applicability of Antimicrobial Peptides/Proteins Secreted by Filamentous Fungi

Florentine Marx-Ladurner

Filamentous fungi secrete a wide array of different proteins into the external medium, which are used for diverse functions, such as nutrient assimilation, quorum sensing, host invasion and colonization, etc. Apart from some secreted enzymes, which have been developed for a variety of commercial uses (mainly for the fermentation industry), only few extracellular proteins are well characterized with respect to their function as pathogenicity or cell signaling factors. Our main scientific interest is to identify, isolate and further characterize on the molecular, structural and functional levels novel extracellular proteins with antimicrobial activity from *Penicillium*

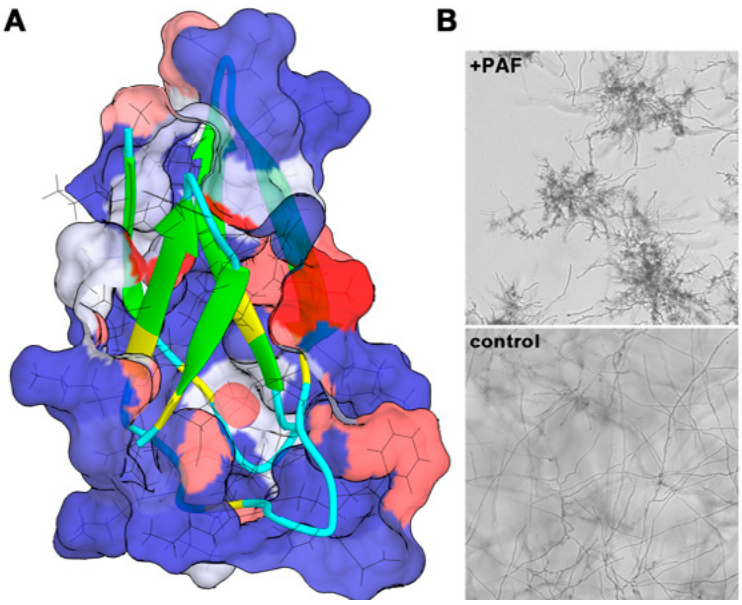

Fig. 3: Structure and function of the small, cationic and cysteine-rich Penicillium chrysogenum antifungal protein PAF.
(A) PAF consists of 55 amino acids and exhibits five anti-parallel β-strands (green arrows) that are connected by four loop regions (blue). The cysteines are marked in yellow and form three disulfide bonds that stabilize the protein. Superimposed on the scheme of the secondary structure are the hydrophobic (red) and hydrophilic (blue) patches exposed on the protein surface that are responsible for full protein activity.
(B) PAF inhibits the growth of the human pathogen Aspergillus fumigatus. Fungal hyphae treated with 64 µM PAF show reduced growth and hyper-branching, a typical effect of PAF on the morphology of sensitive fungi. In the untreated control neither growth reduction nor changes in morphology can be detected.

chrysogenum, *Aspergillus nidulans* and *Aspergillus fumigatus*. Antimicrobial proteins are promising candidates for the development of novel therapies applicable in medicine as well as in agriculture and in the food industry to prevent and treat microbial infections. Therefore, the detailed characterization of these proteins is of crucial importance and a prerequisite for the development of new therapeutic approaches and their successful application in the future.

Major Achievements:

First steps towards biotechnological utilization of antimicrobial proteins and understanding their structure-function relationship.

Future Goals:

Identification of molecular targets for the development of new therapeutic drugs. Characterization of additional cellular functions of antifungal proteins apart from their antimicrobial activity. Development of new chimeric antifungal proteins with enhanced activity and improved specificity.

Lipocalins and their Involvement in Innate Immunity and Allergy

Bernhard Redl

We investigate structural and functional features of human lipocalins. The protein superfamily of lipocalins consists of small, mainly secretory proteins defined on the basis of conserved amino acid sequence motifs and their common structure. Functionally, they are important extracellular carriers of lipophilic compounds in vertebrates, invertebrates, plants and bacteria. There is increasing evidence that this group of proteins is involved in a variety of physiological processes including retinoid, fatty acid and pheromone signaling, immunomodulation, inflammation, detoxification, modulation of growth and metabolism, tissue development, apoptosis, and even behavioral processes. Whereas the structural basis of lipocalin-ligand binding is now well understood, there is a major lack of knowledge regarding the mechanisms by which lipocalins exert their biological effects. This is mainly due to the fact that only limited data are available on lipocalin receptors and lipocalin-receptor interactions, although it is well accepted that many, if not all, of these proteins are able to bind to specific cell receptors. Our main research focus is on the identification of cellular lipocalin receptors, characterization of the molecular mechanisms of receptor-ligand interaction and the biological processes beyond receptor binding. In addition, we study novel functions of lipocalins in innate immmunity and allergy.

Major Achievements:

Elucidation of the lipocalin allergen uptake in dendritic cells

Future Goals:

Identification and characterization of novel lipocalin receptors with a focus on human proteins.

- We will use a set of biochemical methods, including *in vivo* crosslinking, affinity purification and mass spectrometry analysis for identification of specific receptors for the lipocalins ApoD and the major dog and cat allergens Can f 1 and Fel d 4.
- Isolation of receptors for human odorant-binding proteins (hOBP) by using phage-display technology.

Epigenetics and Epitranscriptomics

Chromatin Remodelling and RNA Modifications

Alexandra Lusser

Eukaryotic DNA is assembled into a nucleoprotein complex termed chromatin. The basic repeating unit of chromatin is the nucleosome, which consists of 147 bp of DNA wrapped around an octamer of the core histones H2A, H2B, H3 and H4. The way in which DNA is organized in the chromatin allows for highly efficient compaction of the genetic material and provides additional levels of control to the regulation of nuclear processes such as transcription, replication, repair and recombination. We are interested to learn how the establishment and maintenance

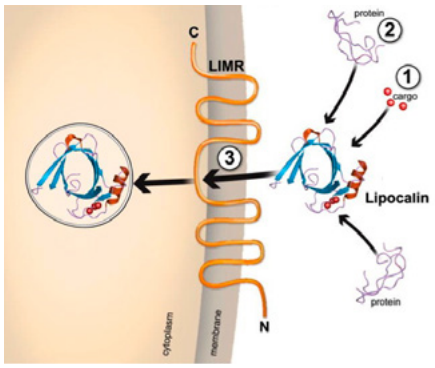

Fig. 4: Types of molecular recognition properties of lipocalins. (1) lipophilic ligands illustrated as cargo. (2) soluble macromolecule ligands such as proteins. (3) a lipocalin-specific membrane receptor is responsible for cellular uptake of the lipocalin-ligand complex.

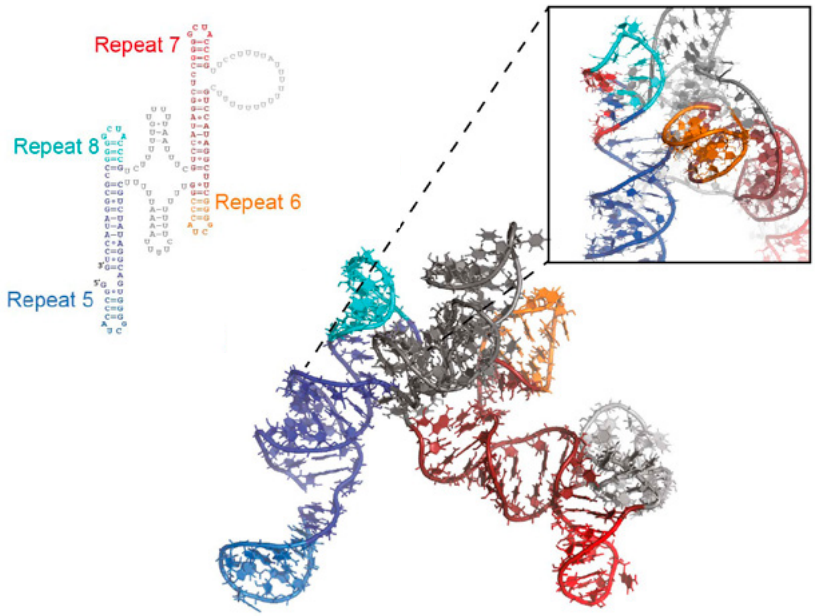

Fig. 5: 3D modelling of the XIST lncRNA region A predicts a stacked helix conformation for repeat 8 (R8). The methylated cytosines in R8 (marked in red in inset) are facing the outer surface of the helix, which can explain the interference of cytosine methylation with PRC2 binding (Amort et. al., 2013).

of eukaryotic chromatin affects those processes. We are approaching this question by studying the molecular mechanisms and biological context of chromatin assembly and remodeling processes. Major research questions in my lab are:
(i) The biochemical analysis of chromatin assembly processes using *in vitro* assays and single molecule techniques in collaboration with the C. Dekker lab at the TU Delft. (ii) The study of biological functions of the ATP-dependent chromatin remodeling factor CHD1 in *Drosophila* and in the mouse and (iii) the study of centromeric chromatin assembly in *Drosophila*. In addition, we have recently become interested in exploring cytosine methylation of poly(A)RNAs and to investigate its impact on gene regulation ("epitranscriptomics").

Major Achievements:
Characterization of the requirement of CHD1 for sperm chromatin reorganization and histone variant incorporation *in vivo*.
Involvement of CHD1 in *Drosophila* stress response and in local immune response.
Identification of distinct cytosine methylation on the long-noncoding RNAs XIST and HOTAIR and its impact on RNA-protein interaction.

Future Goals:
Study of biological roles of CHD1 in *Drosophila*
Study the prevalence and physiological significance of RNA base modifications

Posttranslational Acetylation of Regulatory Non-histone Proteins

Peter Loidl

Histones are prominent substrates of posttranslational modifications, like acetylation, methylation, phosphorylation and others which all can cause structural and functional rearrangements in chromatin and therefore represent essential elements of the complex epigenetic histone code. During the last years it became more and more clear that a huge number of non-histone proteins are substrates for enzymes that were initially identified as histone-modifying enzymes: this holds true, in particular, for histone acetyltransferases (HATs) and HDACs. The focus of our research is the analysis of functional consequences of acetylation of non-histone proteins, such as the nucleolar transcription factors UBF and PAF53 and the cell cycle regulatory protein Rb2/p130.

Major Achievements:
Identification of UBF and PAF53 as well as of Rb2/p130 as substrates for posttranslational acetylation.
Demonstration of cell-cycle dependence of Rb2/p130 acetylation and characterization of the cross talk between Rb2/p130 acetylation and cell cycle-dependent phosphorylation.

Future Goals:
Study of the effects of mutations of acetylatable lysines in Rb2/p130 on cell cycle progression.

Selected Publications

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SURFACE & COATINGS TECHNOLOGY. 2014; 254: p. 344–351.

Antibacterial activity of rifamycins for M. smegmatis with comparison of oxidation and binding to tear lipocalin. Staudinger T, Redl B, Glasgow BJ. BIOCHIMICA ET BIOPHYSICA ACTA-PROTEINS AND PROTEOMICS. 2014; 1844: p. 750–758.

Selected Funding

- In search of novel human lipocalin receptors, FWF, Bernhard Redl
- New antifungal strategies: structure and function of NFAP, FWF-Meitner Program, Lazlo Galgóczi
- Novel molecular mechanisms of iron sensing and homeostasis in filamentous fungi, FWF (D-A-CH), Hubertus Haas
- Characterization of heme metabolism in Aspergillus fumigatus, FWF, Hubertus Haas
- Host response in opportunistic infections, HOROS PhD Program, FWF, Hubertus Haas
- Systematic identification of antifungal drug targets by a metabolic network approach (AspMetNet), FWF (Infect-ERA), Hubertus Haas
- Hunting for new antifungal strategies: the antifungal protein PAF, FWF, Florentine Marx-Ladurner
- Structure and function of the antifungal proteins PAFB and NFAP, OTKA-FWF bilateral funding, Florentine Marx-Ladurner
- Cytosine methylation as a new mechanism to regulate long non-coding RNAs, TWF/FWF, Alexandra Lusser
- Study of centromeric chromatin assembly pathways in Drosophila melanogaster, MCBO-PhD Program, FWF, Alexandra Lusser

Collaborations

Elaine Bignell, Imperial College, London, UK; Axel Brakhage, F. Schiller University Jena, Germany; Robert Cramer, Geisel School of Medicine at Dartmouth, USA; Michael J. Hynes, Univ. of Melbourne, Australia; Jean-Paul Latgé, Institut Pasteur, Paris, France; Antonio DiPietro, Univ. Cordoba, Spain; William Nierman, George Washington Univ., Rockville, USA; gillian Turgeon, Cornell Univ., Ithaca, USA; Cees Dekker, Nynke Dekker, Technical University Delft, Netherlands; Chin-Yan Lim, A*-STAR, Singapore; Dmitry Fyodorov, Albert Einstein College of Medicine, Bronx, USA; Gyula Batta, University of Debrecen, Hungary; László Galgóczi, University of Szeged, Hungary; Nick D. Read, University of Manchester, UK; José F. Marcos, IATA, Valencia, Spain; Nancy Keller, University of Wisconsin, Madison, USA; Manfred Jung, Albert-Ludwigs-Universität Freiburg, Germany; Antonello Mai, Università degli Studi di Roma "La Sapienza", Italy; Gianluca Sbardella, Università di Salerno, Fisciano, Italy; Arne Skerra, TU Munich, Freising, Germany; Ben J. Glasgow, University of California, Los Angeles, USA.

Experimental Pathophysiology and Immunology

Head of Division (interim):
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Keywords

Autoimmunity, molecular endocrinology, atherosclerosis, systemic sclerosis, fibrosis, teaching Pathophysiology to medical, PhD (MCBO) and Molecular Medicine students

Research Focus

- The Immunology of Atherosclerosis. Heat shock protein 60, "danger signal" "attracting" preexisting innate and adaptive anti-Hsp60 immunological reactions.
- The Immunology of Fibrosis, impaired function of regulatory T cells (Treg).
- Pathogenesis and therapy of systemic sclerosis.

General Facts

The former institute of EXPERIMENTAL PATHOLOGY was initiated in the late 19th century. Moritz Loewit, from the Institute of "Experimental Pathology" in Prague, moved in 1887 to Innsbruck to become the first professor here. Hermann Pfeiffer was chief from 1919–1921, Gustav Bayer followed him in 1922 and led the institute until 1938 when the NS regime forced him, an intellectual Jew, to end his life. After WW2, Theodor von der Wense rebuilt the institute, and acted as Ordinarius until 1973. He died in 1977 (http://de.wikipedia.org/wiki/Theodor_von_der_Wense).
Kurt Loewit, a descendant of the above mentioned Moritz Loewit, took over as interim chief until 1975, when Georg Wick was nominated. Wick – an immunologist with long-term training in USA in the laboratory of Witebsky, the founder of the concept of autoimmunity – extended the institute to a large unit of sometimes 50 collaborators working in different fields, i.e. besides immunology also in endocrinology and molecular biology. A large armamentarium of research as well as diagnostic methods was implemented. Later, the institute was renamed as Institute of PATHOPHYSIOLOGY (reflecting its teaching subject more properly), and finally divided into 3 smaller units (Divisions), i.e.

- Experimental Pathophysiology & Immunology (Georg Wick, later interimistically Lukas A. Huber)
- Molecular Pathophysiology (Reinhard Kofler)
- Developmental Immunology (Andreas Villunger)

All three joined the Biocenter, where they act independently with respect to their research interests, yet are still combined in their teaching duties in what is called BEREICH PATHOPHYSIOLOGIE.

Research

Laboratory of Autoimmunity
Georg Wick

The Immunology of Atherosclerosis

This project of the last two decades resulted in the formulation of a new "Autoimmune Concept for the Development of Atherosclerosis", supported by solid data from *in vitro* and animal experiments as well as from cross-sectional and prospective longitudinal studies in human cohorts. In essence, this concept states that classical atherosclerosis risk factors first act as endothelial stressors inducing the expression of a stress protein (heat shock protein 60 – Hsp60) which then acts as a "danger signal" and thus serves as a target for pre-existing innate and adaptive anti-Hsp60 immunity. Our present research is focused on

a) the elucidation of the migratory pathways of HSP60-reactive T-cells into the arterial intima and
b) the continuation and extension of our EU FR7-funded project TOLERAGE that resulted in the development of an Hsp60-based, orally tolerizing vaccine against atherosclerosis.

The Immunology of Fibrosis

Fibrosis is an important consequence of various pathological conditions ranging from tissue damage, over inflammation, reactions against foreign body implants to "spontaneous" fibrotic diseases, always being associated with inflammatory immunologic processes. An impaired function of regulatory T cells (Treg) within fibrotic tissues has been recently shown by us. www.autoimmunity.at

Systemic Sclerosis – Roswitha Sgonc

The group is interested primarily in the pathogenesis and therapy of systemic sclerosis (SSc), which is studied in human patients as well as in the spontaneous avian model UCD-200/206, the only animal model that manifests the whole clinical, histopathological and serological spectrum of human SSc. Thus, only the comparative study of UCD-200/206 chickens and human SSc made it possible to identify microvascular endothelial cells as the primary target of the autoimmune attack.
After many years studying pathomechanisms and genetic factors underlying the disease, we are now focusing on the development of novel therapeutic approaches. There is an unmet need for an effective pro-angiogenic therapy of ischemic lesions in patients with SSc. Vascular alterations in both human and avian SSc predominantly affect the microvasculature. Initially, endothelial cell apoptosis is induced by anti-endothelial cell antibody-dependent cellular cytotoxicity (ADCC) via the Fas/Fas ligand pathway. Intimal proliferation, occlusion of blood vessels, and capillary rarefaction lead to decreased blood flow, a state of chronic ischemia, and to clinical manifestations such as fingertip ulcers and comb lesions. Tissue hypoxia normally induces angiogenesis, but in SSc vascular repair and angiogenesis seem to be strongly disturbed. One of the key molecules in the induction of angiogenesis is vascular endothelial growth factor (VEGF). In SSc chronic and uncontrolled over-expression of VEGF results in chaotic vessels, and intractable fingertip ulcers. Vice versa, VEGF is a potent mediator of angiogenesis if it is available in a temporally and spatially controlled fashion. We have addressed this therapeutic dilemma in SSc by a novel approach using a VEGF121 variant that covalently binds to fibrin, and gets released on demand by cellular enzymatic activity, only as long as needed. With this approach we mimic

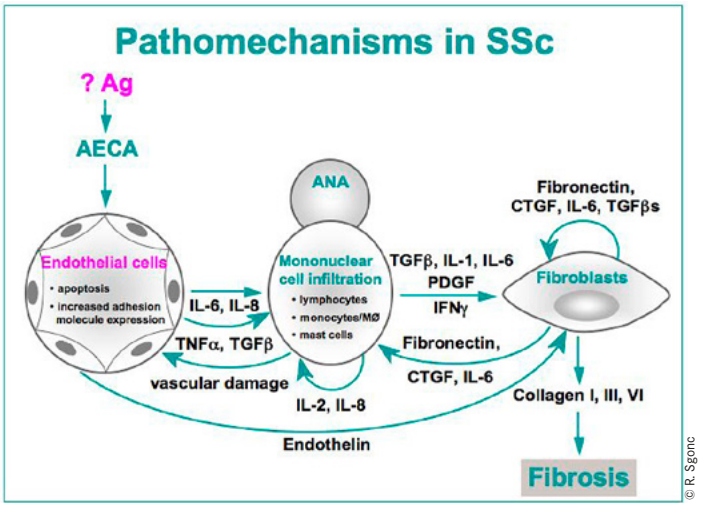

Fig. 1: Model for the development and pathophysiology of systemic sclerosis.

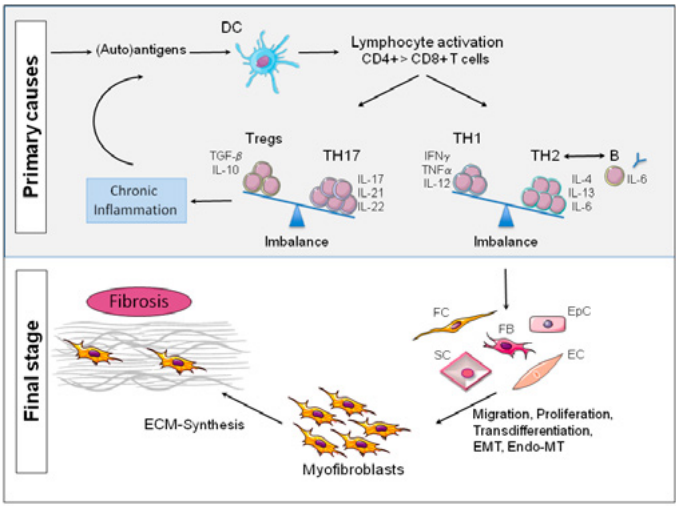

Fig. 2: Adaptive immune resonse in fibrosis.

nature, where longer VEGF isoforms are bound to extracellular matrix components until liberated in a tightly controlled manner by local enzymatic activity of cells invading the matrix. Using UCD-206 chickens, we could show that cell-demanded release of locally applied fibrin-bound VEGF121 leads to the formation of morphologically normal blood vessels, and clinical improvement of early and late ischemic lesions. Over all, 79.3% of the lesions treated with VEGF121-fibrin showed clinical improvement, whereas 71.0% of fibrin treated controls, and 93.1% of untreated lesions deteriorated. This was accompanied by significantly increased growth of stable microvessels, up-regulation of the pro-angiogenic VEGF receptor-2 (VEGFR-2) and its regulator TAL-1, and increase of endogenous endothelial VEGF expression. This study suggests that cell-demanded release of VEGF121 from fibrin matrix induces controlled angiogenesis by differential regulation of VEGFR-1 and VEGFR-2 expression shifting the balance towards the pro-angiogenic VEGFR-2, and shows the potential of covalently conjugated VEGF-fibrin matrices for the therapy of ischemic lesions.

Major Achievement:

Effective therapy of ischemic skin lesions in an animal model of SSc.

Future Goals:

Elucidation of novel therapeutic strategies in SSc.

Teaching Pathophysiology – Molecular Endocrinology – Siegfried Schwarz

The Laboratory of Molecular Endocrinology has focussed on various hormone/neurotransmitter binding proteins and receptors as well as their ligands.

Key papers describe:

- Discovery of Sex Hormone Binding Globulin (SHBG) in cerebrospinal fluid (CSF) and interaction of SHBG with Danazol (non-genomic actions of steroids)
- First demonstration of homocysteate as an NMDA-selective excitatory agonist
- First description of an epitope map of the glycoprotein hormone hCG
- Construction of epitope-selective immunoassays for glycoprotein hormones
- Demonstration of different orientations of receptor-bound agonistic vs. antagonistic hCG
- Prediction of the 3D structure of the extracellular domain of the hCG receptor
- Characterization of an apoptotic activity within urinary hCG preparations towards Kaposi's sarcoma cells
- Demonstration of the importance of vasopressin in critically ill patients

Siegfried Schwarz teaches Pathophysiology to Medical, PhD (MCBO) and Molecular Medicine students in most of the modules ("Human Body", "Regulation of Bodily Functions", "Endocrine S. (system)", "Blood S." and venipuncture practicum, "Heart & Vascular S.", "Kidney", "Lung", "Neurological S.", "Embryology", "Aging", "Bone S.", previously also "Skin S.", and "Gastroenterological S.". He has written several textbooks: "Pathophysiology – Molecular, Cellular and Systemic Basis of Diseases", Maudrich, Vienna, 2007, and "Molecules of Life and Mutations", Karger, Basel, 2002.

Selected Publications

The role of heat shock proteins in atherosclerosis. Wick G, Jakic B, Buszko M, Wick MC, Grundtman C. Nat Rev Cardiol. 2014 Sep;11(9):516-29. Review. PMID: 25027488.

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The BH3-only protein Bad is dispensable for TNF-mediated cell death. Ottina E, Sochalska M, Sgonc R, Villunger A. Cell Death Dis. 2015 Jan 22;6:e1611. doi: 10.1038/cddis.2014.575. PMID: 25611386.

Selected Funding

- Effects of VEGF121 modified fibrin on ischemic lesions in systemic sclerosis: a new therapeutic approach. FWF: P23230-B13, Roswitha Gruber-Sgonc
- The role of Vascular Associated Lymphoid Tissue (VALT) in the Development of Atherosclerosis-"Inside out or outside in",TWF, Bojana Jakic
- Lokale Immunreaktionen bei der Entstehung der Atherosklerose [Das vaskulär assoziierte lymphoide Gewebe (VALT) bei Atherosklerose], OeNB, Georg Wick

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Keywords

Cell cycle, mitosis, apoptosis, childhood acute lymphoblastic leukaemia, glucocorticoid, expression profiling, functional gene analysis, gene knock-out and knock-down by RNAi, viral vector systems, cyclin dependent kinase

Research Focus

- Molecular mechanisms of the anti-leukaemic effects of glucocorticoids (GC) using gene expression profiling of children with acute lymphoblastic leukaemia during GC treatment followed by bioinformatics and functional gene analyses.
- Identification and functional analysis of proteins required for faithful chromosome segregation during mitosis.
- Analysis of non-cell cycle related functions of cyclin-dependent kinases and of mitotic ubiquitin ligase (APC/C) function during development.

General Facts

The Division of Molecular Pathophysiology (DMP) aims at a better molecular understanding of fundamental biological processes, like regulation of cell cycle (Geley) or cell death induction in leukaemia cells (Kofler) with the ultimate goal to apply this knowledge to improve therapy and diagnosis of human diseases.
The Applied Bioinformatics Group (Rainer) supports our high-throughput analyses and the MUI-Expression Profiling Facility, which is also attached to the DMP.
Arno Helmberg coordinates our teaching obligations and serves as Vice Chairperson of the Senate of our University.
The research in our Division is supported by grants from the FWF, the MCBO graduate college and various other sources including the Cancer Aid Society and Tyrolean Cancer Research Institute that is headed by Reinhard Kofler.

Research

Leukaemia Apoptosis
Reinhard Kofler

Glucocorticoids (GC) trigger cell death and cell cycle arrest in certain lymphoid cells and are therefore used for the therapy of lymphoid malignancies, most importantly childhood acute lymphoblastic leukaemia (ALL). We aim to understand the anti-leukaemic effects of GC and the causes for GC resistance to develop concepts for improved therapies.
To this end, we determined gene expression profiles of ALL cells in children prior to, and in the course of GC treatment, using whole genome expression profiling. By inclusion of peripheral blood lymphocytes from GC-exposed non-leukemic donors, ALL cell lines and mouse thymocytes, an essentially complete list of GC-regulated candidate genes in clinical settings and experimental systems was generated, allowing immediate analysis of any gene for its potential significance to GC-induced cell death or cell cycle arrest. In addition to conventional gene expression profiling, we performed alternative transcripts analysis, GC receptor binding site definition (ChIP-on-CHIP), translatome analyses, and microRNA profiling.
Our "Applied Bioinformatics Group" (see below) performs integrative analyses of these data and generates lists of candidate genes and pathways that need to be functionally tested for their potential biological role. For this we have developed lentiviral expression systems allowing efficient analysis of many genes in multiple cell lines.

Current Results:
Defining GC-regulated genes and transcripts in a variety of experimental and clinical systems revealed an unexpected heterogeneity and complexity of this response encompassing both protein- and microRNA-encoding genes. Although GC may cause changes in protein levels in the absence of mRNA regulations, the translational efficiency of transcripts is not affected by GC. Concerning the transcriptional response to GC *in vivo*, it varies considerably in the different molecular subtypes of this disease. Regarding the anti-leukaemic effect, repression of mRNA for key regulators of G2/M transition was commonly observed in all ALL subtypes whereas we failed to observe a common transcriptional control of apoptosis genes. The data suggest that GC-induced cell death does not result from transcriptional regulation of the apoptotic machinery itself but might rather result from a widespread deregulation of gene expression.

Major Achievements:
- Defining the GC-regulated transcriptome in children during systemic GC monotherapy and numerous other biologically relevant lymphoid systems including the first identification of GC-regulated microRNAs
- Functional analyses of numerous GC response genes
- Delineating the genes responsible for GC-induced cell cycle arrest and providing novel concepts explaining GC-induced cell death

Future Goals:
- Completion of our analyses of GC-induced cell death by novel bioinformatics tools
- Development of a fluorescence-activated cell sorting (FACS)-based assay to determine cancer-killing activity in leukocytes for potential cell-based cancer therapy

Cell Cycle Control
Stephan Geley

Cellular reproduction relies on the faithful copying and segregation of the genome during defined phases of the cell division cycle, which is controlled by cyclin-dependent kinases (CDK). CDK1 is required for entry into mitosis and formation of the mitotic spindle, a microtubule-based apparatus required for chromosome segregation. The *microtubule-based motor proteins*, dynein and kinesins, play important roles in aligning chromosomes within the mitotic spindle, allowing their equational segregation into daughter cells. Spindle formation, chromosome segregation and exit from mitosis are carefully monitored by the spindle assembly checkpoint (SAC) to avoid aneuploidy, which can result in

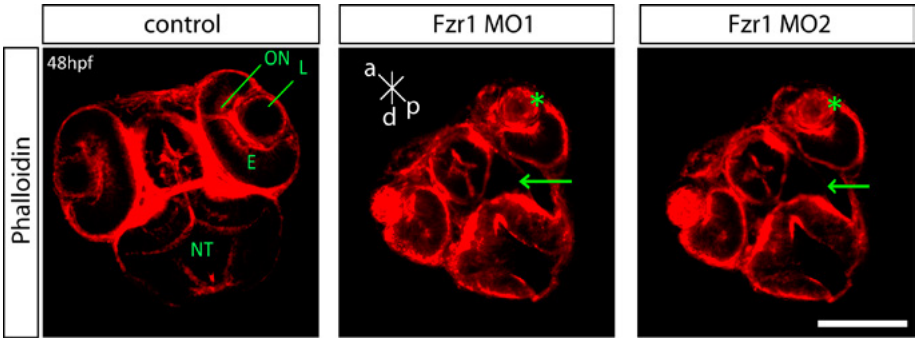

Fig. 1: Fzr1 is essential for vertebrate development. Zebrafish embryos were depleted from Fzr1 by morpholino antisense technology and show severe developmental retardation.

severe birth defects or cancer. The SAC controls the activity of the anaphase-promoting complex/cyclosome (APC/C) ubiquitin ligase, which controls chromosome segregation and exit from mitosis. After mitosis the APC/C remains activated by *FZR1* to establish G1 phase, which is required for cellular growth as well as cellular differentiation. Only 4 of the known 26 *CDKs* are involved in cell cycle regulation. The other members are either involved in transcription or have other, less well characterised, functions.

Results:

Microtubule based motor proteins:

The chromokinesins KIF4A and KIF22(hKid) contribute to chromosome congression. hKid is the major polar ejection force that counteracts dynein-dependent poleward chromosome movements. The main motor responsible for metaphase plate formation is the kinetochore motor Cenp-E, but hKid is required for the correct orientation of chromosome arms. Kif4A regulates chromosome compaction and might regulate kinetochore stiffness. Dynein is recruited to the kinetochores via Spindly. Spindly needs to be farnesylated for its localisation and function at the kinetochore.

FZR1 function in vertebrate development:

FZR1 is a substrate recruitment factor of the ubiquitin ligase APC/C. It activates the APC/C during late mitosis and in G1-phase. Loss of Fzr1 function causes shortening of G1-phase and CDK-activity dependent premature entry into S-phase, which causes DNA damage and p53 responses that can lead to senescence, cell cycle arrest or apoptosis. We have generated Fzr1 deficient mice and zebrafish and, in addition to the effects on cell cycle regulation, found that Fzr1 is essential for vertebrate development by regulating ciliogenesis.

Novel CDKs and their functions:

CDK14,15 and 16,17,18 are a group of poorly characterised CDKs that can all interact with and become activated by membrane bound cyclin Y. These kinases show overlapping expression patterns. In vertebrates, we have defined CDK16 as being essential for spermatogenesis and could show that cyclin Y binding is regulated by 14-3-3 proteins and phosphorylation.

Major Achievements:

- FZR1 knock-out mice and zebrafish model system (in collaboration with P. Aanstad, LFU, Innsbruck)
- Role of chromokinesins in mitosis (in collaboration with H. Maiato, Porto)
- Regulation of CDK16 by CCNY
- Regulation of Spindly by lipidation
- Development of conditional RNAi and gene knock-out systems

Future Goals:

Define the role of Fzr1 in ciliogenesis, understand how farnesylation controls the function of Spindly at kinetochores, investigate the role of KIF4A in chromosome compaction, identify substrates of CCNY-CDK16.

Applied Bioinformatics
Johannes Rainer

Our primary research focus is on whole-genome gene expression analyses where we are particularly interested in the analysis of high-density microarray and high throughput sequencing data and the development of new as well as adaptation of existing methods for their analysis. In this context we are analysing data sets generated in our leukaemia apoptosis group, to determine the transcriptional effects of glucocorticoids in acute lymphoblastic leukaemia and to delineate and understand the treatment response and resistance mechanisms in such patients. In addition, we provide support for clients of the Expression Profiling Unit and perform data analyses of the microarray data sets.

Current Projects:

Identification of genes facilitating glucocorticoid therapy response in children with acute lymphoblastic leukaemia using multiple regression analysis of microarray and clinical data

Major Achievements:

We defined the transcriptional response of ALL cells to treatment with synthetic GCs prednisolone and dexamethasone; investigated the role of GCs in whole genome translational gene regulation, developed a method to determine chromosome copy number alterations based on whole genome gene expression data, and improved pre-processing and differential splicing analysis for Affymetrix Exon microarrays.

Selected Publications

CLP1 links tRNA metabolism to progressive motor-neuron loss. Hanada T, Weitzer S, Mair B, Bernreuther C, Wainger BJ, Ichida J, Hanada R, Orthofer M, Cronin SJ, Komnenovic V, Minis A, Sato F, Mimata H, Yoshimura A, Tamir I, Rainer J, Kofler R, Yaron A, Eggan KC, Woolf CJ, Glatzel M, Herbst R, Martinez J, Penninger JM. NATURE. 2013; 495: p. 474–480.

The synthetic glucocorticoids prednisolone and dexamethasone regulate the same genes in acute lymphoblastic leukemia cells. Bindreither D, Ecker S, Gschirr B, Kofler A, Kofler R, Rainer J. BMC GENOMICS. 2014; 15: p. 662.

Kinetochore motors drive congression of peripheral polar chromosomes by overcoming random arm-ejection forces. Barisic M, Aguiar P, Geley S, Maiato H. Nat Cell Biol. 2014 Dec;16(12):1249–56.

Human chromokinesins promote chromosome congression and spindle microtubule dynamics during mitosis. Wandke C, Barisic M, Sigl R, Rauch V, Wolf F, Amaro AC, Tan CH, Pereira AJ, Kutay U, Maiato H, Meraldi P, Geley S. J Cell Biol. 2012 Sep 3;198(5):847–63.

Cyclin-dependent kinase 16/PCTAIRE kinase 1 is activated by cyclin Y and is essential for spermatogenesis. Mikolcevic P, Sigl R, Rauch V, Hess MW, Pfaller K, Barisic M, Pelliniemi LJ, Boesl M, Geley S. Mol Cell Biol. 2012 Feb;32(4):868–79.

Selected Funding

- MCBO Graduate Programme (W1101-P13), FWF, Reinhard Kofler
- MCBO Graduate Programme (W1101-P06), FWF, Stephan Geley
- RANSFOG EU FP6 LSHC-CT-2004-503438, Stephan Geley

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- T. Hunt,Cancer Research UK, London)
- R. Fässler, MPI Martinsried, Munich
- P. Meraldi, Univ. Geneva, Switzerland
- H. Maiato, Univ. Porto, Portugal
- M. Morgan, Fred Hutchinson Cancer Research Center, Seattle, USA
- F. Theis, Helmholtz-Zentrum München, Germany
- P. Aanstad and D. Meyer, LFU Innsbruck

Core Facilities

Expression Profiling Unit (EPU, Affymetrix Core Facility): http://biocenter.i-med.ac.at/expression-profiling-unit

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Research Focus/Keywords

- Apoptosis & Tumor Biology
- Non-coding RNAs in Hematopoiesis
- Glucocorticoids & Immunology

General Facts

Work of the different groups in this division focuses on the development of the immune system with an emphasis on cell death signalling, its cross-talk with the cell cycle machinery and the role of steroid hormones in the establishment of self-tolerance and miRNA function.

Research

Apoptosis, Tumor Biology & Leukocyte Development
Andreas Villunger

BH3-Only Proteins in Cell Death and Disease

Whether a cell continues to live in response to diverse forms of stress or undergoes apoptosis along the intrinsic cell death signaling pathway is largely determined by the complex interplay between individual members of the Bcl-2 protein family that can either promote or prevent apoptosis.

Survival-promoting Bcl-2 family members, i.e. Bcl-2, Bcl-xL, Bcl-w, Mcl-1 and A1 share four common Bcl-2 homology domains (BH1-BH4). All of these proteins are critical for cell survival, since the loss of any one of them causes the premature cell death of certain cell types. Consistently, over-expression of Bcl-2 pro-survival molecules is associated with prolonged cell survival and resistance to cytotoxic drugs in a number of model systems, but more importantly, also in tumor patients.
The pro-apoptotic Bcl-2 family members can be divided into two classes: the Bax-like proteins, i.e. Bax, Bak, Bok that contain three BH-domains (BH123 or multi-domain pro-apoptotic Bcl-2 proteins) and the BH3-only proteins. The latter include Bim, Bid, Puma, Noxa, Bmf, Bad, Hrk and Bik that are unrelated in their sequence to each other or other Bcl-2 family members (except for the BH3-domain).
We utilise genetically modified model systems to study the role of pro-survival Bcl-2 family proteins and BH3-only proteins in tumor and lymphocyte development.

Caspase-2, Cell Cycle Control and the DNA-Damage Response

Cells that have been exposed to DNA-damaging influences aim to repair the inflicted damage. However, when this attempt fails, cells usually activate an apoptotic program to avoid the spread of cells with compromized genomes. The molecular basis of these life/death decisions is still not entirely clear.
The p53-induced protein with a death domain (PIDD) has been identified as a gene activated in response to p53 upon DNA-damage. Together with the adapter molecule RAIDD, PIDD has been implicated in the activation of Caspase-2, an endopeptidase implicated in apoptosis and cell cycle control. PIDD has recently also been implicated in DNA damage-induced NF-kB activation and cytokine release, promoting the transcription of inflammatory genes by forming a complex with the kinase RIP-1 and Nemo. Caspase-2 is an ill-defined protease that has been implicated in multiple cellular responses including the one triggered by deprivation of metabolites, heat shock or DNA damage triggered cell cycle control. However, the contribution of caspase-2 to these responses is in many cases still unclear (Fig. 2).
We are currently investigating the role of these proteins in tumor suppression and aim to identify Caspase 2-specific substrates in order to gain further insight into the functions of this multi-protein complex.

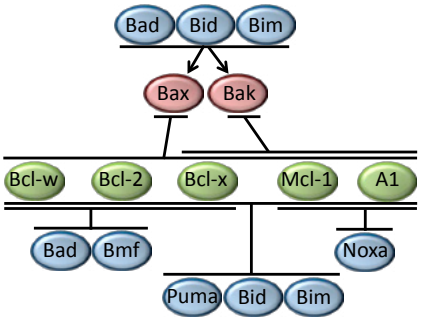

Fig. 1: Liaisons in the Bcl2 family. The Bcl2 family can be categorized into three classes of proteins that control mitochondrial cell death by complex protein-protein interactions, indicated here. These interactions are based on different affinities between individual family members and are influenced by various posttranslational protein modifications.

Ongoing Projects:
BH3-only proteins in the regulation of B cell survival
Lymphocyte development and function in the absence of A1
PIDD in caspase-2 and NF-kB activation
Tumor suppression/promotion by Caspase-2 and its partners
Identification of Caspase-2 substrates

Non-Coding RNAs in Hematopoiesis
Sebastian Herzog

In the last decade, our understanding of the human genome and its regulation has dramatically changed. Initially considered as “junk”, it is now clear that the non-protein coding regions, which comprises about 98% of the ~$3 \cdot 10^9$ DNA bases, is extensively transcribed and gives rise to numerous non-coding RNAs. The function of these non-coding RNAs, however, is often unclear.

MicroRNAs in Early Lymphocyte Development and Transformation

MicroRNAs (miRNAs) are small, non-coding RNAs that mediate posttranscriptional silencing of a predicted 60% of protein-coding genes in mammals. Since their discovery, they have emerged as central mediators of many, if not all biological processes. In our work, we aim to decipher how miRNAs regulate complex transcriptional networks, focusing on lymphocyte development as a well established model system. In particular, we want to elucidate the role of individual miRNAs under physiological conditions as well as upon aberrant expression, which mimics an oncogenic situation. To this end, we combine gain- and

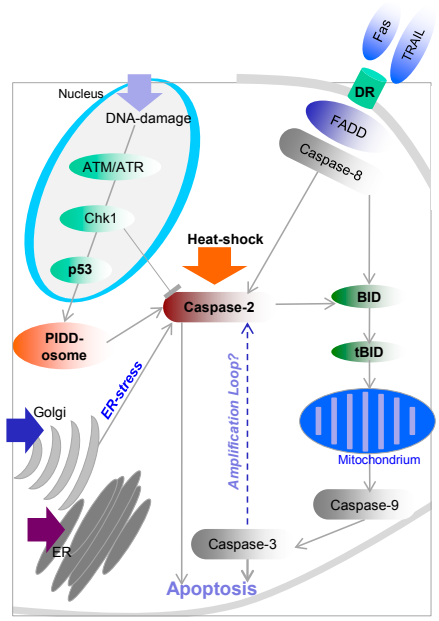

Fig. 2: Schematic model summarizing the most important apoptotic path-ways with a suggested involvement of caspase-2 activity, i.e. cell death in response to DNA-damage, ER-stress, heat shock, and death receptor (DR) ligation. ATM, Ataxia telangiectasia mutated; ATR, Ataxia telangiectasia and Rad3 related; PIDDosome, protein complex consisting of PIDD, RAIDD and caspase-2; TRAIL, tumor necrosis factor related apoptosis inducing ligand; FADD, Fas-associated death domain (modified according to G. Krumschnabel et al., 2009)

loss-of-function approaches, both *in vitro* as well as *in vivo*, with biochemical and molecular techniques.

LincRNAs in Hematopoiesis and Immune Function

Projects such as ENCODE have clearly demonstrated that the non-coding part of the human genome is extensively transcribed and contributes significantly to the orchestration and fine-tuning of transcriptional programmes both in health and disease. Among the non-coding RNA species identified so far, the group of long non-coding RNAs (lncRNAs), which are arbitrarily defined as the set of ncRNAs with a length of more than 200 nucleotides, are the least well understood. In a MUI-START-funded project, we initially applied RNAseq to the challenge of defining the lymphocyte linRNA transcriptome. The expression of most of the lincRNAs appears to be restricted to certain developmental stages, suggesting the have a specific functional role in the associated processes. However, in order to decipher the function of individual lincRNAs, we now use shRNA knockdown and CRISPR/Cas9-mediated genome modification together with RNA pulldown.

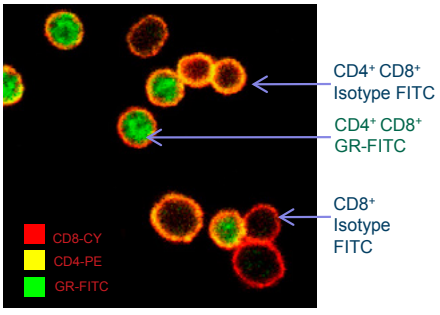

Fig. 3: Glucocorticoid receptor (GR) expression in thymocyte subsets. Thymo-cytes were stained for CD4, CD8 and GR, washed and mounted with Mowiol. Isotype control and GR stained thymo-cytes were mixed 1:1.

Regulation of Immunity

Jan Wiegers

Impact of life span on regulatory T cell maturation and function

Regulatory T cells (T_{reg}) expressing the transcription factor Foxp3 play an essential role in maintaining immune homeostasis and preventing autoimmunity. A spontaneous loss of function-mutation in *foxp3* in 'scurfy' mice leads to fulminant lymphoproliferation and multi-organ autoimmunity. A more detailed knowledge of the factors that affect T_{reg} maturation and number in the thymus and T_{reg} homeostasis under either normal conditions or during the course of an immune response is essential for the development of potent and more efficient therapeutics for autoimmune diseases. It is also currently unclear how life span influences the capacity of T_{reg} to suppress immunity. As a means to study maturation and function of T_{reg} cells, we use *foxp3*^{GFP} knock-in mice that coexpress GFP under the control of the endogenous *foxp3* promoter. This allows convenient detection and purification of T_{reg} cells by flow cytometry and it is possible to isolate nearly 100% pure T_{reg} cells using this approach.

Glucocorticoids and T Cell Development

Selection processes in the thymus ensure that mature peripheral T cells fulfill two essential criteria: activation by foreign peptides bound to (host) MHC molecules, but tolerance to self-derived peptides presented in the same context. To this end, thymocytes that express T cell receptors (TCRs) with high avidity for self antigen:MHC and therefore are potentially autoreactive, undergo apoptosis (negative selection). In contrast, thymocytes expressing TCR with moderate avidity for self antigen:MHC are rescued and differentiate into mature T cells that migrate to the periphery (positive selection). Glucocorticoid hormones (GC) have been suggested to influence these processes, or example by inducing apoptosis in developing T cells with the thymus itself producing GCs! In addition, GC resistance of thymocytes against GC-induced apoptosis is associated with autoimmune diseases. We focus therefore on the following questions: i) what is the molecular background of thymocyte resistance to GC-induced apoptosis in animal models of autoimmune diseases?, and ii) what factors determine sensitivity to GC-induced apoptosis in immature vs. mature thymocytes (Fig. 3)?

Selected Publications

Deregulated cell death and lymphocyte homeostasis cause premature lethality in mice lacking the BH3-only proteins Bim and Bmf. Labi Verena, Woess Claudia, Tuzlak Selma, Erlacher Miriam, Bouillet Philippe, Strasser Andreas, Tzankov Alexandar, Villunger Andreas. BLOOD. 2014; 123: p. 2652–2662.

Minor cell-death defects but reduced tumor latency in mice lacking the BH3-only proteins Bad and Bmf. Baumgartner F, Woess C, Pedit V, Tzankov A, Labi V, Villunger A.
ONCOGENE. 2013; 32: p. 621–630.

Loss of PIDD limits NF-KB activation and cytokine production but not cell survival or transformation after DNA damage. Bock FJ, Krumschnabel G, Manzl C, Peintner L, Tanzer MC, Hermann-Kleiter N, Baier G, Llacuna L, Yelamos J, Villunger A. CELL DEATH AND DIFFERENTIATION. 2013; 20: p. 546–557.

Death of p53-defective cells triggered by forced mitotic entry in the presence of DNA damage is not uniquely dependent on Caspase-2 or the PIDDosome. Manzl C, Fava LL, Krumschnabel G, Peintner L, Tanzer MC, Soratroi C, Bock FJ, Schuler F, Luef B, Geley S, Villunger A. CELL DEATH & DISEASE. 2013; 4: p. e942.

Haematopoietic stem cell survival and transplantation efficacy is limited by the BH3-only proteins Bim and Bmf. Labi V, Bertele D, Woess C, Tischner D, Bock FJ, Schwemmers S, Pahl HL, Geley S, Kunze M, Niemeyer CM, Villunger A, Erlacher M.
EMBO MOLECULAR MEDICINE. 2013; 5: p. 122–136.

Increased leukocyte survival and accelerated onset of lymphoma in the absence of MCL-1 S159-phosphorylation. Lindner SE, Wissler M, Gründer A, Aumann K, Ottina E, Peintner L, Brauns-Schubert P, Preiss F, Herzog S, Borner C, Charvet C, Villunger A, Pahl HL, Maurer U.
Oncogene. 2014 Oct 30;33(44):5221–4.

Selected Funding

- The role of Checkpoint kinase 1 (Chk1) in normal hematopoiesis and Myc-driven transformation. Schuler F., ÖAW
- Investigating the role of prosurvival Bcl-2 family member A1 in T cell mediated immunity, Tuzlak S., ÖAW
- Neue Einsichten in die Bcl2 Familie, Villunger A., FWF
- Die Rolle des PIDDosoms in der Tumorentstehung, Villunger A., FWF
- Die Rolle von BH3 Proteinen in der B Zell Homöostase, Villunger A., FWF
- Glukokortikoide und regulatorische T-Zellen, Wiegers G.-J., FWF

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- Veronika Sexl, Vienna, AT
- Jörg Hackermüller at Helmholtz Center for Environmental Research (UFZ), Leipzig, DE
- Falus A., Dept. of Genetics, Cell- and Immunobiology (earlier Dept. of Biology) at Semmelweis University, Budapest, HU
- Reul J. M., Laboratories of Integrative Neuroscience and Endocrinology (LINE), University of Bristol, UK
- Boyd R. L., Department of Immunology, Monash University, Clayton, Victoria, Australia

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Keywords

Bioinformatics, computational genomics, next generation sequencing, gene expression, cancer, immunology, mathematical modeling, data integration

Research Focus

- Analyses of diverse functional genomics data in the context of human diseases and integration with clinicopathological information.
- Modeling of the interaction between tumor and the immune system

General Facts

The research activities at the Division of Bioinformatics are directed towards two major thrusts:

1. Computational genomics. We computationally explore diverse functional genomics data in the context of human diseases. By analyzing high-dimensional data sets we aim to identify and prioritize candidate genes and further characterize pathways contributing to the pathophysiology of diseases.
2. Cancer immunology. Our aim is to decipher tumor-immune cell interaction using a combined computational-experimental approach. Specifically, we are addressing the question as to how is the immune system shapes the mutational spectrum of the tumor during progression.

Bioinformatics Services

We provide bioinformatics services for researchers at the Biocenter and at the Innsbruck Medical University as well as for external experimental collaborators. A high-performance computational infrastructure and a number of software tools are maintained and continuously adapted to state-of-the-art software technology (see http://icbi.at). The software development is directed towards specialized databases, analytical pipelines, and web-services. We also advise scientists on designing experiments and support analyses of high-dimensional data sets including:

- whole-genome/whole-exome data,
- RNA-Seq,
- ChIP-Seq,
- microbiome,
- high-content microscopy data, and
- proteomics data

Research

Computational Genomics

Recent advances in genome sequencing technologies are rapidly changing the research and routine work of biologists and human geneticists. Due to the brisk decline of costs per base pair, next-generation sequencing (NGS) is now affordable even for small-to-mid sized laboratories. Whole-genome sequencing and whole-exome sequencing have proven to be valuable methods enabling discovery of the genetic causes of rare Mendelian disorders as well as of complex diseases. The current bottleneck is not the sequencing of the DNA itself but lies in structuring the processes of data management and in the sophisticated computational analysis of the experimental data. In order to get meaningful biological results, each step of the analysis workflow (as for example depicted in Fig. 1) needs to be carefully considered, and appropriate specific tools need to be used for particular experimental setups. Furthermore, the challenge of 'next-generation biology/genetics' is to narrow down the list of candidate variants and interpret the remaining variants. The major focus of our research activities is to narrow down the genome search space by integrating and analyzing disparate data sources including various omics data and clinical data. We aim to identify causative genes, prioritize candidates for experimental studies, and further characterize pathways contributing to the pathophysiology of diseases.

Cancer Immunology

Most advanced solid tumors remain incurable and are resistant to chemotherapeutics and targeted therapies. A series of recent studies reported baffling intratumor heterogeneity which may contribute to this failure. While increasing attention is being paid to the mutational spectrum of various cancers, little attention has been devoted either to define the immunogenicity of these mutations or to characterize the immune responses they elicit. Identification of nonsynonymous mutations processed and presented in an immunologically relevant manner will not only highlight the mechanisms driving tumor progression but will also provide a rich source of novel immunotherapeutic targets. Thus, it is of utmost importance to decipher the cross-talk between the tumor and the immune system during tumor development. Our long-term goal is to develop a mechanistic multi-scale

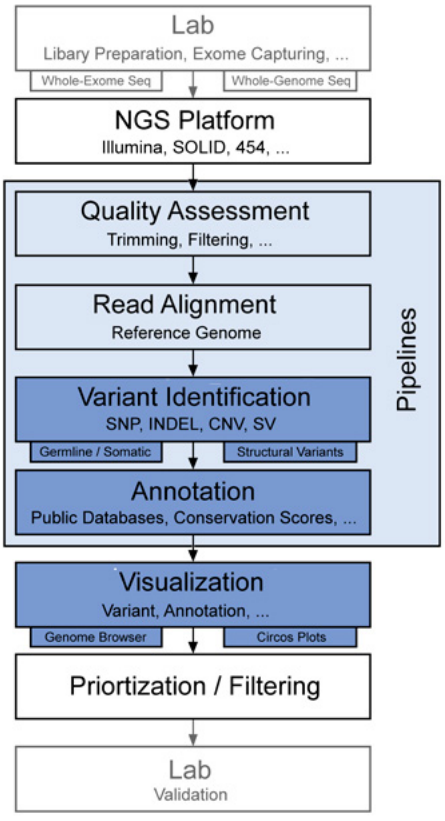

Fig. 1: Basic workflow of whole-exome (whole-genome) sequencing projects for variant detecion

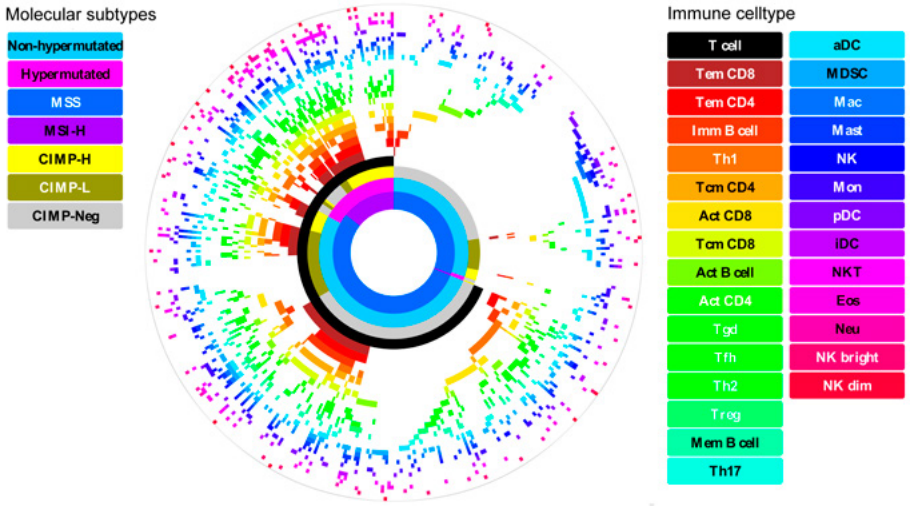

Fig. 2: Spinchart of molecular phenotypes (3 inner circles) and immunophenotypes in 598 colorectal cancer patients

model and investigate the tumor-immune cell interaction in colorectal cancer and in a number of different solid tumor types including breast and lung adenocarcinoma. Towards this goal we are exploring the immunogenicity of the colorectal cancer mutanome using deep mining of publicly available data sets and carrying out experimental studies using cell and mouse models. By analyzing RNAseq data of more than 500 colorectal cancer patients we could obtain the landscape of infiltrating immune cell types within the different moclecular subtypes (see Fig. 2). From the non-synonymous mutations of these patients we were also able to predict the tumor-epitopes (neo-antigens) and could show that those are rarely shared between patients, indicating that therapeutic vaccination needs to be personalized rather than provided for a larger cohort. The most shared epitope candidates are shown in Fig. 3; the epitope TEYKLVVVGAV generated by mutations in the KRAS gene was shared by 28 colorectal cancer patients. Additionally, we are building mathematical models at various scales and performing simulations that will help us to identify immune signals controlling tumor heterogeneity, clonal evolution and tumor progression, which can then be experimentally verified.

Selected Publications

Characterization of the immunophenotypes and the antigenomes of colorectal cancers reveals distinct tumor escape mechanisms and novel targets for immunotherapy. Angelova M, Charoentong P, Hackl H, Fischer M, Snajder R, Krogsdam AM, Waldner MJ, Bindea G, Mlecnik B, Galon J, Trajanoski Z.
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Pabinger S, Dander A, Fischer M, Snajder R, Sperk M, Efremova M, Krabichler B, Speicher MR, Zschocke J, Trajanoski Z.
BRIEFINGS IN BIOINFORMATICS. 2014; 15: p. 256–278.

Co-expressed genes prepositioned in spatial neighborhoods stochastically associate with SC35 speckles and RNA polymerase II factories. Rieder D, Ploner C, Krogsdam AM, Stocker G, Fischer M, Scheideler M, Dani C, Amri E-Z, Mueller WG, McNally JG, Trajanoski Z.
CELLULAR AND MOLECULAR LIFE SCIENCES. 2014; 71: p. 1741–1759.

Spatio-temporal dynamics of intratumoral cells reveal the immune landscape in human cancer.
Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, Obenauf AC, Angel H, Frederiksen T, Lafontaine L, Berger A, Bruneval P, Fridman WH, Becker C, Speicher MR, Trajanoski Z, Galon Z.
IMMUNITY. 2013; 39:p. 782–795.

GPViz: dynamic visualization of genomic regions and variants affecting protein domains.
Snajder R, Trajanoski Z, Hackl H.
BIOINFORMATICS. 2013; 29: p. 2195–2196.

Selected Funding

- SFB Cell Proliferation and Cell Death in Tumors, FWF, Zlatko Trajanoski
- DK MCBO, FWF, Zlatko Trajanoski
- Bioinformatics Tyrol, Standortagentur Tirol , Zlatko Trajanoski
- Oncotyrol, Zlatko Trajanoski
- APERIM, EU Horizon2020, Zlatko Trajanoski (coordinator)

Collaborations

Jerome Galon, INSERM U872, Paris, France

Fig. 3: Neo-antigens shared in at least 7 of the 598 colorectal cancer patients; more commonly shared epitopes are shown in a lager font (Wordle), the gene symbols of the corresponding mutated genes are shown in brackets.

Physiology

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Keywords

Neurophysiology, renal physiology, muscle physiology, lung physiology, cell volume regulation, ion channels, toxicology, electrophysiology, cell biology, nociception

Research Focus

Scientific research at the Division of Physiology, Innsbruck, focuses on basic and preclinical translational experimental work in the areas of neurophysiology and the physiology of muscle and epithelial organs. Current research projects include the science of normal biomolecular functions in healthy individuals including their organs and component cells. An understanding of normal functions can lay the groundwork to explore the pathogenesis of common diseases like COPD, renal dysfunction or chronic pain. The principal level of research is at the level of cellular models, organs and systems, and employs an integrated interdisciplinary approach. Significant opportunities for innovation are expected to arise from ongoing projects developing human iPSCs into humanised model systems and microRNAs as novel biomarkers and druggable targets for chronic neuropathic pain disorders.

General Facts

The major task of the Division of Physiology is the study and teaching of human physiology. Physiology aims to understand how organisms survive and function. This is a challenging subject dealing with physical and chemical factors that are responsible for the origin, development and progression of life. The study of physiology includes the understanding of the workings of a given cell and its interaction with the cellular environment, through to the complex interaction of different cell types in tissues and organs and the interactions of these organ systems which are critical for the maintenance of whole body homeostasis and life. By understanding the normal function of organisms and their parts, we can better understand the processes that occur when these systems go awry in disease states. Eight research groups are involved in cutting edge research in the fields of nociception, calcium signalling, cell membranes and renal and alveolar epithelial physiology We employ a wide range of models and techniques including cell culture, imaging, gene and protein expression, calcium microfluorimetric measurements, high resolution live microscopy and electrophysiology. The eight research groups are partners in local, national and international consortia and are funded by the European Commission (4 projects), the FWF (7 projects), the ÖNB and private foundations with funding totalling € 4.2 million.

Research

On the Trail of Chronic Pain
Michaela Kress

Chronic pain syndromes which develop after nerve damage, trauma, or surgery are characterized by persistent and severe pain. They induce anxiety and depression and greatly impair patients' quality of life. One in five Europeans suffer from chronic pain, many of them for more than two years, some even longer. Chronic pain therefore constitutes not only a heavy burden for individual patients and their families, but also for national health systems in Europe since treatment costs can take up between 1.5 and 3% of a country's gross domestic product (GDP) per year. Advancing scientific research in this field is thus a societal need and a crucial undertaking in order to facilitate improved patient care. The main research aim of the group is to understand the pathogenesis of neuropathic and neurogenic pain disorders. We tackle these challenges with an interdisciplinary approach and a wide spectrum of methods and model systems including primary neuron cultures and neuronal cell lines (Fig. 1).

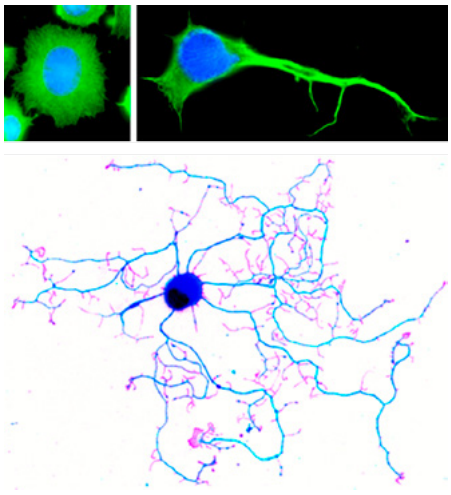

Fig. 1: Undifferentiated (top left) and differentiated (top right) neuroblastoma cell and GFP transfected sensory neuron (lower panel, blue) and actin staining (purple).

1. Neuroimmune Interactions

We explore interactions between the nervous system and the immune system that occur upon nerve injury. At present we are mainly interested in proinflammatory cytokines (interleukin 6, LIF, OSM), and the effects they have on neuronal function and regeneration after nerve injury. We currently focus on the regulation of ion channels and neuron excitability (Fig. 2) by signals originating from immune cells including microglia and the neurons themselves in a research project and a PhD project both funded by the FWF. Neurons can be reprogrammed *in vitro* with viral vectors as shown in Fig. 3 and this technology is used to explore the signalosome of cytokine receptors and of non-coding RNAs which have recently emerged as a novel family of cellular regulators.

2. Non-Coding RNAs

As novel players, non-coding RNAs and their suitability as disease biomarkers or treatment strategies are assessed. With *ncRNAPain*, a new European research project sets out to further explore the biological mechanisms underlying chronic pain. Endowed with an overall funding budget of 6 million euros by the European Commission for four years, the project focusses on non-coding RiboNucleic Acids (ncRNAs). M. Kress coordinates the ncRNAPain consortium which together with A. Hüttenhofer, Z. Trajanoski (both Biocenter), F. Kronenberg (Div. Gen. Epidemiology) and 10 international partners aims to decode these biological molecules' role, which perform multiple vital roles in our genetic make-up and in the generation of chronic pain syndromes.

Calcium Channels in Muscle and Brain
Bernhard E. Flucher, Gerald Obermair

Voltage-gated calcium channels are key regulators of cellular functions in electrically excitable cells. They control the communication between nerve and muscle cells, the force of muscle contraction, and are importantly involved in regulating muscle growth and differentiation during development and in response to exercise. In nerve cells they regulate a variety of vitally important functions including neurotransmitter release, gene regulation, and neuronal plasticity. The importance of voltage-gated calcium channels is reflected by a range of disorders related to aberrant calcium channel functions such as the muscle diseases myotonic dystrophy and malignant hyperthermia as well as neurological diseases including migraine, epilepsy, autism, ataxia, chronic pain, mood disorders, and Parkinson's and Alzheimer's disease. Our research teams use state-of-the-art molecular genetics, molecular and cell biology, electrophysiology, histology, and high-resolution microscopy approaches to study calcium channel functions in muscle and nerve cells:

1. Calcium Channels in the Neuro-Muscular System

In the past years we discovered the molecular identity and specific functions of several hitherto uncharacterised channel isoforms. Structure-function studies revealed the molecular determinants of the unique biophysical properties of the skeletal muscle calcium channel. Recently we demonstrated the importance of controlling calcium influx for muscle fiber type determination and how increased calcium influx leads to muscle disease.

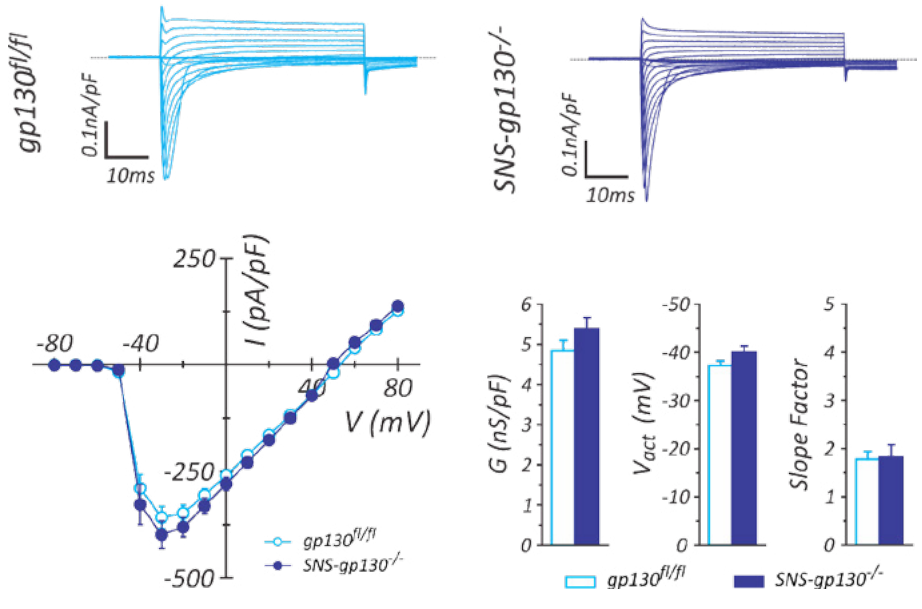

Fig. 2: Voltage-gated sodium current traces and analysis

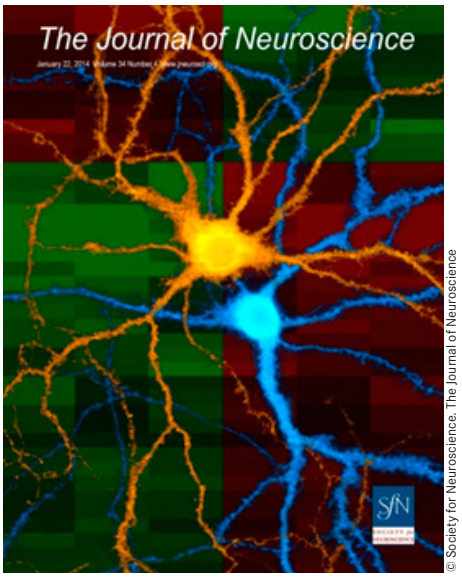

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Fig. 3: Composite image of immunofluorescence-labelled cultured neurons from lethargic ($Ca_V\,\beta_4$-null mutant) mice reconstituted with specific splice variants of the calcium channel β_4 subunit. Expression profiling (heat map in the background) revealed that the nuclear β_{4e} subunit (orange) regulates expression of neuronal genes including that of $Ca_V2.1$, its own primary channel partner in cerebellar synapses.

2. Calcium Channels in the Brain

In synapses presynaptic calcium channels control the release of neurotransmitter in response to action potentials and post-synaptic calcium channels are involved in mechanisms of synaptic plasticity. Ongoing projects are concerned with the assembly and composition of synaptic calcium channel complexes and their involvement in the development of the neuro-muscular junction. For example, at present we are addressing the roles of two specific constituents of brain calcium channels, both in basic cell biological mechanisms, such as synaptic transmission and synapse formation, as well as their involvement in neurological disorders such as epilepsy and Parkinson's disease (Fig. 4).

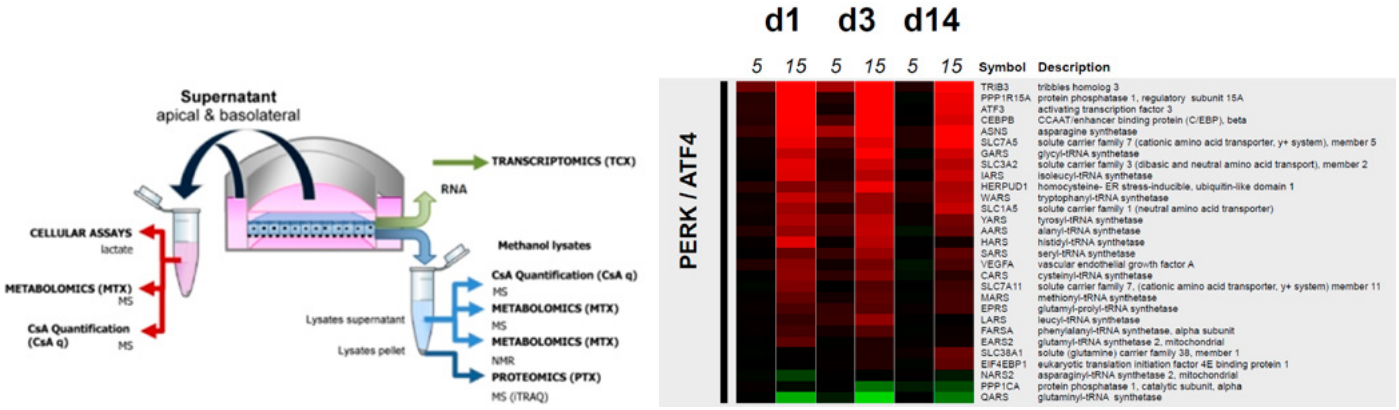

Fig. 4: Mechanism of cyclosporine A induced renal epithelial cell injury. Human RPTEC/TERT1 cells were cultured on microporous supports and treated for 14 days with 0, 5 and 15 µM CsA. Samples were harvested for transcriptomics, proteomics and metabolomics. The heat map depicts the activation of the ATF4 pathway with 15 µM CsA, but not with 5 µM at the indicated days (d).

Kidney Function and Mechanisms of Kidney Diseases
Gerhard Gstraunthaler, Judith Lechner, Paul Jennings

Research of the renal groups is focused on studying the physiology of proximal tubular cells, which play a major role in the development of acute and chronic kidney diseases.

1. Biomarkers of Renal Injury

We are investigating the molecular mechanism of chemical induced stress in cultured human proximal tubular cells and we are also attempting to identify novel mechanistic biomarkers of proximal tubular injury (EU projects PredictIV, Detective). Some of the pathways frequently altered in chemical induced stress are Nrf2 (oxidative stress), p53 (DNA damage), HIF1alpha (hypoxia) and ATF4 (the unfolded protein response). The delineation of these and other pathways have been achieved by applying omic techniques (transcriptomics, proteomics and metabolomics) and often coincide with the loss of differentiation markers.

2. Improved Assay Systems

In order to develop and improve *in vitro* systems for chemical safety assessment as alternatives to animal testing, several human and animal renal tubular cell lines were characterized in depth and human induced pluripotent stem cell differentiation into renal lineages has been studied (EU IMI-Project StemBANCC, Fig. 5). Human platelet lysates were developed as substitute for fetal bovine serum in cell culture media and have been successfully applied to adult adipose-derived stem cell cultures providing a fully humanized, animal-derived component-free culture system to be used in stem cell technology and tissue engineering.

3. Gender Medicine

As a new line of research, studies on sex specific differences in renal tubular cell physiology have been implemented (Science Fund of the Austrian Central Bank). Periodical changes in renal tubular cell physiology phased by the female hormone cycle have been detected, which are potentially linked to the lower susceptibility of women to renal failure as compared with men.

Respiratory Cell Physiology
Thomas Haller

Quantitative as well as qualitative perturbations in the pulmonary surfactant system of different etiologies, including a disruption of the type II cell homeostasis (Fig. 6), are increasingly considered as underlying causes of a spectrum of idiopathic respiratory distress and interstitial lung diseases, some of which are associated with a significant morbidity and mortality. The research performed by the respiratory cell physiology group focuses in particular on the regulation and mechanisms of surfactant secretion by the type II pneumocytes, the significance and the biophysical properties of surfactant at the respiratory air-liquid interface, and on alveolar epithelial cell physiology in general, with a current emphasis on the refinement of organotypic cell culture systems (*lung-on-a-chip*). In the past years, for example, we identified the air-liquid phase boundary as a major determinant in cell signalling, gene expression and exocytosis of surfactant and its extracellular transformation into functional films.

Insulin Secretion and Cell Volume Regulation
Johannes Fürst

Diabetes mellitus occurs throughout the world but is more common (especially type 2) in more developed countries. Its prevalence is increasing rapidly and an estimated 750 million people will have diabetes by 2030. Although genetic background and environmental (i.e. dietary) factors have been associated with diabetes pathogenesis the underlying physiological mechanisms need to be explored in more detail. Our main interest is studying the regulation of insulin secretion in pancreatic beta cells *in vitro*, with a focus on the contribution of cell volume regulatory mechanisms.

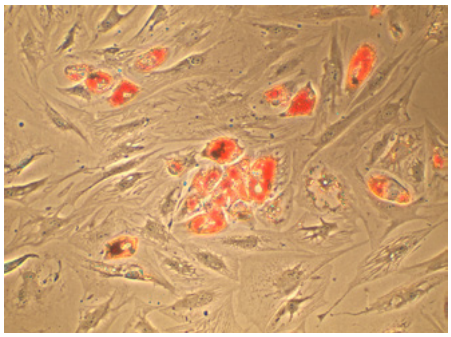

Fig. 5: iPSCs differentiated into adipocyte like cells

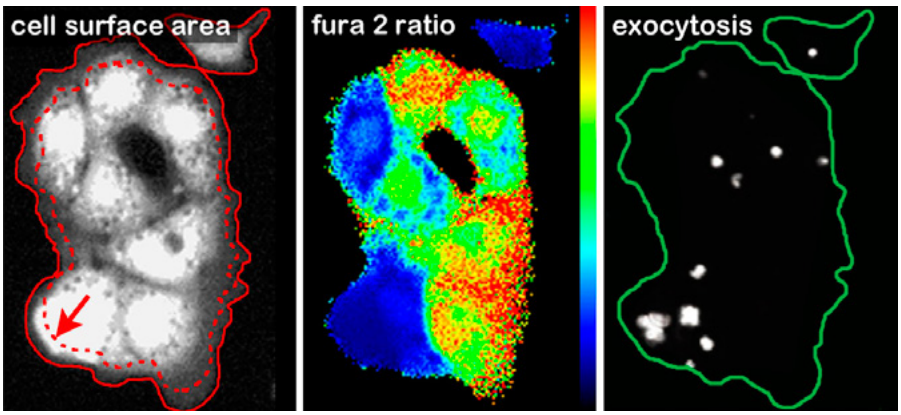

Fig. 6: Stretch-induced Ca^{2+}-signalling and exocytosis in alveolar type II cells

Selected Publications

Deletion of Interleukin-6 Signal Transducer gp130 in Small Sensory Neurons Attenuates Mechanonociception and Down-Regulates TRPA1 Expression. Malsch Philipp, Andratsch Manfred Vogl, Christian Link, Andrea S, Alzheimer Christian, Brierley Stuart M, Hughes Patrick A, Kress Michaela.
JOURNAL OF NEUROSCIENCE. 2014; 34: p. 9845–9856.

Peripheral Nerve Regeneration and NGF-Dependent Neurite Outgrowth of Adult Sensory Neurons Converge on STAT3 Phosphorylation Downstream of Neuropoietic Cytokine Receptor gp130. Quarta Serena, Baeumer Bastian E, Scherbakov Nadja, Andratsch Manfred, Rose John Stefan, Dechant Georg, Bandtlow Christine E, Kress Michaela.
JOURNAL OF NEUROSCIENCE. 2014; 34: p. 13222–13233.

Sphingosine-1-Phosphate-Induced Nociceptor Excitation and Ongoing Pain Behavior in Mice and Humans Is Largely Mediated by S1P3 Receptor. Camprubi-Robles M, Mair N, Andratsch M, Benetti C, Beroukas D, Rukwied R, Langeslag M, Proia RL, Schmelz M, Montiel AVF, Haberberger RV, Kress, M.
JOURNAL OF NEUROSCIENCE. 2013; 33: p. 2582–2592.

Differential Neuronal Targeting of a New and Two Known Calcium Channel beta(4) Subunit Splice Variants Correlates with Their Regulation of Gene Expression. Etemad Solmaz, Obermair Gerald J, Bindreither Daniel, Benedetti Ariane, Stanika Ruslan, Di Biase Valentina, Burtscher Verena, Koschak Alexandra, Kofler Reinhard, Geley Stephan, Wille Alexandra, Lusser Alexandra, Flockerzi Veit, Flucher Bernhard E.
JOURNAL OF NEUROSCIENCE. 2014; 34: p. 1446–1461.

Stable incorporation versus dynamic exchange of beta subunits in a native Ca^{2+} channel complex. Campiglio Marta, Di Biase Valentina, Tuluc Petronel, Flucher Bernhard E.
JOURNAL OF CELL SCIENCE. 2013; 126: p. 2092–2101.

SEURAT-1 liver gold reference compounds: a mechanism-based review. Jennings Paul, Schwarz Michael, Landesmann Brigitte, Maggioni Silvia, Goumenou Marina, Bower David, Leonard Martin O, Wiseman Jeffrey S.
ARCHIVES OF TOXICOLOGY. 2014; 88: p. 2099–2133.

An overview of transcriptional regulation in response to toxicological insult. Jennings P, Limonciel A, Felice L, Leonard MO.
ARCHIVES OF TOXICOLOGY. 2013; 87: p. 49–72.

Selected Funding

- EC-FP7, (No 602133) ncRNAPain: Non-coding RNAs for personalised pain medicine, Michaela Kress
- EU 7th Framework, Predict-IV, Paul Jennings
- EU 7th Framework, DETECTIVE, Paul Jennings
- IMI-Projekt StemBANCC, Paul Jennings, Gerhard Gstraunthaler
- FWF, P25345: S1P and post-operative pain, Michaela Kress
- FWF, W1206: Doctoral College "Signal processing in neurons", Michaela Kress
- FWF, P23479: Expression and function of a new skeletal muscle calcium channel splice variant, Bernhard E. Flucher
- FWF, P24079: Synapses and disease in calcium channel alpha2-delta subunit mouse models, Gerald Obermair
- FWF, P27031: The role of calcium channels in acetylcholine receptor pre-patterning during neuromuscular junction development Bernhard E. Flucher
- FWF, W1101: Doctoral College in "Molecular Cell Biology and Oncology" 4th funding period; Speaker: Bernhard E. Flucher
- FWF, SFB F4415: Importance of intra- and extracellular Cav1.3 modulators for synapse stability in normal and diseased striatal medium spiny neurons. SFB: Cell signalling in chronic CNS disorders, Gerald Obermair and Bernhard E. Flucher
- FWF, P20472: Cells at air-liquid interfaces, Thomas Haller
- D-150700-017-011: Stiftung ProCare, Gerhard Gstraunthaler

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Biomedical Physics

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Keywords

Biophotonics, optical tweezers, nonlinear microscopy, CARS microscopy, Raman microscopy, digital holographic microscopy, phase contrast, spatial light modulators, UV measurements, solar UV radiation

Research Focus

- Optical micro-manipulation: contact-free handling of microscopic particles (micro-organisms, micro-beads, living cells, cell organelles, or DNA-strands) with laser light.
  Highlights: trapping of the largest swimming micro-organisms ever trapped "all-optically"; combined acoustic and optical trapping of even larger specimens.
- Holographic microscopy: wavefront shaping with miniaturized liquid crystal displays, so-called Spatial Light Modulators (SLMs) inside an optical microscope, to create novel types of microscopy techniques.
  Highlights: spiral phase contrast, halo-free Zernike phase contrast, multiplane imaging, single-shot quantitative differential interference contrast, lensless imaging through a scattering medium.
- Chemical (vibrational) imaging: label-free technique to visualize molecules in a sample by their vibrational "fingerprint" by means of the Raman effect (spontaneous Raman or Coherent anti-Stokes Raman Scattering = CARS).
  Highlights: non-scanning (wide-field) CARS microscopy, phase-sensitive CARS.
- Solar UV radiation: optimisation of spectroradiometric instruments and development of analysis techniques for solar radiation spectra and aerosol optical depth.
  Highlights: the Austrian UV measurement network (UV-Index).

General Facts

The Division of Biomedical Physics pursues application-oriented basic research projects devoted to the development of novel physical methods and technologies in medicine or cell biology. Currently there exist two Research Groups: the Biomedical Optics Group and the UV-Radiation Group. The research is largely funded externally, e.g. by FWF, ERC, and EU network grants.
The Biomedical Optics Group has a high visibility in the international Biophotonics community, in particular for contributions to Holographic Optical Tweezers and to Synthetic Holographic Microscopy. The research focus lies on wavefront shaping with so-called Spatial Light Modulators (SLMs), miniaturized liquid crystal displays with individually addressable micrometer-sized pixels.
The UV-Radiation group is interested in various aspects of solar UV radiation. They optimise spectroradiometric instruments and develop analysis techniques to measure solar radiation spectra and aerosol optical depth. They operate the Austrian UV monitoring network.

Recent special recognitions and awards:
The Division of Biomedical Physics has hosted several international conferences in the last few years, including the *Trends in Optical Manipulation* conference series in Obergurgl.
Monika Ritsch-Marte was recently elected Fellow of the Optical Society of America and elected into the Austrian Academy of Sciences. Alexander Jesacher received the prestigious Young Researcher Award of the Erlangen Graduate School in Advanced Optical Technology (SAOT).

Research

Biomedical Optics
Monika Ritsch-Marte and Stefan Bernet

Holographic Optical Tweezers shape light into optical trapping patterns which can move or pull microscopic particles, such as micro-organisms, micro-beads, living cells, cell organelles, or DNA-strands, in a controlled and contact-free way.
Recently the research group has strived at pushing the limits of trapping towards increasingly large particles, including fast swimming organisms (e.g. flagellates or Euglena species). The "macro-tweezers" system, a dual beam mirror trap with a large field of view, was established and used to catch the largest living specimens ever trapped by exclusively optical means. To increase the scope even further, an ultrasonic standing wave was created which confines the particles to a plane in the middle of the probe chamber – enabling computer-controlled manipulation of specimens of interest by optical tweezers, e.g. for uncontaminated sampling for PCR. Moreover, in collaboration with a Biophysics group in Amsterdam, acoustic trapping was adapted for massively parallel probing of macromolecules in a lab-on-a-chip device (cf. Fig. 1).

Synthetic Holographic Microscopy employs SLM-based wavefrontntrol to enhance a microscope in specific ways: One can flexibly emulate various contrast mechanisms (e.g. brightfield, darkfield or phase contrast), create multiplexed images (combining different imaging settings in one recorded image), or steer and pattern the illumination in

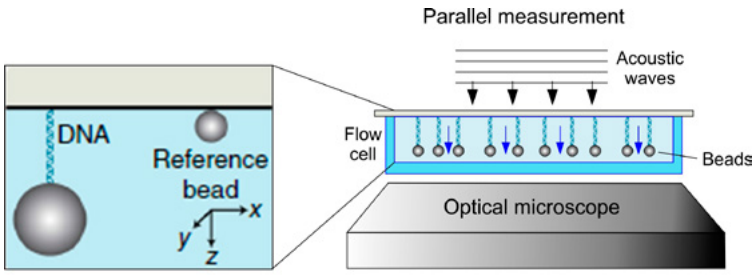

Fig. 1: Acoustic Force Spectroscopy, developed in collaboration with the VU Amsterdam, uses an acoustic manipulation device that can exert forces from subpiconewtons to hundreds of piconewtons on thousands of biomolecules (such as single- or double-stranded DNA) in parallel in lab-on-a-chip devices (G. Sitters et al., Nature Methods 12, 47, 2015).

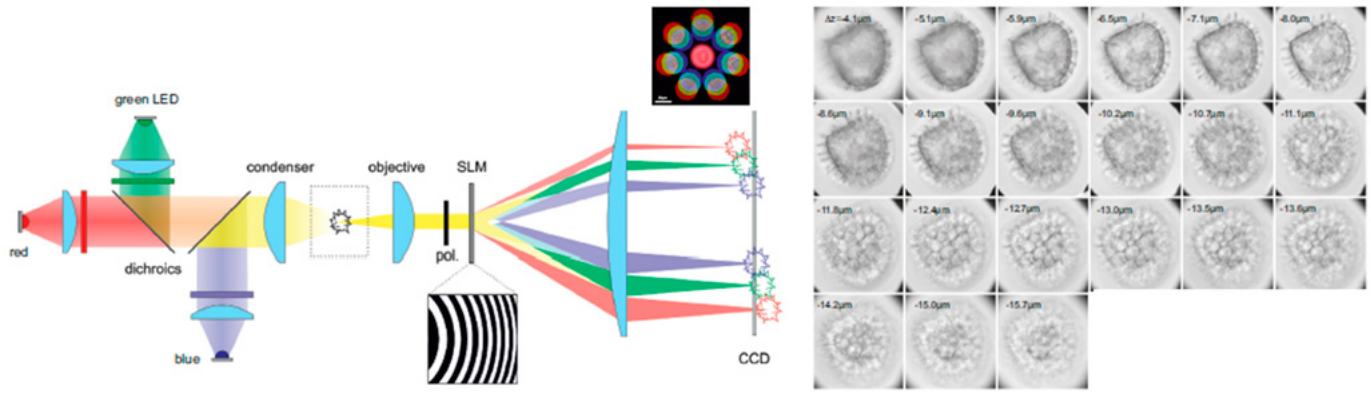

Fig. 2: Synthetic Holographic Microscopy: Multi-plane imaging by wavefront shaping with a spatial light modulator. Using RGB illumination and a colour camera, 21 planes of the sample (a spore) could be imaged simultaneously (A. Jesacher et al., Optics Express, 21, 11150, 2013).

the microscope for structured illumination microscopy.
Last year the approach was used to develop a method for diffractive multi-plane imaging, i.e. the instantaneous optical imaging of the entire volume of a thick transparent sample. With multicolor LED illumination and a colour camera, time-synchronous imaging of 21 focal planes was demonstrated successfully (cf. Fig. 2).

Raman Microscopy provides information on the chemical contents of a sample without the need to introduce exogenous dyes. Spontaneous Raman illuminates the sample with a laser and looks at the spectrum of the inelastically scattered light. The Raman signal can be resonantly enhanced, by using two laser beams of different colour: If the frequency difference of two laser beams matches a Raman-active vibration of targeted molecules, a blue-shifted anti-Stokes signal is generated by a resonant four-photon-effect called Coherent Anti-Stokes Raman Scattering (CARS). The combination of CARS with microscopic imaging leads to CARS microscopy, which enables fast recording of chemical maps on a micrometer scale. From a practical point of view, CARS microscopy resembles fluorescence microscopy, but without the need for fluorescent dyes. In the past a non-scanning wide-field CARS microscope was developed in Innsbruck.
In the past two years *phase-sensitive* measurements of the CARS signal were recorded with a special camera, in collaboration with the Institut Fresnel in Marseilles. This allows one to retrieve also the *spontaneous* Raman spectrum directly from the CARS spectrum, to gain complementary information. As a second line of action the feasibility and practicality of super-resolution in CARS-microscopy is under investigation.

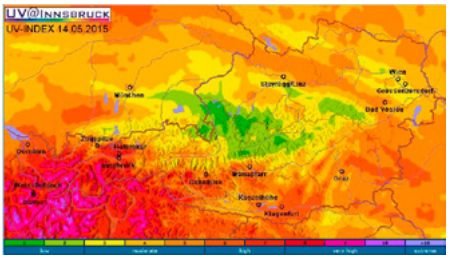

Fig. 3: The Div. for Biomedical Physics operates the Austrian UV measurement network generating the on-line UV-Index for Austria, which is updated every few minutes.

UV-Radiation
Mario Blumthaler
In the past two years the research group has continued to optimise spectroradiometric measurements of solar radiation using array spectroradiometers. Precise determination and correction of stray light is necessary for any interpretation of biological effects of UV measurements because of the steep slope of the solar spectrum in the UVB wavelength range, and the high sensitivity of biological tissues at these wavelengths. As a result, the healthful effect of Vitamin D production and the negative effect of erythema can be quantified in dependence on the environmental conditions (day of the year, time of the day, altitude, snow cover, amount of ozone, amount of aerosols). The absolute calibration of UV detectors in the laboratory is traceable to the German reference laboratory Physikalisch-Technische Bundesanstalt (PTB) and the outdoor measurements are regularly compared with measurements of the reference laboratory of the World Meteorological Organisation. Based on its capabilities for high quality UV measurements, the UV group is responsible for the quality control and publication of the Austrian UV monitoring network within a long term research grant of the Austrian Governmental Department for the Environment.

At the moment, the results of 16 stations in Austria and nearby Bavaria and Switzerland are published in near real time (www.uv-index.at), together with a regional map, showing the distribution of the level of UV exposure modulated by the actual cloud cover, derived from actual pictures of the Meteosat satellite. The data are presented in units of the 'UV-index', which is an internationally agreed quantity for harmful UV exposure, taking into account the sensitivity of the human skin to UV radiation. An example of these maps is shown in Fig. 3, in which the measurement sites are marked. It gives the maximum UV-index on 14.05.2015, clearly influenced by cloudiness and topography.

The capability for absolute UV measurements is also applied for measurements of artificial UV sources as, e.g. used in sun beds in solaria. In cooperation with international agencies (e.g. Commission Internationale de l'Eclairage CIE) these data are interpreted in terms of harmful and potentially healthy effects. Measurements in connection with workplace security and protection were also carried out.

Selected Publications

Wide-field vibrational phase imaging in an extremely folded box-CARS geometry. Berto P, Jesacher A, Roider C, Monneret S, Rigneault H, Ritsch-Marte M. OPTICS LETTERS. 2013; 38: p. 709–711 [Selected for the Virtual Journal for Biomedical Optics 8 (4), May 2013].

Enhancing diffractive multi-plane microscopy using coloured illumination. Jesacher A, Roider C, Ritsch-Marte M. OPTICS EXPRESS. 2013; 21: p. 11150–11161 [Selected for the Virtual Journal for Biomedical Optics 8 (6), June 2013].

Axial super-localisation using rotating point spread functions shaped by polarisation-dependent phase modulation. Roider C, Jesacher A, Bernet S, Ritsch-Marte M. OPTICS EXPRESS. 2014; 22: p. 4029–4037 [Selected for the Virtual Journal for Biomedical Optics 9 (4), April 2014] .

Lensless imaging through thin diffusive media. Harm W, Roider C, Jesacher A, Bernet S, Ritsch-Marte M. OPTICS EXPRESS. 2014; 22: p. 22146–22156 [Selected for the Virtual Journal for Biomedical Optics 9 (11), Nov. 2014].

Stray light correction of array spectroradiometers for solar UV measurements. Nevas S, Gröbner J, Egli L, Blumthaler M. APPLIED OPTICS. 2014; 53: p. 4313–4319.

Selected Funding

- Coherently Advanced Tissue and Cell Holographic Imaging and Trapping, ERC Advanced Investigator Grant P247024, Ritsch-Marte Monika, 2010–2015
- Advanced Wide-field CARS Microscopy, Austrian Science Fund FWF-Project P22085, Ritsch-Marte Monika, 2010–2013
- Christian Doppler Laboratory for Microscopic and Spectroscopic Material Characterisation (MS-MACH), Christian Doppler Forschungsgesellschaft, (Coordinator: Assoc.Prof. D. Stifter, Johannes Kepler Universität Linz), Ritsch-Marte Monika, 2010-2017
- Traceability for surface spectral solar UV radiation, EMRP researcher grant, ENV03-REG1, Blumthaler Mario, 2011–2014

Collaborations

- Rigneault Hervé, Institut Fresnel, Marseille, France
- Padgett Miles, University of Glasgow, UK
- Piestun Rafael, University of Colorado, Boulder, USA
- Wuite Gijs, Vrije Universiteit Amsterdam, Amsterdam, NL
- Nevas Julian, Physikalisch-Technische Bundesanstalt, Berlin, DE
- Gröbner Julian, World Radiation Center, Davos, Switzerland

Cell Genetics

Head of Division:
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Keywords

T lymphocyte signalling, T helper cell differentiation, T cell effector functions, autoimmunity, cancer immunity, innovative immunological therapy concepts

Research Focus

The Cell Genetics Team has expertise in signal transduction, mouse genetics, the differentiation of effector/memory T cells and the ability of these cells to alter adaptive immune responses. In particular, we have gained experience in investigating molecular signalling processes through the use of **hypothesis-driven mechanistic studies and by utilising** unbiased mass spectrometry based screens and next generation sequencing to characterise novel **protein-protein and protein-DNA interactomes and transcriptomes.**

General Facts

The function of mature T cells is to recognize and respond to foreign antigens by a complex activation process involving differentiation of the resting cell into a proliferating lymphoblast that actively secretes immune-regulatory cytokines or displays targeted cytotoxicity, ultimately leading to recruitment of innate immune cell types and the initiation of an effective immune response.

In order to understand the physiology and pathophysiology of T lymphocytes, it is necessary to decode the biochemical processes that integrate the signals received from antigens, cytokines, and integrins as well as inhibitory receptors. Our work aims to explore and identify gene products of distinct members of the AGC family of **protein serine/threonine kinases** and their **effector substrates** that act as key players in mediating proper T cell effector functions and in fine-tuning the **immune response**. The underlying goal of the work is to understand the selective functions of these proteins in signal transduction pathways in lymphocytes and to use this information to develop strategies for manipulating the immune response, either in order to promote immunosuppression in the context of autoimmune diseases, graft rejection and inflammatory responses or for augmentation as part of an innovative cancer immunotherapy-based approach.

Research

Cell Genetics Team: Gottfried Baier, Natascha Kleiter, Thomas Gruber, Nikolaus Thuille, Kerstin Siegmund, Christa Pfeifhofer-Obermair, Victoria Klepsch, Sebastian Peer *et al.*

Due to its biological complexity cancer is still poorly understood. It has been shown both experimentally and epidemiologically that chronic inflammation can predispose individuals to cancer, and may additionally represent an inseparable aspect of clinically prevalent cancer entities.
Therefore, the decoding of both tumour and immune cell functions in cancer progression will be of the utmost importance in combating this frequently incurable disease.
My team and I were the first to reveal the **lymphocyte-intrinsic PKC/NR2F6/Cbl-b axis** as an essential signalling node **governing the complex host-tumour interactions** at the crossroads between **inflammation and cancer**.
Modulation of this lymphocyte-intrinsic signalling pathway renders CD4⁺ and CD8⁺ effector T cells capable of rejecting otherwise

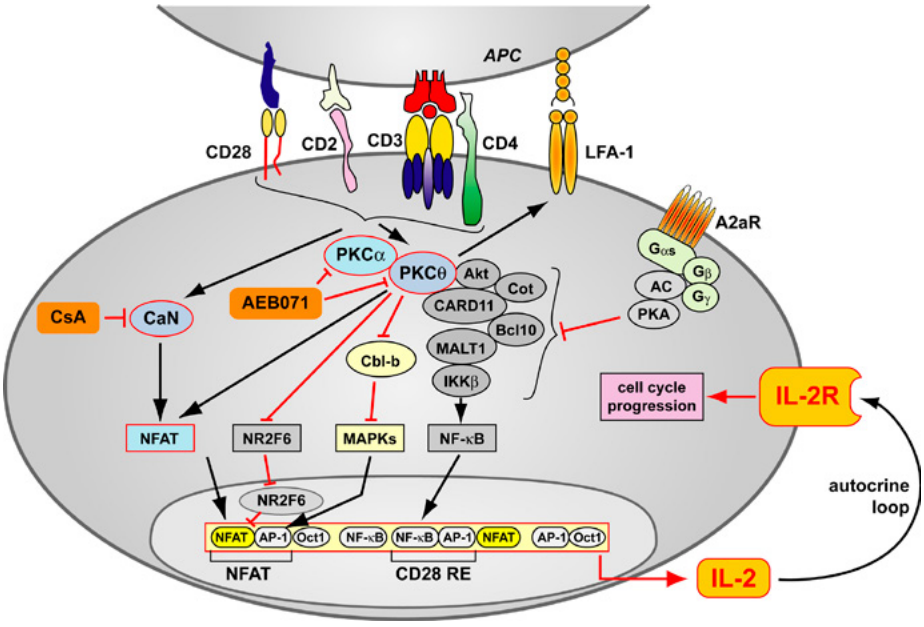
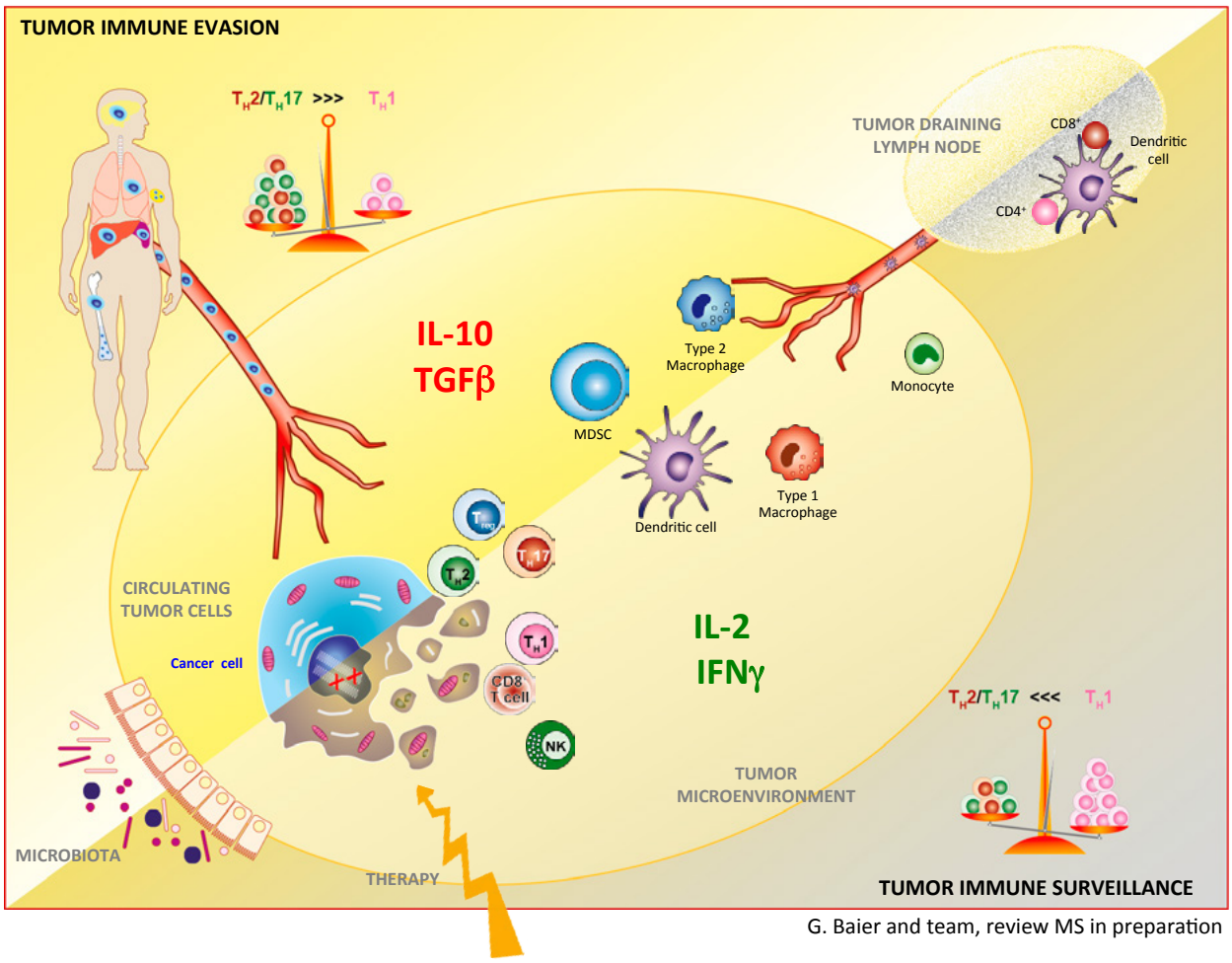


Fig. 1: The major research topic of the group relates to the biochemical, molecular and functional analysis of the signal transducing protein kinase network within the haematopoietic system.



G. Baier and team, review MS in preparation

Re-Educating an effective anti-tumor immunity during cancer therapy

Fig. 2: Our research aims to elucidate the underlying inter- and intracellular mechanisms that shape the microenvironment at the tumour site either to support or to prevent tumour initiation, progression or tumour immune surveillance.

lethal tumour burdens and their metastases in experimental murine cancer model systems *in vivo*. Mechanistically, *Nr2f6* as well as *Cblb* knockout mice thereby display an immune contexture at the tumour site that allows superior anti-tumour T cell responses, increasing the survival rates of tumour-bearing mice.

Since it has already been established that cancer-mediated immune evasion can lead to T cell dysfunction, our data strongly suggest that T cell-based therapies could significantly benefit from modulation of this novel NR2F6/Cbl-b inhibitory signalling pathway. Such a strategy of **intracellular NR2F6 and/or Cbl-b checkpoint-targeting** will improve the efficacy and broaden the applicability of cancer immunotherapy regimens, and thus has the potential in the future to **lead to prolonged patient survival**.

Selected Publications

Orphan nuclear receptor NR2F6 acts as an essential gatekeeper of Th17 CD4+ T cell effector functions.
Hermann-Kleiter N, Baier G.
CELL COMMUNICATION AND SIGNALING (CCS). 2014; 12: p. 38.

The E3 ligase Cbl-b and TAM receptors regulate cancer metastasis via natural killer cells.
Paolino M, Choidas A, Wallner S, Pranjic B, Uribesalgo I, Loeser S, Jamieson AM, Langdon WY, Ikeda F, Fededa JP, Cronin SJ, Nitsch R, Schultz-Fademrecht C, Eickhoff J, Menninger S, Unger A, Torka R, Gruber T, Hinterleitner R, Baier G, Wolf D, Ullrich A, Klebl BM, Penninger JM.
NATURE. 2014; 507: p. 508–512.

Cbl-b mediates TGFß sensitivity by downregulating inhibitory SMAD7 in primary T cells.
Gruber T, Hinterleitner R, Hermann-Kleiter N, Meisel M, Kleiter I, Wang CM, Viola A, Pfeifhofer-Obermair C, Baier G.
J Mol Cell Biol. 2013 Dec;5(6):358–68.

Engineering effective T-cell based antitumor immunity.
Gruber T, Hinterleitner R, Pfeifhofer-Obermair C, Wolf D, Baier G.
Oncoimmunology. 2013 Feb 1;2(2):e22893.

The Kinase PKC alpha Selectively Upregulates Interleukin-17A during Th17 Cell Immune Responses. Meisel M, Hermann-Kleiter N, Hinterleitner R, Gruber T, Wachowicz K, Pfeifhofer-Obermair C, Fresser F, Leitges M, Soldani C, Viola A, Kaminski S, Baier G.
Immunity. 2013 Jan 24;38(1):41–52.

Selected Funding

- Systems Biology of T Cell Activation, Acronym: SYBILLA, plus BMfWF funding; http://www.sybilla-t-cell.de/; EC grant/FP7-HEALTH-Large-scale Integrating Project
- Molecular mechanisms regulating tumor immunology; http://www.sfb021.at/, FWF
- T cell-intrinsic role of PKCα in canonical TGFβR signalling, FWF
- Cbl-b inhibitory signalling pathways in cancer, FFG Bridge
- TaNeDS research collaboration in cancer biology; Daiichi Sankyo Ltd., Tokyo, Japan

Collaborations

- Jürgen Wagner and Gerhard Zencke; Novartis Pharma, Basel, Switzerland
- Michael Leitges, Biotechnology Centre of Oslo, University of Oslo, Norway
- Amnon Altman, LIAI, San Diego, USA
- Steve Shaw, NIH, Bethesda, USA
- Noah Isakov, Ben Gurion University of the Negev, Israel
- Wallace Langdon, University of Western Australia, Perth, AUS
- Arthur Kaser, Department of Gastroenterology, Cambridge, UK

Genetic Epidemiology

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Keywords

Genetic epidemiology, lipoprotein metabolism, complex phenotypes, genome-wide association studies, mitochondrial DNA, computational genetics, cloud computing, risk factors, cardiovascular disease, biomarkers

Research Focus

We aim to identify determinants of health and disease related to genetic variability, environmental components and biochemical parameters and to study their physiological or pathophysiological functions. Our phenotypes of interest are complex in nature due to their interplay and are related to atherosclerosis, diabetes mellitus, metabolic syndrome, cancer, and associated intermediate phenotypes such as lipoprotein metabolism and inflammation.

General Facts

Our Institute serves as a bridge between basic and clinical research. We have three different pillars that develop their strength by an interleaved collaboration.

1. A protein chemistry and cell culture laboratory performs a variety of functional and epidemiologic studies regarding phenotypes related to lipoprotein metabolism and other metabolic phenotypes.
2. A molecular-genetic lab performs sequencing and genotyping for various projects, with a strong focus on mitochondrial DNA as well as on targeted evaluation of certain candidate genes.
3. The computational & statistical genetics lab focusses on statistics, epidemiology, computer science, and bioinformatics and represents an important cross-link between the various research groups.

Besides these three pillars our institute includes the "Sequencing & Genotyping Core Facility" that offers Sanger-sequencing, large scale genotyping projects and management of large epidemiological studies. The output and success of our institute is based on a constant dialogue between the disciplines in a problem-oriented and critical elucidation of the research questions.

Research

Protein Chemistry Lab

Lipoprotein(a) [Lp(a)] and its apolipoprotein(a) isoforms, apolipoprotein A-IV and afamin belong to the three most intensively studied proteins in our lab. During recent years we measured these proteins in roughly 20,000 individuals from major population-based studies from Europe and the US. These measurements are the basis for genome-wide association studies (see below).
Lp(a) and its genetic determinants have been one of the main topics since the foundation of this institute in 2004. We are associating these measurements with various diseases and disease-associated parameters such as cardiovascular disease, peripheral arterial disease, kidney disease and diabetes mellitus. Genetically determined apo(a) isoforms are the strongest genetic risk factor for cardiovascular disease. In a recent analysis in three independent populations including more than 6000 individuals we showed a causal relationship between Lp(a) concentrations and peripheral arterial disease.
A further apolipoprotein studied in our lab is apolipoprotein A-IV (apoA-IV). For this apolipoprotein we could show an association with cardiovascular disease. Furthermore, patients with kidney disease have pronounced elevations of apoA-IV which are associated with progression of chronic kidney disease. In patients with end-stage renal disease apoA-IV is associated with all-cause mortality and sudden cardiac death.
Finally, afamin is a human plasma vitamin E–binding glycoprotein primarily expressed in the liver. After initial biochemical characterisation we started first functional studies and demonstrated that transgenic mice overexpressing afamin had increased body weight and serum concentrations of lipids and glucose. In line with these results we showed in three population-based studies including >5000 participants that afamin is strongly associated with the prevalence and development of metabolic syndrome and its components. Further studies in patients with pregnancy complications and polycystic ovary syndrome confirmed the association between afamin and metabolic syndrome-like phenotypes.

Molecular-Genetic Lab

This lab is in charge of the DNA work related to various genetic-epidemiological cohorts. It performs targeted sequencing and genotyping of complex regions with specially designed assays. Measurement of relative telomere length in several cohorts and its association with cardiovascular disease, kidney disease, and cancer shed new light on this marker of aging.
Beside the nuclear genome, one of our research topics relates to mitochondrial DNA (mtDNA). Being strictly maternally inherited without recombination, mtDNA is a powerful tool to reconstruct maternal relatedness based on sequence polymorphisms. Mutations in mitochondrial genes have been linked to several complex diseases. Therefore, mtDNA is targeted in medical-, population- and also forensic genetics. Our group established a comprehensive workflow for mtDNA analysis comprising next generation deep sequencing strategies as well as accurate data management. Our open source software tools eCOMPAGT, HaploGrep and mtDNA-Server are contributions to an automated mtDNA data processing. These pipelines in hand, we were able to evaluate phylogenetic aspects in the multi-ethnic population of Myanmar.

Fig. 1: Analysis of sequencing data

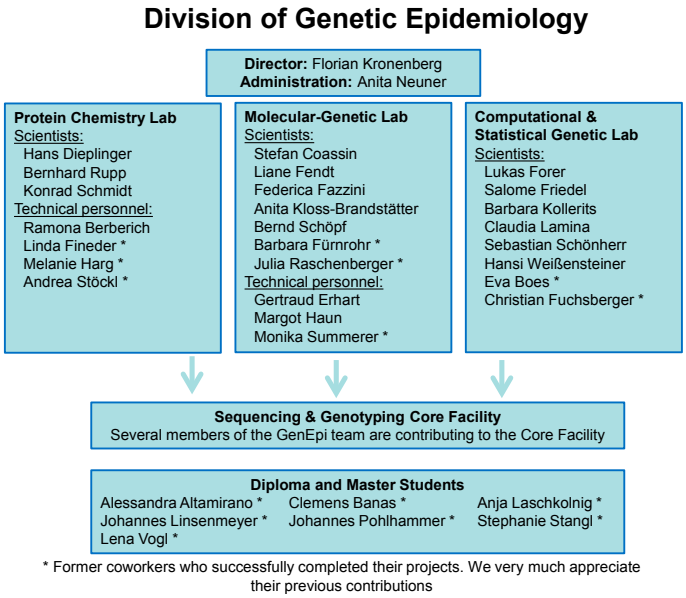

Fig. 2: Coworkers of the Division of Genetic Epidemiology

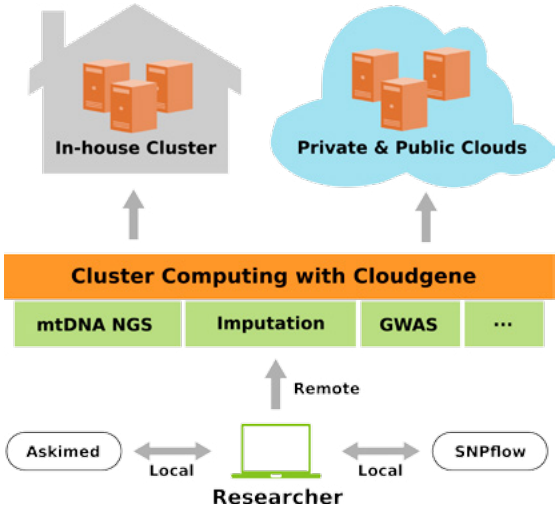

Fig. 3: The Division of Genetic Epidemiology developed several open-source software solutions for local computing and remote computing. Currently three different services are provided within Cloudgene, executed in a massively parallel way.

Furthermore, we are currently investigating the role of mitochondrial mutations in prostate- and oral squamous cell carcinomas, elucidating whether somatic mutations are involved in disease development and the further prognosis of the disease.

Computational & Statistical Genetic Lab
This lab is characterized by a profound interplay between statistics, epidemiology, computer science and bioinformatics. In genome-wide association studies (GWAS) we bring together the data from phenotyping done e.g. in the protein chemistry lab with the genotype data and we try to find hitherto unknown associations with genes. Within the last ten years we were involved in several GWAS consortia. Our own main focus is on studies with Lp(a), apoA-IV and afamin, but we are also involved in consortia evaluating phenotypes such as adiponectin, peripheral arterial disease, BMI and waist circumference, metabolites, measures of kidney function and others. Using these methods resulted in a tenfold increase in the number of known gene-phenotype associations.
One aim of this lab is to apply computer science to the field of molecular biology and medical genetics. Since genetics turned into a big data science, we provide researchers ready-to-use analysis pipelines in cloud environments without the necessity to become acquainted with the underlying technical details. One of our efforts resulted in the novel data parallelization platform Cloudgene. The success of this platform can be seen in the Michigan Imputation Server, in which Cloudgene builds the underlying architecture. From July 2014 to August 2015 over 1 million genomes have been successfully imputed using this free service. Besides the imputation service, two additional workflows (mtDNA NGS, GWAS) have been integrated into Cloudgene and provided to the community as free services. In addition, we are involved in several large scale population studies (e.g. the German Chronic Kidney Disease Study, ncRNA-Pain Study), in which we manage huge amounts of data and improve the overall quality of collecting phenotypic information. These efforts resulted in two open source software solutions: Askimed for managing phenotypes and SNPflow for the standardized and automatic quality control of genotyping data.

Selected Publications

Lipoprotein(a) concentrations, apolipoprotein(a) phenotypes and peripheral arterial disease in three independent cohorts. Laschkolnig A, Kollerits B, Lamina C, Meisinger C, Rantner B, Stadler M, Peters A, Koenig W, Stöckl A, Dähnhardt D, Böger CA, Krämer BK, Fraedrich G, Strauch K, Kronenberg F.
Cardiovascular Research. 103:28-36, 2014.

Plasma concentrations of afamin are associated with the prevalence and development of metabolic syndrome. Kronenberg F, Kollerits B, Kiechl S, Lamina C, Kedenko L, Meisinger C, Willeit J, Huth C, Wietzorrek G, Altmann ME, Thorand B, Melmer A, Dähnhardt D, Santer P, Rathmann W, Paulweber B, Koenig W, Peters A, Adham IM, Dieplinger H.
Circ. Cardiovasc. Genet. 7:822-829, 2014.

SNPflow: a lightweight application for the processing, storing and automatic quality checking of genotyping assays. Weissensteiner H, Haun M, Schönherr S, Neuner M, Forer L, Specht G, Kloss-Brandstätter A, Kronenberg F, Coassin S.
PLoS One. 8: e59508, 2013.

Correlation between a positive family risk score and peripheral artery disease in one case-control and two population-based studies. Lamina C, Linsenmeyer J, Weissensteiner H, Kollerits B, Meisinger C, Rantner B, Stöckl D, Stadler M, Klein-Weigel P, Peters A, Fraedrich G, Kronenberg F.
Atherosclerosis. 237:243-250, 2014.

Comparison and evaluation of cardiac biomarkers in patients with intermittent claudication: Results from the CAVASIC Study. Kollerits B, Sturm G, Lamina C, Hammerer-Lercher A, Rantner B, Stadler M, Ziera T, Struck J, Klein-Weigel P, Fraedrich G, Kronenberg F. Clin. Chem. 59:692-702, 2013.

Selected Funding

- SAXCESS "Stucture-function analysis of the human plasma glycoprotein afamin, a potential drug target in the treatment of metabolic syndrome.", EU (Marie Curie), Hans Dieplinger
- "ncRNAPain: Non-coding RNAs in neurogenic and neuropathic pain mechanisms and their application for risk assessment, patient stratification and personalised pain medicine", EU-FP7, Florian Kronenberg
- "A genome-wide approach to evaluate the genetic basis of lipoprotein(a)", FWF, Claudia Lamina
- "Analysis of rare variants from sequencing data", FWF (Schrödinger Rückkehrpr.), Christian Fuchsberger

Collaborations

- Gonçalo Abecasis, Center of Statistical Genetics, University of Michigan, Ann Arbor, USA
- Enis Afgan, Ruđer Bošković Institute Zagreb, Croatia & Johns Hopkins University, Baltimore, USA
- Steven C. Hunt, Cardiovascular Genetics Division, University of Utah, Salt Lake City, USA
- Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany
- Günther Specht, Department of Database and Information Systems; Institute of Computer Science, University of Innsbruck, Innsbruck, Austria
- Matthew Bowler, Synchrotron Diffraction, EMBL Grenoble, France

Core Facilities

The Sequencing & Genotyping Core Facility owns state-of-the-art equipment for Sanger sequencing, high throughput genotyping and qPCR and fragment analysis.
- Sequenom MassARRAY4 MALDI-TOF System: multiplex genotyping and methylation analysis
- QuantStudio 6 Flex System: large scale genotyping and qPCR
- 3130xl and 3730s Systems: Sanger sequencing and fragment analysis using either 16 (low throughput) and 48 capillaries (high throughput)
- Fragment Analyzer: automated fragment analysis for NGS library QC
- 8 and 96 channel TECAN pipetting robots for large pipetting jobs and automated sample normalization

Human Genetics

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Keywords

Human genetics, molecular genetics, cytogenetics, mitochondrial genetics, transcript analysis, tumour disposition syndromes, genetic skin diseases, metabolic medicine, cancer genetics

Research Focus

- Genetic causes of rare diseases, including:
  - Developmental disorders, intellectual disability and dysmorphic syndromes
  - Inherited metabolic diseases
  - Genetic skin diseases
  - Genetic disease of the teeth and periodontal tissue
- Genetic causes of tumours and tumour dispositions, including:
  - Inherited cancer disposition syndromes
  - Breast and ovarian cancer
  - Hamartomatous tumours
  - Cytogenetics of haematological malignancies
- Transcription and transcript processing of mitochondrial DNA (mtDNA)
- Transcription and transcript processing of nuclear genes, in particular splice mechanisms
- New methods of genetic laboratory diagnosis, mutation databases, molecular genetic quality control

General Facts

The primary aim of the Division of Human Genetics is clarifying the genetic determinants of health and disease in humans, with special focus on rare diseases that are inherited as monogenic traits, and on genetic variants that have a major impact on human biology and substantial disease relevance. This aim is achieved by combining comprehensive patient services and expertise in clinical genetics, molecular genetics and cytogenetics with basic research. The institute includes the *Centre for Medical Genetics Innsbruck* which provides medical genetic services for the entire Western Austria with extensive outpatient clinics and inpatient consultation in Innsbruck and several regional hospitals. The diagnostic laboratories cover all relevant methods for DNA, RNA and chromosome analysis including classical cytogenetics, fluorescence-in-situ hybridization (FISH), DNA-Array (molecular karyotyping), tumour cytogenetics, Sanger sequencing for a large number of individual genes, massively parallel ("next generation") sequencing – both panel and clinical exome – multiplex-ligation-dependent probe amplification (MLPA), methylation and imprinting analyses, fragment length typing and Southern Blot for microsatellite repeat analyses, and others. Due to the close link with the large basic research unit, interesting observations or unclarified cases may be directly transferred into further investigations on a research basis. The diagnostic laboratories are equipped for a wide range of relevant cell biology techniques with a special focus on DNA and RNA analyses and the functional analysis of genetic alterations. The division is dedicated to interdisciplinary collaboration and is happy to carry out both diagnostic tests and research investigations for a large number of hospital centres in Innsbruck and elsewhere.

Research

Mitochondrial RNA Maturation and its Diseases

Johannes Zschocke, Albert Amberger, Andrea Deutschmann

Mitochondria are the powerhouses of the cell. They have a central function in energy production and play vital roles in several cellular processes. Cellular energy is mainly produced by the respiratory protein complexes in mitochondria. Numerous genetic alterations lead to impaired mitochondrial respiration and result in human pathologies, generally referred to as "mitochondrial diseases". Most of the proteins of the respiratory chain are encoded by nuclear DNA; however, 13 respiratory complex proteins (mRNAs), two ribosomal RNAs (rRNAs) and a complete set of 22 transfer RNAs (tRNAs) are encoded by mitochondrial DNA (mtDNA), a circular genome inside mitochondria.

One essential step in mitochondrial maintenance is mitochondrial RNA (mtRNA) transcript processing. Transcription of the mtDNA occurs on both DNA strands and produces long polycistronic transcripts of mRNAs and rRNAs, usually interspersed with tRNAs. Mitochondrial protein translation requires the correct processing of the polycistronic RNA molecules at the 5´end and 3´end of the interspersed tRNAs to release mature mRNAs, tRNAs, and rRNAs. The initial processing step, the endonucleolytic cleavage of precursor tRNAs at the 5´end, is performed by RNase P, an enzyme complex composed of three different proteins (MRPP1, HSD10, and MRPP3). Processing at the 3´end is done by tRNase Z, a single protein coded by the *ELAC2* gene.

We found that missense mutations in the genes for *HSD10* and *MRPP3* resulted in reduced tRNA processing which lead to mitochondrial damage due to impaired respiratory complex formation. In *HSD10* disease, for instance, patients usually display a progressive neurodegenerative disease course with loss of cognitive and motor function, epilepsy and progressive cardiomyopathy, and usually death in childhood. Importantly, tRNA processing is the first step in post-transcriptional mtRNA maturation which includes base modification, RNA surveillance, RNA packaging, and finally RNA decay. It is estimated that approximately 300 nuclear coded proteins are involved in mitochondrial gene expression and only some of them are known to be involved in mitochondrial disorders. However, there are many unsolved cases of mitochondrial disease, and defining genetic causes and patho-mechanisms remains a major challenge. In our projects, we focus on novel mutations which disrupt mtRNA biogenesis.

Major Achievements: Identification, clinical characterization, and functional analysis of *HSD10* disease; defining new defects in mtRNA processing which contribute to mitochondrial disorders.
Future Goals: Developing diagnostic tools and establishing novel disease models to

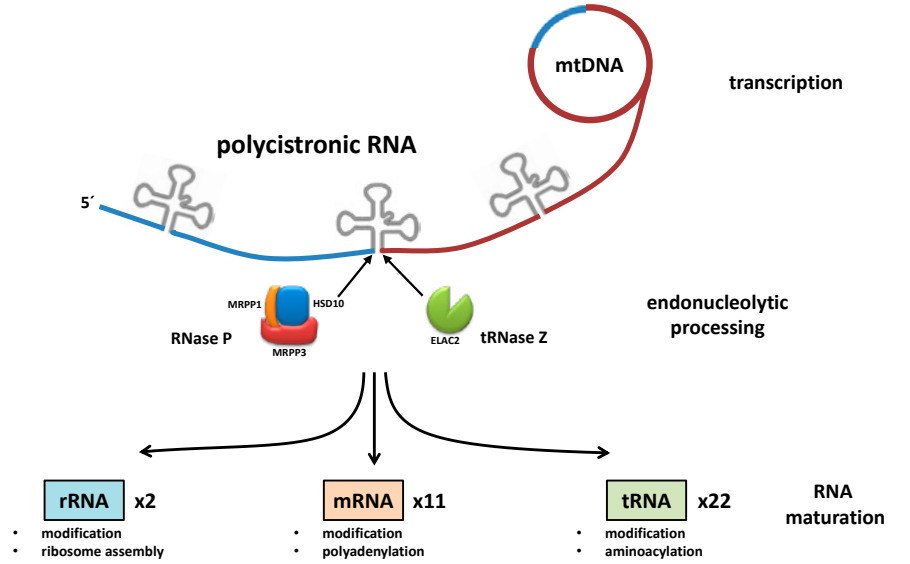

Fig. 1: Schematic overview of mitochondrial RNA metabolism. The mitochondrial rRNAs, mRNAs and tRNAs are transcribed from the L- and H-strands as polycistronic units that undergo endonucleolytic processing by RNase P and tRNase Z. Following the liberation of the individual mRNA, rRNA and tRNA transcripts, they undergo post-transcriptional modifications. Several nucleotides of rRNAs are modified necessary for proper mitochondrial ribosome biogenesis. A poly(A) tail is added to mRNAs. Mitochondrial tRNAs undergo extensive post-transcriptional nucleotide modification, in addition of being aminoacylated with a cognate amino acid.

understand the remarkable heterogeneity of human mitochondrial diseases caused by defects in mtRNA metabolism.

Cancer Genetics
Katharina Wimmer, Julia Vogt, Johannes Zschocke
This research group is strongly associated with the molecular diagnostic lab of the institute that offers molecular genetic investigations for a broad spectrum of cancer susceptibility syndromes.

One of the major aims of the research lab is the development and improvement of diagnostic tools for the identification and classification of mutations that escape standard techniques. The lab developed RNA-based assays that substantially increase mutation detection rates in several tumour suppressor genes. These approaches can effectively uncover splice alterations caused by mutations that either fully escape the detection of gDNA based assays or cannot be readily classified as deleterious from the analysis of gDNA only. The evaluation of these 'atypical' splice mutations e.g. in NF1 also allowed elucidating basic mechanism of splice site definition and inactivation. RNA-based assays have also proved to be pivotal to circumvent diagnostic obstacles that are caused by the presence of pseudo-genes of the mismatch repair gene *PMS2*. We are now planning to transfer the experience and knowledge gained with RNA-based mutation analysis by Sanger sequencing into the massive parallel/next generation sequencing (NGS) era.

A second aim of the research lab is the genetic and clinical characterization of constitutive mismatch repair deficiency (CMMRD) syndrome, a rare autosomal recessively inherited cancer susceptibility syndrome caused by biallelic mutations in one of the four DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2*. Biallelic *PMS2* mutations for which we developed highly sensitive and reliable analysis account for approximately 60% of all cases of this syndrome. CMMRD shows clinical overlap with other cancer susceptibility syndromes, in particular neurofibromatosis type 1 (NF1), familial adenomatous polyposis and Lynch syndrome, and has only recently been recognized as a distinct childhood cancer susceptibility syndrome. As such, there is still a lack of knowledge on the natural history of this syndrome.

A third cancer research project, in close collaboration with the University Hospital of Gynaecology and Obstetrics, is aimed at the molecular characterization of ovarian cancer tissue by tumour-based massive parallel sequencing analyses.

Major Achievements: RNA-based assays for comprehensive characterization of mutations e.g. in the *NF1* and *PMS2* genes; substantial and ongoing contributions to the delineation of tumour spectrum and non-neoplastic features in CMMRD; lead development of clinical diagnostic criteria for the diagnosis CMMRD in a European consortium; identification of a prevalent *BRCA1* mutation in the Tyrolean Zillertal and Lower Inn valleys which impacts on cancer incidence and patient care in this region.
Future Goals: evaluation of 'atypical' splice mutations with the aim to deduce commonly applicable rules for the selection of variants likely to affect mRNA splicing for further mRNA analyses; development of strategies for the detection of mutation-induced splice alterations by NGS; delineation of the pathogenetic mechanisms, in particular secondary somatic mutations, underlying the development of neoplastic and non-neoplastic features in CMMRD patients; evaluation of clinical data on CMMRD patients in close collaboration with the European consortium and with the ultimate goal to improve the management of CMMRD patients

Genetic Skin Diseases
Hans Christian Hennies, Katja Eckl
The skin, the largest human organ, is a highly structured, multi-layered organ that is indispensable for the protection of the organism from the environment. It is particularly exposed, together with lung and gut, and prone to potentially life-threatening reactions of external agents. It exhibits not only a clearly defined morphology but is also characterized by a close interplay with the immune system, which complements structural features in the defence line against hostile intruders.

The dermatogenetics research group is especially interested in the molecular characterization of rare skin diseases. We have mainly focused on severe **disorders of keratinization**, including generalized autosomal recessive congenital ichthyoses (ARCI) and palmoplantar keratodermas. Using homozygosity mapping and high-throughput sequencing techniques, we have been analysing the mutation spectrum in ARCI, which can be caused by mutations in more than nine different genes. Using exome sequencing combined with linkage analysis, we have for the first time identified mutations in *CERS3*, the gene for ceramide synthase 3, associated with ARCI and revealed the importance of **very long acyl chain ceramides** for epidermal barrier function (Fig. 2).

A major impediment to translational research in rare skin diseases stems from the lack of suitable disease models. We have generated ***in vitro*** **full-skin models** with primary keratinocytes and fibroblasts. Skin models for congenital ichthyosis and other keratinization disorders were made using either patient cells or inactivation of single genes through RNA interference.
Availability of patient keratinocytes, however, is often very limited and their ability to proliferate is restricted to few passages; RNA interference, on the other hand, can also interfere with other, unwanted pathways. We have therefore embarked on the use of **induced pluripotent stem (iPS) cells** for skin modelling. To this end, patient fibroblasts are reprogrammed with stemness factors, and iPS cells are differentiated to the epithelial fate and further to epidermal keratinocytes (Fig. 3). These cells can be used for generating skin models, analysing specific therapeutics, and also systematic investigations of potential drugs.
Current therapy for ARCI is still mostly symptomatic, and topical application of drugs is impeded by the epidermal barrier activity and difficulties in the bioavailability over larger skin areas. We have therefore tested the efficacy of **recombinant enzyme as a drug** for topical application in ARCI using transglutaminase 1 deficient skin models. The protein was transferred into the epidermis with the help of nanotransporters, and the epidermal barrier function was indeed effectively reconstituted after repeated treatments of the ARCI skin model with enzyme/transporter formulations. Based on these results we are confident that locally substituted proteins are functional in the viable epidermis and can compensate for the defects of disease-associated genes.

Ectodermal Diseases
Johannes Zschocke, Anna Schossig, Robert Gruber
The identification and characterization of rare genetic diseases affecting skin, skin appendages, and teeth entails collaborative projects with PD Dr. Ines Kapferer, Department of Dentistry, and Prof. Dr. Matthias Schmuth, Department of Dermatology.

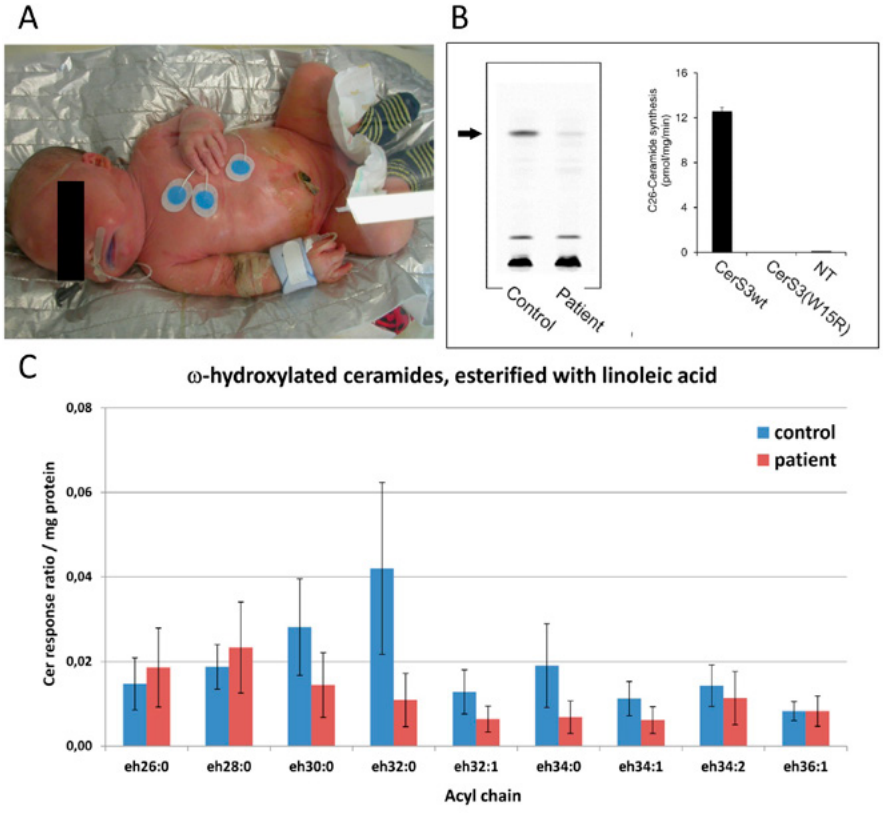

Fig. 2: Congenital ichthyosis can be caused by ceramide synthase-3 deficiency (from Eckl et al, J Invest Dermatol 2013 133: 2202–2211). A) Clinical presentation. B) Enzyme activity was largely reduced in differentiated keratinocytes from the patient. Overexpression of mutant CERS3 demonstrated almost complete loss of enzyme activity. C) Mutations in CERS3 led to loss of very long acyl chain ceramides in patient skin. Amounts of free esterified ω-hydroxylated ceramides with very long acyl chains were significantly reduced in lipid extracts from patient keratinocytes.

One of the research projects is aimed at the characterization of genetic alterations that cause aggressive periodontitis; this OeNB-funded project is led by Dr. Kapferer who has recruited a Tyrolean 4-generation family with aggressive periodontitis in conjunction with clinical features of Ehlers-Danlos syndrome (representing an entity traditionally described as EDS type VIII. Aggressive periodontitis (in contrast to chronic periodontitis) is a rare inflammatory disease leading to periodontal tissue destruction and, if untreated, tooth loss at a young age. It is caused by a perturbation of the homeostasis between the subgingival microbiota and the host defences in susceptible individuals. EDS VIII is a clinically heterogeneous disorder characterized by the combination of periodontal disease and variable connective tissue features. A limited number of patients and pedigrees with this condition have been described. The members of the Tyrolean family have been clinically and immunologically characterized, and we performed a parametric linkage analysis and exome sequencing. At present a candidate gene in the chromosomal region 12p13 is under functional investigation. In transfected cells the effect of the mutation on the immunologic function and the connective tissue structure is tested.

Additional projects include the investigation of the genetic causes of rare dental diseases such as Kohlschütter-Tönz syndrome, a rare genetic disorder with amelogenesis imperfecta and epilepsy, and radicular dentin dysplasia, characterized by abnormal dentin formation and early tooth loss due to abnormal development of tooth roots. Parametric linkage analysis in adequate families is followed by exome sequencing and functional characterization of candidate mutations.

Identification and characterization of inherited skin disorders is the research focus in the collaboration with the Department of Dermatology, with special attention on inherited disorders of keratinization. In a regular dermatology-genetics clinic, patients with rare inherited skin conditions receive comprehensive clinical care and diagnostic work-up involving, where appropriate, an NGS multi gene panel analysis developed in our institute, covering genetic disorders of keratinization and a selection of connective tissue disorders. Patients with specific phenotypes of unclear, presumably genetic cause are offered further evaluation by linkage analysis (where appropriate) and exome sequencing as well as functional studies.

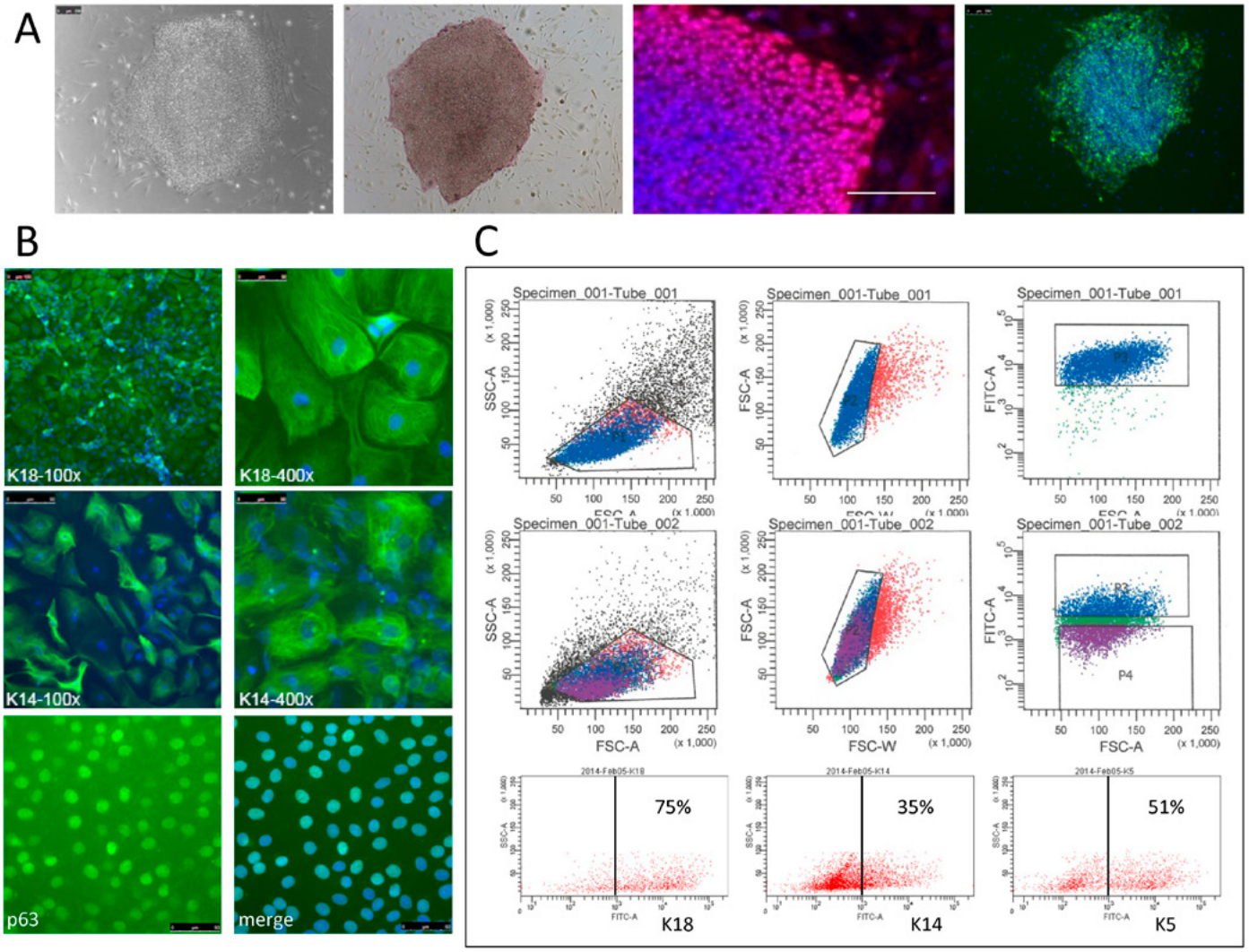

Fig. 3: Generation of epidermal keratinocytes by differentiation of induced pluripotent stem cells. A) Pluripotent stem cells were obtained by reprogramming of fibroblasts as shown by typical morphology, activity of alkaline phosphatase, and staining signals for Oct4 and Tra1-81 (left to right). B) Differentiation of induced pluripotent stem cells to the ectodermal fate showed synthesis of epithelial marker keratin 18, epidermal marker keratin 14, and ectodermal gatekeeper p63. C) Primary (first row) and iPS-derived keratinocytes were positive for epithelial markers CD104 (first and second row) and keratins 18, 14, and 5 (third row) in FACS analysis..

Selected Publications

Mutation or knock-down of 17beta-hydroxysteroid dehydrogenase type 10 cause loss of MRPP1 and impaired processing of mitochondrial heavy strand transcripts. Deutschmann AJ, Amberger A, Zavadil C, Steinbeisser H, Mayr JA, Feichtinger RG, Oerum S, Yue WW, Zschocke J.
HUM MOL GENET. 2014, 23:3618–3628.

Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, Gerdes AM, Goldberg Y, Ilencikova D, Muleris M, Duval A, Lavoine N, Ruiz-Ponte C, Slavc I, Burkhardt B, Brugieres L.
J MED GENET. 2014, 51:355–65.

Impaired ceramide synthesis causes autosomal recessive congenital ichthyosis and reveals the importance of ceramide acyl chain length for epidermal terminal differentiation. Eckl KM, Tidhar R, Thiele H, Oji V, Hausser I, Brodesser S, Preil ML, Önal-Akan A, Stock F, Becker K, Casper R, Nürnberg G, Altmüller J, Nürnberg P, Traupe H, Futerman AH, Hennies HC.
J INVEST DERMATOL. 2013, 133:2202–2211.

Increased cutaneous absorption reflects impaired barrier function of reconstructed skin models mimicking keratinisation disorders. Eckl KM, Weindl G, Ackermann K, Küchler S, Casper R, Radowski MR, Haag R, Hennies HC*, Schäfer-Korting M.
EXP DERMATOL. 2014, 23:286–288.

Kohlschütter-Tönz Syndrome: Mutations in ROGDI and Evidence of Genetic Heterogeneity. Tucci A, Kara E, Schossig A, Wolf NI, Plagnol V, Fawcett K, Paisan-Ruiz C, Moore M, Hernandez D, Musumeci S, Tennison M, Hennekam R, Palmeri S, Malandrini A, Raskin S, Donnai D, Hennig C, Tzschach A, Hordijk R, Bast T, Wimmer K, Lo CN, Shorvon S, Mefford H, Eichler EE, Hall R, Hayes I, Hardy J, Singleton A, Zschocke J, Houlden H.
HUMAN MUTATION. 2013, 34(2); 296–300.

Selected Funding

- Genetische und funktionelle Studien der molekularen Basis der aggressiven Parodontitis, OeNB, Ines Kapferer-Seebacher, Anna Schossig
- Mitochondriale RNA-Prozessierung bei der HSD10-Krankheit und anderen primären Mitochondriopathien, Stiftung Propter Homines,Johannes Zschocke
- Unravelling orphan diseases: High-throughput genomics for rare skin diseases; OeNB; Hans Christian Hennies.
- Topical application of proteins as a new therapy option for the treatment of severe, genetic skin diseases; DFG/FWF; Hans Christian Hennies.
- In vitro and *in vivo* models of congenital rare skin diseases for molecular characterization and drug screening; ERA Net/E-Rare; Hans Christian Hennies.
- 3D melanocyte skin models; Max Planck Minerva Programme; Katja Eckl.
- Skin models for genodermatoses; FFG; Katja Eckl.

Collaborations

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- William Newman, Centre for Genomic Medicine, University of Manchester, UK
- Johannes Mayr, SALK, Austria
- Ute Moog, Institute of Human Genetics, Medical Center Heidelberg, Germany
- Agnès Bloch-Zupan, Faculty of Oral Medicine, University of Strasbourg
- Ludwine Messiaen, University of Alabama at Birmingham, Birmingham, AL, USA
- Christian Kratz, Department of Pediatric Hematology & Oncology, Hannover Medical School, Hannover, Germany
- Multiple Members of the European Consortium Care for CMMRD (C4CMMRD)
- Tony Futerman, Weizmann Institute of Science, Rehovot, Israel
- Sarah Hedtrich, Freie Universität, Berlin, Germany
- Peter Nürnberg, Universität zu Köln, Köln, Germany
- Eli Sprecher, Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv, Israel

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Keywords

Pharmacology, immunology, biochemistry, molecular biology, biophysics, physiology, structural biology, developmental biology, phylogeny

Research Focus

- The Grabner lab focusses on structural-functional studies of multiple components of the skeletal muscle excitation-contraction (EC) coupling machinery, using zebrafish and mouse as model organisms. Another focus of the Grabner lab is the role of the Ca^{2+}-activated Cl^- channel in skeletal muscle EC coupling.
- Sandra Santos-Sierra: Pharmacological modulation of the innate immune response: Our research interests center on understanding the human innate immune response in inflammatory diseases, in particular phagocytes activity and signaling processes therein involved. Based on this knowledge we intend to develop novel substances that may be specifically applied in the modulation of the immune activity (stimulation or down-regulation).

General Facts

Until his emeritation in 2009, Hartmut Glossmann was director of the Division of Biochemical Pharmacology. In October 2009, Hans-Günther Knaus was appointed interim director.
The Division of Biochemical Pharmacology is substructured into two largely independent research groups, headed by Sandra Santos-Sierra and Manfred Grabner.

Research

Manfred Grabner
The basic mechanism of skeletal muscle contraction is the release of Ca^{2+} from SR stores. Two distinct Ca^{2+} channels, the voltage-gated L-type Ca^{2+} channel or dihydropyridine receptor (DHPR) of the surface membrane and the intracellular Ca^{2+} release channel or ryanodine receptor (RyR1) of the SR, play together in this complex process called excitation-contraction (EC) coupling (see Fig. 1). Our research focus is to reveal the structure-function relationship of this fascinating Ca^{2+} channel crosstalk in skeletal muscle. We succeeded to fine map domains in the DHPR α_{1S} and β_{1a} subunit that are crucial for this protein-protein signal transduction. Besides structure-functional domain mapping, our research is devoted to investigate the role of the Ca^{2+} current through the skeletal muscle DHPR (Fig. 1), which is – in contrast to cardiac EC coupling – not (directly) involved in skeletal muscle EC coupling. To this aim (supported by FWF grant P23229-B09) we created a k.i. mouse model that lacks this enigmatic DHPR inward current. Extensive *in vivo*, *ex vivo* and *in vitro* experiments identified this mysterious Ca^{2+} influx as vestigial (paper in preparation). For the DHPR - RyR1 protein-protein interaction in skeletal muscle, precise membrane targeting is indispensable. It is required that four DHPRs congregate in a square formation opposite the four homo-domains of the RyR1; a constellation known as skeletal muscle tetrad.

Recent Major Achievements:
We investigated the role of the essential DHPR β_{1a} subunit for DHPR voltage sensing. In vitro expression of β_{1a}/β_3 chimeras in β_1-null zebrafish relaxed myotubes revealed a pivotal role of the Src homology 3 (SH3) domain and the C terminus of β_{1a} in charge movement restoration. Furthermore, substitution of a P by A in the putative SH3-binding polyproline motif in the proximal C terminus of β_{1a} (also of the cardiac/neuronal β_{2a} and β_4) fully obstructed α_{1S} charge movement. Consequently, we postulate a model according to which β subunits, probably via the SH3-C-terminal polyproline interaction, adapt a discrete conformation required to modify the α_{1S} conformation apt for voltage sensing in skeletal muscle (Fig. 2).
Future Goals: In our new FWF grant (P27392-B21) we want to explore molecular

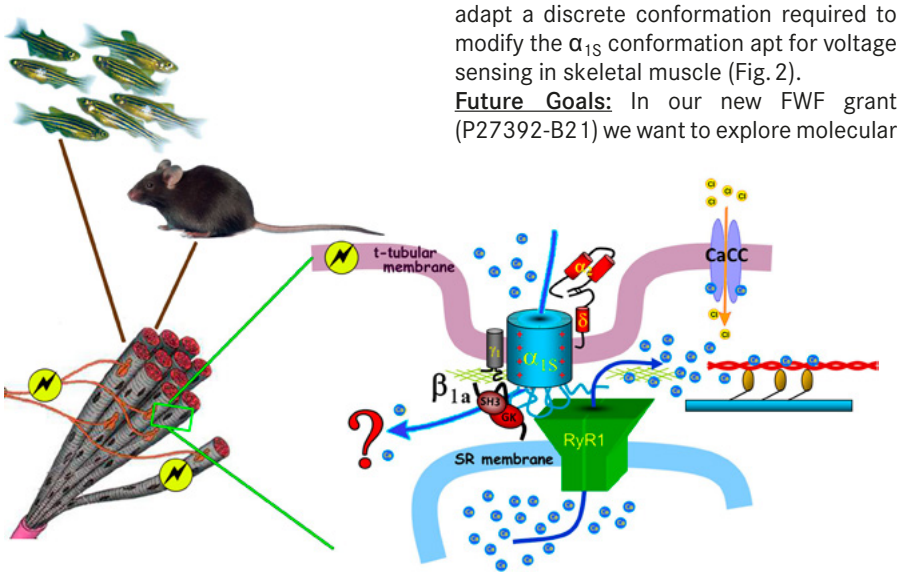

Fig. 1: Sketch of the skeletal muscle EC coupling machinery depicting the main focus of our research. Using zebrafish and mouse model organisms we are trying to unravel the structure-function relationship of different components (viz. DHPRα1S, β1a, CaCC, etc.) of the skeletal muscle EC coupling machinery. This additional in-depth comprehension can serve as the starting point for the development of a new generation of ion channel drugs with enhanced selectivity.

regions of the DHPR β_{1a} subunit, essential for DHPR tetrad formation. In addition, our research also focuses on the role of the Ca^{2+}-activated Cl^- channel (CaCC; Fig. 1) in zebrafish skeletal muscle which is activated during EC coupling (MCBO, FWF W1101-B12). CaCC currents might play a role in shaping the muscle action potential.

Pharmacological Modulation of the Innate Immune Response

Sandra Santos-Sierra

The innate immune system plays a crucial role not only in fighting infections, but also in numerous diseases and pathological conditions including cancer. Toll-like receptors (TLRs) are main components of this system. They recognize pathogens via ligation of pathogen associated molecular patterns (PAMPS), likewise they bind some host derived ligands resulting from tissue damage (DAMPS). Thus, the central role of TLRs in various inflammatory processes and in sepsis is well recognized. For this reason, the discovery of substances with modulatory activity on TLR signaling may have important implications in the therapy of a broad spectrum of pathologies linked to inflammation.

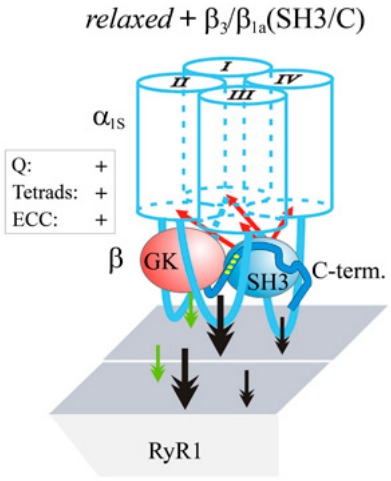

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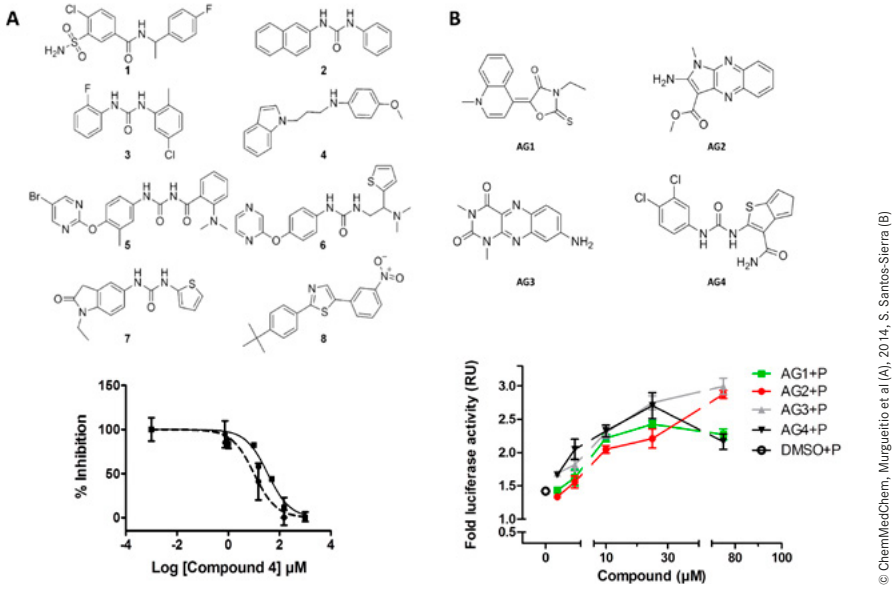
Fig. 2: Model of β-induced restoration of EC coupling parameters. Substitution of the β3 SH3 domain together with the C-terminus by corresponding β1a sequence leads to full restoration of β-induced charge movement and thus proper EC coupling. According to our model the β1a SH3 domain and C-terminus (blue) bind intra-molecularly via the SH3-PXXP interaction (yellow dots) to adapt the accurate β conformation which in turn strongly induces (thick red arrows) the correct, fully functional conformation of the DHPRα1S core region (4 cylinders), and thus restoring all parameters of skeletal muscle EC coupling (modified from Dayal et al, 2013, PNAS).



© ChemMedChem, Murgueitio et al (A), 2014, S. Santos-Sierra (B)

Fig. 3: A. Small-molecules TLR2 antagonists. The inhibitory concentration lies in the low micromolar range and it was determined as the inhibition in TNFα production by human monocytes after TLR2 stimulation. B. Small-molecules TLR2 agonists. The compounds synergize with known TLR2 ligands (as shown in luciferase experiments) pointing to a possible allosteric binding site in the receptor.

Toll-like receptor 2 (TLR2) recognizes bacterial di- and tri-acylated lipopeptides and also some host endogenous ligands released after tissue damage (e.g. HMGB1, hyaluronan). However, up to date there has been a lack of synthetic TLR2 modulators. We have developed several compounds, small-molecules, which are bona fide TLR2 ligands. These were retrieved from a combined in silico/*in vitro* screening for their potential to bind TLR2 in HEK293 cells overexpressing the receptor and bearing an NFκB-dependent reporter construct.

Two groups of compounds were selected and their mechanism of action is under characterization: First, TLR2-antagonists which bind the TLR2/1 and TLR2/6 heterodimers at the lipopeptide ligand (Pam3CSK4) binding site, as indicated by molecular modeling (Fig. 3 A); Second, TLR2-agonists whose binding mode is structurally not defined yet, as these compounds have synergistic activity with other TLR2 ligands (Fig. 3 B). The activity of the different compounds in mouse and human immune cells has been tested and proof of their *in vivo* activity is under way.

In order to modulate TLR activity, small-molecules show better properties than natural TLR2 ligands (e.g. their synthesis is cheaper and they can be purified to clinical grade). Consequently, the novel TLR2-antagonists may be applied in pathologies where TLR2 over activation leads to an increased inflammatory response and on the other hand, TLR2-agonists may be used in adjuvanticity in those settings in which the immune system shows unresponsiveness.

Selected Publications

Domain cooperativity in the β1a subunit is essential for dihydropyridine receptor voltage sensing in skeletal muscle.
Dayal A, Bhat V, Franzini-Armstrong C, Grabner M.
PROC NATL ACAD SCI USA. 2013, 110(18):7488–7493.

Prospective virtual screening in a sparse data scenario: design of small-molecule TLR2 antagonists.
Murgueitio MS, Henneke P, Glossmann H, Santos-Sierra S* and Wolber G*.
ChemMedChem. 2014 Apr;9(4):813–22.

Selected Funding

- Structure-function link in the DHPR β1a subunit for tetrad formation and skeletal muscle motility (P27392-B21); FWF, Manfred Grabner / Coapplicant, Dr. Anamika Dayal
- Molecular Cell Biology and Oncology (W1101-B12); FWF, Manfred Grabner.
- Else Kroner Fresenius Stiftung, Sandra Sierra-Santos

Collaborations

- Clara Franzini-Armstrong, Department of Cell and Developmental Biology, University of Pennsylvania, Philadelphia, U.S.A.
- Francesco Zorzato, Dipartimento di Scienze Della Vita e Biotecnologie, Universitá Ferrara, Ferrara, Italy
- Werner Melzer, Institut für Angewandte Physiologie, Universität Ulm, Ulm, Germany
- Paul D. Allen, Molecular Biosciences, University of California at Davis, U.S.A.
- Isaac Pessah, College of Biological Sciences, University of California at Davis, U.S.A.
- Roger Bannister, School of Medicine, Division of Cardiology, University of Colorado, U.S.A.
- G. Wolber, Institute of Pharmacy, Free University of Berlin, Germany.
- P. Henneke, Center for Chronic Immunodeficiency, University Medical Center Freiburg, Germany.
- J. Kirchmair, Center for Bioinformatics, University of Hamburg, Germany.
- K. Liedl and J. Fuchs, Faculty of Chemistry and Pharmacy, Leopold-Franzens-University Innsbruck, Austria.
- F Lagler, Paracelsus Medical University Salzburg, Austria.

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Keywords

Ion channels, protein biochemistry, antibodies, proteomics, immunoprecipitation

Research Focus

Our research unit focusses on certain key aspects of voltage- and ligand-gated ion channels. We are interested in the subunit composition of several ion channel families as well as their cellular and subcellular distribution. In addition, our research aims to identify the respective ion channel nanodomains through immunoprecipitation experiments as well as through high-sensitivity sequencing by mass spectrometry.

General Facts

Our research unit is quite small in terms of associated personnel, resources and associated lab space. We reside on the ground level of the Pharmacology/Genetics building in Peter-Mayr Strasse 1 in approx. 110m^2 of lab- and office space. We have access to a single animal holding room (mice) which is shared with the scientists of the Division for Biochemical Pharmacology. The majority of equipment and facilities is shared with other Pharmacology units (Division for Biochemical Pharmacology or the Institute of Pharmacology). Our unit employs a total of 6 people. Besides the division head and a part-time administrator, 2 research assistants and an animal care keeper are staff members. The PhD student is employed through a PhD program. Both research assistants and the division head are MDs and also have clinical duties, especially related to the institutional ethics committee.

Research

Our lab is primarily interested in investigating the composition, microenvironment and distribution of various ion channels, in particular several classes of potassium and TRPV channels. All these channels appear to associate with other molecular components in complexes, so-called 'microdomains'. We aim to establish the composition of these ion channel complexes by use of various detergent solubilization protocols, immunoprecipitation experiments and sequencing of isolated ion channel complexes through mass spectrometry.

Composition of the TRPV1 Microdomain in the Peripheral Nervous System.
Hans-Günther Knaus

The Transient Receptor Potential Vanilloid 1 (TRPV1, vanilloid receptor 1) ion channel plays a key role in the perception of thermal and inflammatory pain. Its molecular environment in dorsal root ganglia (DRG) has however been largely unexplored. The channel complex from mouse DRG was detergent-solubilized, isolated by immunoprecipitation using a panel of sequence-directed antibodies against the TRPV1 protein and mouse DRG membranes, and subsequently analyzed by mass spectrometry. A number of potential TRPV1 interaction partners were identified, amongst them cytoskeletal proteins, signal transduction molecules, and established ion channel subunits. Based on stringent specificity criteria, the voltage-gated K^+ channel beta 2 subunit (Kvβ2), an accessory subunit of voltage-gated K^+ channels, was identified as being associated with native TRPV1 channels. Reverse co-immunoprecipitation and antibody co-staining experiments confirmed the TRPV1/Kvβ2 association. Patch-clamp experiments in the presence of Kvβ2 resulted in a significant increase of capsaicin-induced outward currents. Biotinylation assays demonstrated that Kvβ2 increased the cell surface expression levels of TRPV1, which supports the electrophysiological data. This project demonstrated the association of a Kvβ subunit with the TRPV1 channel, and indicated that such interaction plays a role in the trafficking of TRPV1 to the plasma membrane.

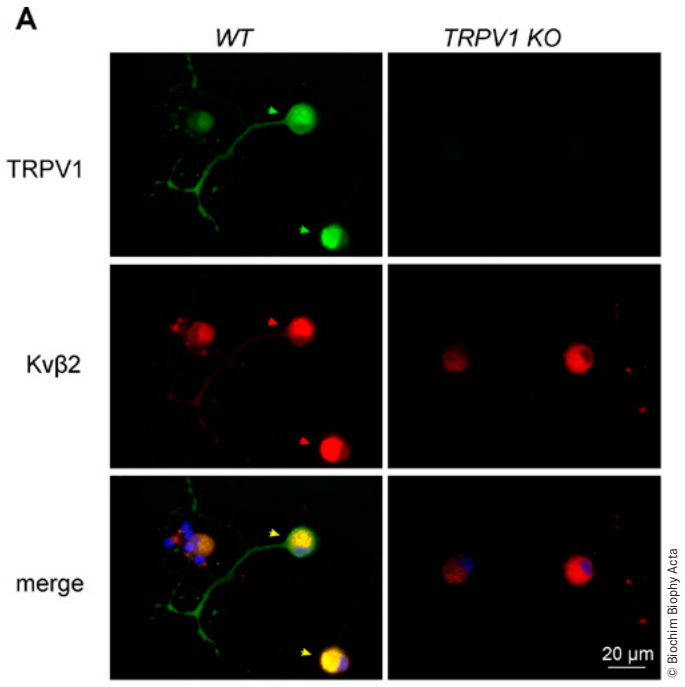

Fig. 1: TRPV1 and Kvβ2 co-expression in sensory neurons: immunostaining of dissociated wildtype (left panels) and TRPV1-/- (right panels) sensory neurons with anti-TRPV1 and Kvβ2 antibodies.

Identification of Potential Novel Interaction Partners of the Sodium-Activated Potassium Channels Slick and Slack in Mouse Brain and their Respective Distribution.
Hans-Günther Knaus

For this research we used a combined approach of (co)-immunoprecipitation studies, Western blot analysis, double immunofluorescence and mass spectrometric sequencing and immunohistochemical distribution studies, in order to investigate protein-protein interactions of the Slick and Slack channels and their respective distribution profiles. We found that Slick and Slack channels co-assemble into the same cellular complex. Double immunofluorescence experiments revealed that Slick and Slack channels co-localize in distinct mouse brain regions. Moreover, we identified the small cytoplasmic protein beta-synuclein and the transmembrane protein 263 (TMEM 263) as novel interaction partners of both, native Slick and Slack channels. In addition, the inactive dipeptidyl-peptidase (DPP 10) and the synapse associated protein 02 (SAP 102) were identified as constituents of the native Slick channel complex in the mouse brain. We were also able to establish the immunohistochmical distribution profiles for Slick and Slack channels in mouse brain sections. In some brain regions, these two potassium channel isoforms are clearly segregated, while in other regions they show significant coexpression, at least at the light microscopical level.

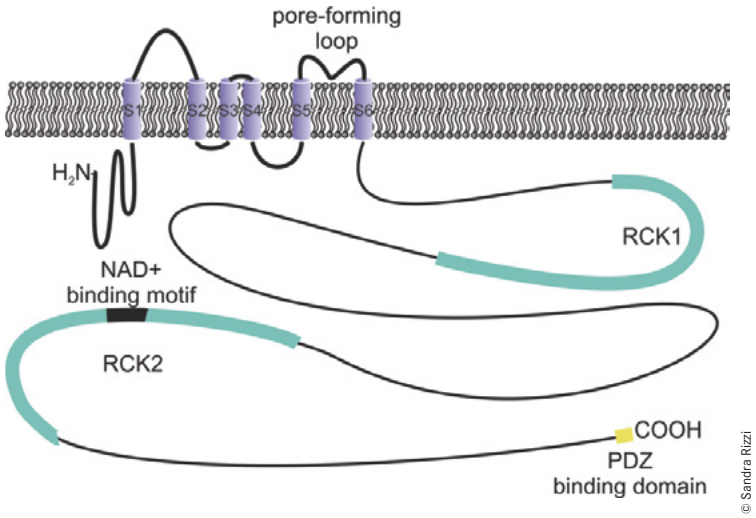

Fig. 2: Model of the transmembrane topology of a Slick / Slack channel.

Major Achievements:
Complete panels of sequence-directed antibodies against a large number of different ion channel families were characterized. By use of these antibodies, the microdomain environments of some of these ion channels were established.
Future Goal: To characterize some of these novel interaction partners in terms of their precise function in the respective ion channel complex.

Pharmacoeconomics: Austrian Drug Prescription Report
Georg Wietzorrek

Data from all prescriptions filled in Austrian pharmacies on public expense by outpatients (2006–2014) from the Federation of Austrian Social Insurance Institutions (Hauptverband der Sozialversicherungsträger) are being analysed for optimization/savings potential, prescription of generics, demands for regulations and further aspects.
Achievements: The results together with a thorough interpretation and a discussion of the pharmacology (including risk-benefit evaluations) of the prescribed substances were provided to the Hauptverband as a scientific basis for further decision-making.
Future Goal: The Austrian Drug Prescription Report will be published as a textbook.

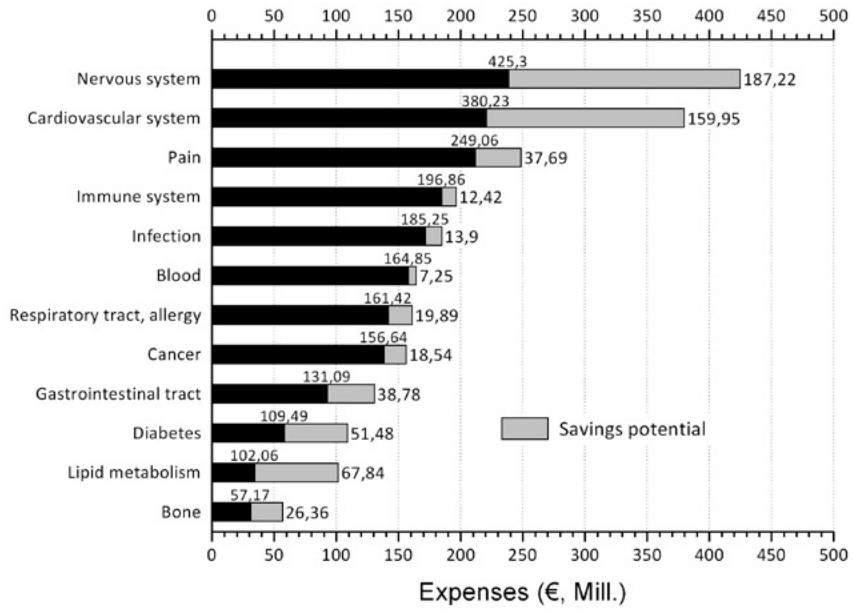

Fig. 3: Public expenses on drugs and calculated savings potential by indications, 2012.

Selected Publications

Subcellular expression and neuroprotective effects of SK channels in human dopaminergic neurons.
Dolga AM, de Andrade A, Meissner L, Knaus HG, Höllerhage M, Christophersen P, Zischka H, Plesnila N, Höglinger GU, Culmsee C.
Cell Death Dis. 2014 Jan 16;5:e999.

Identification of voltage-gated K(+) channel beta 2 (Kvβ2) subunit as a novel interaction partner of the pain transducer Transient Receptor Potential Vanilloid 1 channel (TRPV1).
Bavassano C, Marvaldi L, Langeslag M, Sarg B, Lindner H, Klimaschewski L, Kress M, Ferrer-Montiel A, Knaus HG.
Biochim Biophys Acta. 2013: p. 3166–75.

Palmitoylation of the β4-subunit regulates surface expression of large conductance calcium-activated potassium channel splice variants.
Chen L, Bi D, Tian L, McClafferty H, Steeb F, Ruth P, Knaus HG, Shipston MJ.
J Biol Chem. 2013; S.13136–44.

Direct association of the reticulon protein RTN1A with the ryanodine receptor 2 in neurons.
Kaya L, Meissner B, Riedl MC, Muik M, Schwarzer C, Ferraguti F, Sarg B, Lindner H, Schweigreiter R, Knaus HG, Romanin C, Bandtlow CE.
Biochim Biophys Acta. 2013; p. 1421–33.

Selected Funding

PhD program SPIN B05, ZFW12060-05, Austrian Research Foundation FWF

Collaborations

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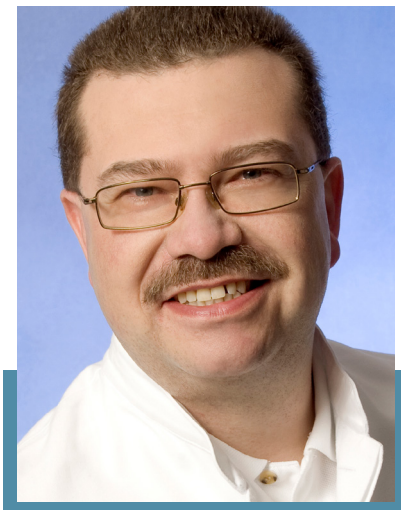
Bernd Fakler, Physiology II, Freiburg, Germany

Clinical and Functional Anatomy



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Keywords

Clinical anatomy, functional anatomy, ultrasonography, phlebology/lymphology, medical education, inner ear

Research Focus

- Clinical and Functional Anatomy in collaboration with several clinical departments (e.g. Traumatology, Visceral Surgery, Plastic and Reconstructive Surgery, Radiology, etc.)
- Developmental Anatomy of the male urinary tract
- Developmental Anatomy of inner ear
- Ultrasound guided blockades of plexus and peripheral nerves

General Facts

Mors Auxilium Vitae – Death Aids Life.
This saying, mounted on a door of the department, aptly characterizes the basic conceptual design and objectives of our group. This means that anatomy is not considered a discipline decoupled from daily medical practice, but the whole Division's activity is focused on the welfare and health of people. The Division therefore sees its main role in the development, exchange and implementation of clinical and clinically applied anatomy used in research and teaching as a basic science with indirect and direct benefits for patients.
The Division of Clinical and Functional Anatomy is staffed by eleven scientific and ten administrative members.
The Division operates laboratory facilities for histology and immunohistology, an ultrasound laboratory, and an extensive body donation program, both for educational and scientific purposes.
The Division contributes much to the preclinical training of future medical practitioners. The broad spectrum of learning activities includes lectures as well as practical exercises. Therefore, also some scientific efforts deal with medical education and the body donation program. Further educational activities include regular courses for the continuing medical education of different medical disciplines. Among these, there are workshops and surgical courses organised in cooperation with the corresponding clinics of the Medical University of Innsbruck and also with international organizations and societies.

Research

The research at the Division of Clinical and Functional Anatomy is grouped around several main topics: development, ultrasound, inner ear, clinical and applied anatomy and medical anatomy education.

Human Development

The main focus within this research topic is the analysis of humans, whereas most developmental research is conducted using species such as rodents, birds or fish. We contributed to the development of the utero-vaginal anlagen, where we could

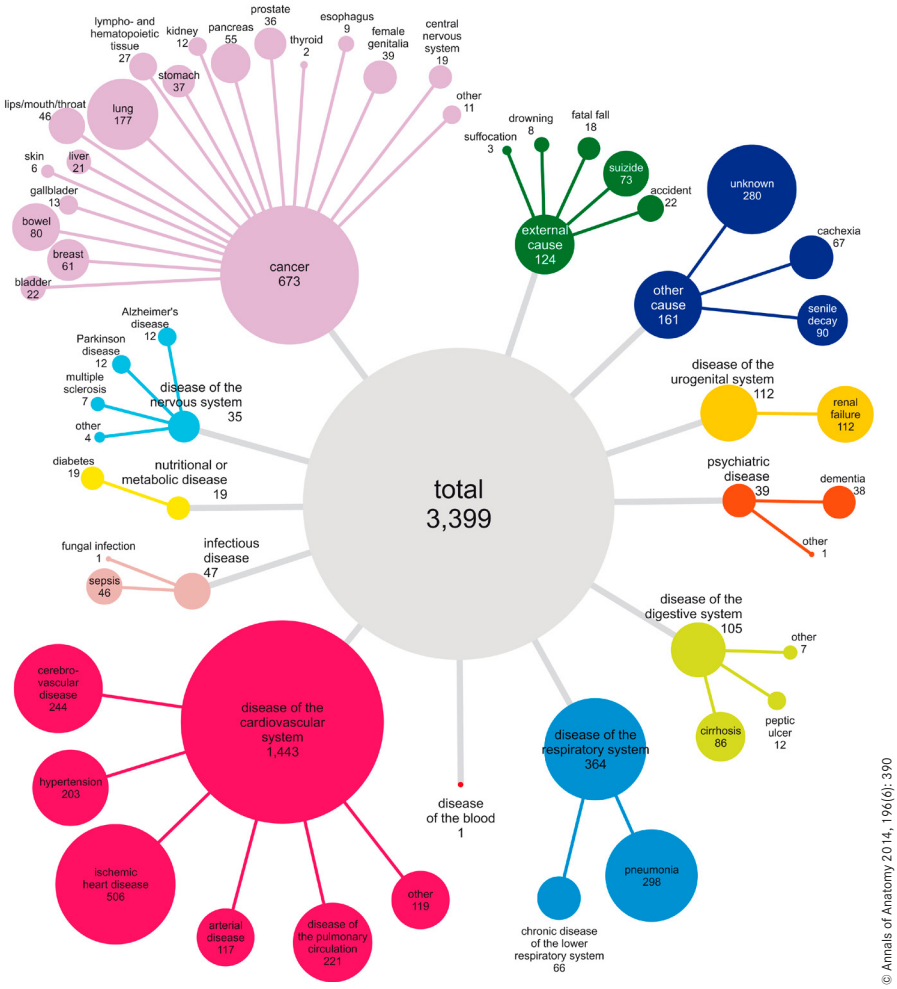

Fig. 1: Causes-of-death data from body donors. The data list the prevailing fatal diseases and external circumstances of the last 25 years (1988–2013) as stated in the death certificates of body donors forwarded to us. The area of each circle is proportional to the absolute number of deaths.

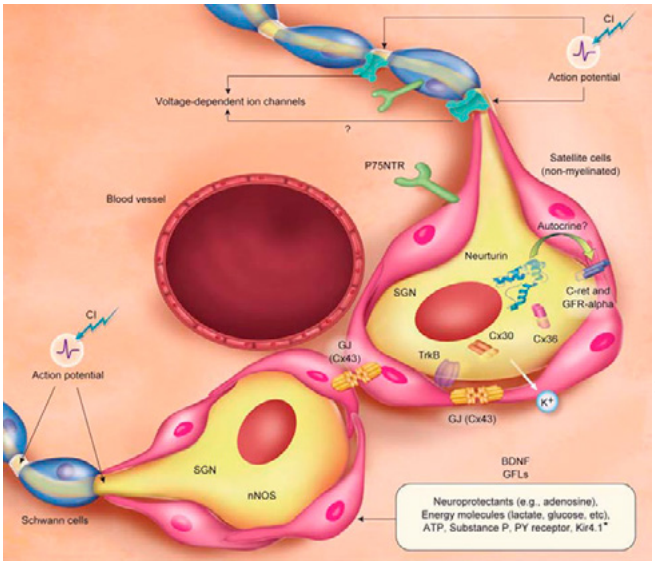

Fig. 2: Graphic illustration of two human mono-polar or "amputated" SG cells with surrounding SGCs (red) together with results from immunohistochemistry (TrkB, tyrosine kinase B receptor; BDNF, brain-derived neurotrophic factor; nNOS, nitric-oxide synthase; GFL, GDNF family ligand; C-ret, GFL receptor; GFRalpha, GDNF family receptor alpha; NTRN, neurturin; hSGNs, human spiral ganglion cells; SGCs, satellite glial cells; GDNF, glial-cellline-derived neurotrophic factor; Cx30, connexin 30; Cx36, connexin 36; P75NTR, P75 neurotrophin receptor).

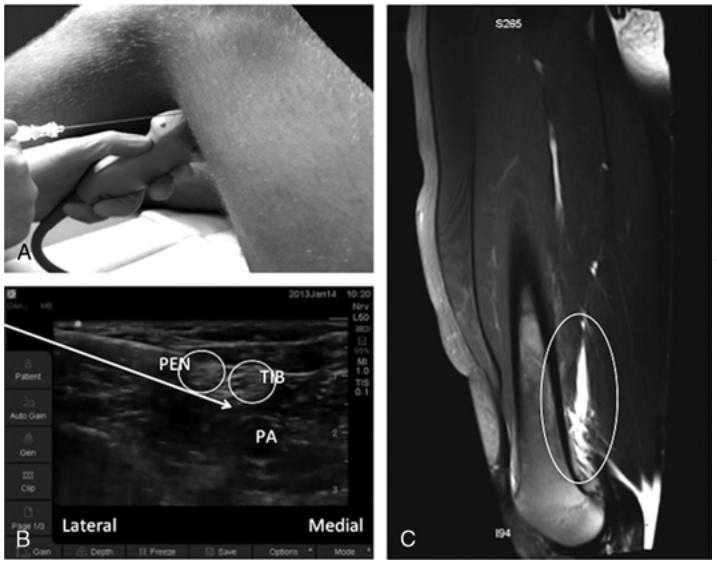

Fig. 3: The popliteal-sciatic block. Model photograph. Scanning of the popliteal fossa (A). The popliteal artery (PA) is seen in the cross-sectional view (B). The tibial nerve (TIB) is localized between the PA and the skin (B). The TIB is then followed by sliding the transducer cephalad until the common peroneal nerve (PEN) merges with the TIB. At this point of the sciatic nerve (SCN) bifurcation, the needle is inserted at a very shallow angle to the transducer from the lateral side of the thigh and advanced in-plane in a lateral-to-medial direction with the end point between the 2 nerves (AB). Magnetic resonance (MR) imaging in the sagittal plane depicts the distribution of the injectate in and above the popliteal fossa spreading both cephalad and caudad to surround the SCN.

show that the epithelial differentiation follows a cephalad direction. In the hindgut, we demonstrated that the expression pattern of distinct HOX genes differs markedly between animal models. The urethral development was analysed with special emphasis on gender-differences. Thus, we could demonstrate a significantly closer bladder outlet in male foetuses compared to females, suggesting that the development of the male inner genitals requires a cellular stimulus by the urogenital sinus epithelium, and we could show that during the development of the female urogenital system the primary incidence is the formation of the urethra. This is followed by the establishment of the vagina, which clearly depends on the proper differentiation of the urogenital system/urethra.

Ultrasound

The primary focus of this line of research is to develop novel ultrasound-guided clinical techniques, such as the block of the superior cervical ganglion, the assessment of different tissues by means of sonoelastography and the comparison of different blocks for regional anaesthesia.

Inner Ear

Research on this topic is performed in close collaboration with Anneliese Schrott-Fischer and Rudolf Glückert from the ENT Department. Together, we investigated the possibility of using silica nanoparticles as vectors for drugs and genes. Furthermore, we found that sepsis leads to significant hearing impairment. This physiological alteration was linked to apoptosis in the supporting cells of the organ of Corti and to a disturbance of the synapses of the inner hair cells.

Clinical and Applied Anatomy

Research in clinical and applied anatomy is mainly driven by questions received from collaborating clinicians.
Therefore, this topic is widespread and covers sub-topics such as the scaphoid bone, the posterolateral corner of the knee, intraoperative pelvic neuromonitoring and the detailed mapping of the nasal muscles.

Medical Education

This topic comprises more general aspects, such as an analysis of the philosophy and ethics of anatomy teaching, but also more specifically, the development of a coloproctological skills laboratory or improving courses in regional anaesthesia.

Selected Publications

Anatomical-coloproctological skills lab.
Aigner F, Resch T, Oberhuber R, Kronberger I, Hoermann R, Fritsch H, Pratschke J, Oberwalder M.
EUROPEAN SURGERY. 2014; 46: p. 21–24.

Development of an Innovative 3D Cell Culture System to Study Tumour – Stroma Interactions in Non-Small Cell Lung Cancer Cells.
Amann A, Zwierzina M, Gamerith G, Bitsche M, Huber JM, Vogel GF, Blumer M, Koeck S, Pechriggl EJ, Kelm JM, Hilbe W, Zwierzina H. PLOS ONE. 2014; 9: p. e92511.

Ultrasound-Guided Single-Penetration Dual-Injection Block for Leg and Foot Surgery A Prospective, Randomized, Double-blind Study.
Borglum J, Johansen K, Christensen MD, Lenz K, Bendtsen TF, Tanggaard K, Christensen AF, Moriggl B, Jensen K. REGIONAL ANESTHESIA AND PAIN MEDICINE. 2014; 39: p. 18–25.

Histomorphometric Evaluation of Ischemia-Reperfusion Injury and the Effect of Preservation Solutions Histidine-Tryptophan-Ketoglutarate and University of Wisconsin in Limb Transplantation.
Hautz T, Hickethier T, Blumer MJF, Bitsche M, Grahammer J, Hermann M, Zelger B, Messner F, Pechriggl EJ, Krapf C, Kimelman M, Brandacher G, Lee WPA, Margreiter R, Pratschke J, Schneeberger S.
TRANSPLANTATION. 2014; 98: p. 713–720.

A New Nasopharyngeal Dynamic Reference Frame Improves Accuracy in Navigated Skull Base Targets.
Kral F, DiFranco M, Puschban J, Hoermann R, Riechelmann H, Freysinger W.
SURGICAL INNOVATION. 2014; 21: p. 283–289.

Neuroanatomy

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Keywords

Cellular neuroscience, peripheral axonal regeneration, glioma, fluorescence imaging, comparative neuroanatomy

Research Focus

- Axotomy-induced plasticity in peripheral neurons
- Receptor tyrosine kinase trafficking in axonal regeneration and glial proliferation

Aims:
Interference with receptor tyrosine kinase trafficking and signalling
- to promote neurite outgrowth and axonal regeneration
- to inhibit glioma proliferation and tumour growth

The Fibroblast Growth Factor Receptor (FGFR1) and regulators of ERK signalling such as Sprouty proteins are in the focus of our studies.

General Facts

The Division of Neuroanatomy at the Medical University of Innsbruck offers lectures and seminars in functional as well as comparative Neuroanatomy for MD and PhD students. Our research is focused on the morphological consequences of growth

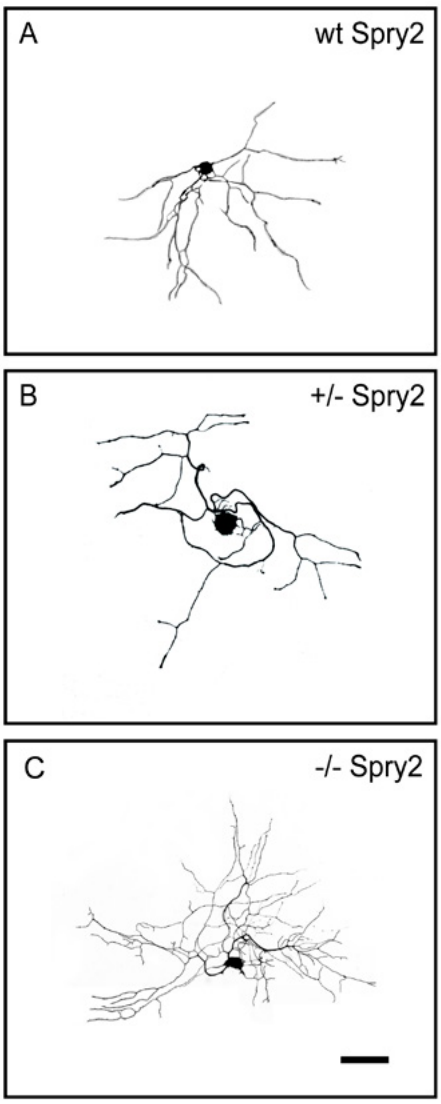

Fig. 2: Sprouty2 deficient sensory neurons in culture reveal different axon outgrowth patterns.

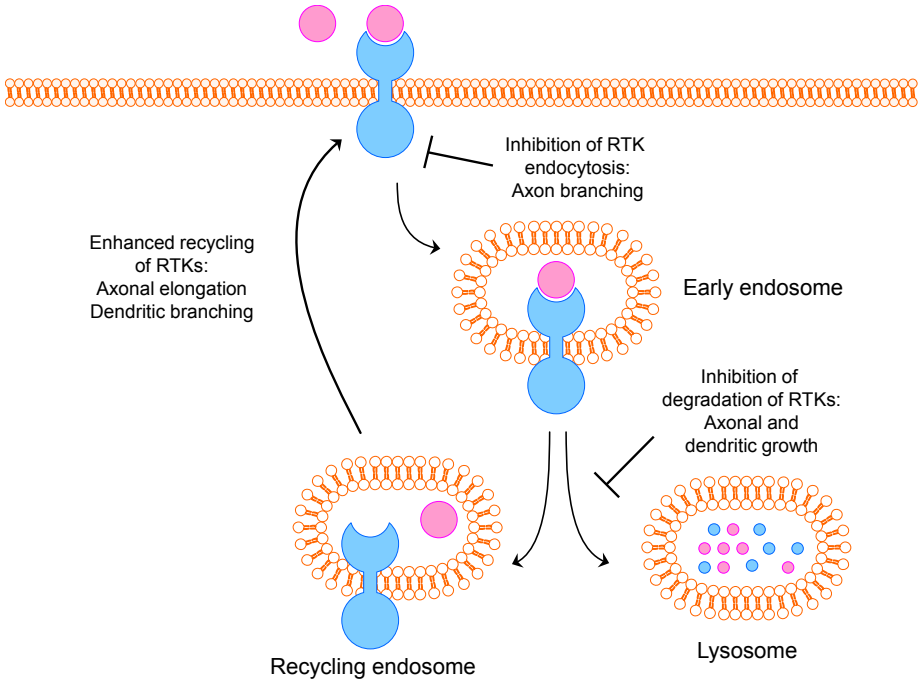

Fig. 1: Trafficking of RTKs in neurons.

factor signalling and receptor tyrosine kinase trafficking. Applying mainly cellular methods combined with high-resolution imaging, we are studying fundamental neurobiological phenomena such as axon outgrowth and glial proliferation.

Research

Peripheral Axon Outgrowth and Nerve Regeneration

In recent years the cellular basis for insufficient or incorrect axonal regeneration and the consequent lack of functional recovery has been unravelled in various laboratories. Neurotrophic factors such as the neurotrophins and the FGFs are crucially involved in stimulating neurite outgrowth

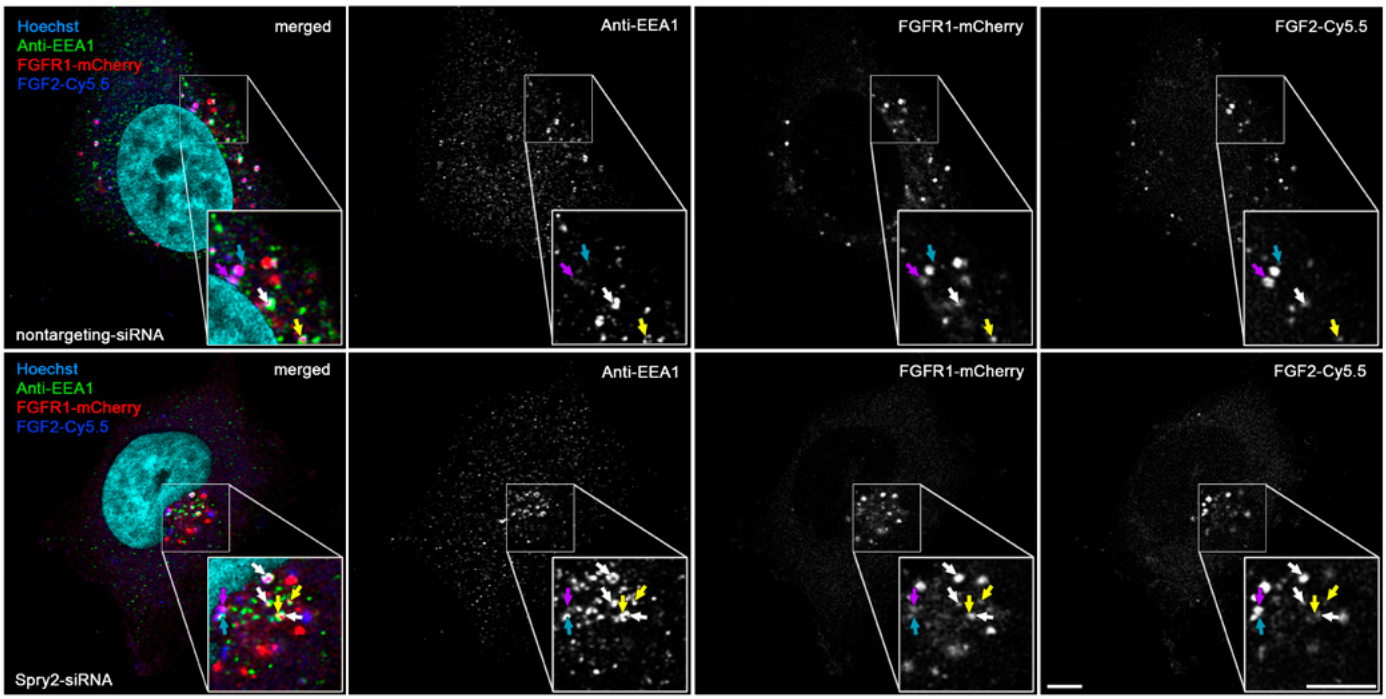

Fig. 3: Multicolor labeling of human glioma cells. U373 cells treated with nontargeting or Spry2-siRNA are shown 3 days after transfection. Early endosomes contain higher amounts of FGFR1 and its ligand FGF-2 in glioma cells with reduced Spry2 levels.

and re-myelination after nerve injury. Ongoing research in many laboratories focusses on three different aspects:

1. The molecular mechanisms of neuronal survival in response to a lesion,
2. the modification of neuronal gene expression patterns required for axonal regeneration and
3. the changes in the axonal environment, particularly within the distal part of the lesioned nerve.

Our laboratory is interested in the elucidation of the intrinsic mechanisms of neuronal survival, neurite outgrowth and peripheral axon regeneration activated by stimulation of receptor tyrosine kinases, in particular FGFR1.

Receptor Tyrosine Kinase Trafficking and Signalling

Extracellular signals activate receptor-triggered intracellular signal transduction pathways. At the same time, receptor tyrosine kinases (RTKs) initiate a cascade of events comprising 'negative signalling', thereby decreasing the amplitude of positive signals and modulating the level of growth factor-induced stimulation. Hence, the same receptor simultaneously induces positive and negative signals. RTKs are activated by ligand binding, autophosphorylated and ubiquitinated, i.e. the small molecule ubiquitin is attached to lysine residues at various sites on them. Following internalization the receptor is either recycled or degraded in the endosomal/lysosomal pathway. Negative receptor signalling involves the coordinated action of ubiquitin ligases such as c-Cbl, adaptor proteins such as Grb2, negative feedback molecules such as Sprouty, cytoplasmatic kinases and phosphoinositol metabolites. We are particularly interested in the trafficking of fibroblast growth factor receptor type 1 and its regulation by Sprouty. FGFRs are abundant in the nervous system and display several key roles in brain development and disease.

Selected Publications

C3 exoenzyme lacks effects on peripheral axon regeneration *in vivo*. Auer M, Allodi I, Mohammed B, Udina E, Neiss W, Navarro X, Klimaschewski L. JOURNAL OF THE PERIPHERAL NERVOUS SYSTEM. 2013, 18, 30–36.

Sorting of FGF receptor type 1 in a human glioma cell line. Irschick R, Trost T, Karp G, Hausott B, Auer M, Claus P, Klimaschewski L. HISTOCHEMISTRY AND CELL BIOLOGY. 2013, 139, 135–148.

Inhibition of calpains fails to improve regeneration through a peripheral nerve conduit. Hausner T, Marvaldi L, Mártone G, Pajere K, Hopf R, Schmidhammer R, Hausott B, Redl H, Nógrádi A, Klimaschewski L. NEUROSCIENCE LETTERS. 2014, 566, 280–285.

Enhanced axon outgrowth and improved long-distance axon regeneration in Sprouty2 deficient mice. Marvaldi L, Thongrong S, Kozłowska A, Frei A, Pritz C O, Bäumer B, Ronchi G, Geuna S, Hausott B, Klimaschewski L. DEVELOPMENTAL NEUROBIOLOGY. 2014, 75, 217–231

Rho-independent stimulation of axon outgrowth and activation of the ERK and Akt signaling pathways by C3 transferase in sensory neurons. Auer M, Schweigreiter R, Hausott B, Thongrong S, Höltje M, Just I, Bandtlow C, Klimaschewski L. FRONTIERS IN CELLULAR NEUROSCIENCE. 2012, 6, 43

Membrane turnover and receptor trafficking in regenerating axons. Hausott B, Klimaschewski L. EUROPEAN JOURNAL OF NEUROSCIENCE. 2015, in press.

Selected Funding

Austrian Science Funds (within the PhD program 'Signal Processing in Neurons' SPIN, W1206-B05)

Collaborations

- Ludwig Boltzmann Institute for Traumatology, Vienna, Austria
- Department of Neurosciences, University of the Basque Country, Spain
- Department of Physiology, Universitat Autonoma de Barcelona, Spain
- Department of Clinical and Biological Sciences, University of Torino, Italy
- Department of Biochemistry, The Norwegian Radium Hospital, Norway
- Center for Anatomy, Hannover Medical School, Germany
- Institute for Anatomy, University Cologne, Germany
- Center for Anatomy, University Berlin (Charite), Germany
- Department of Genetics and Bioengineering, Yeditepe University Istanbul, Turkey

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Keywords

Histology, electron microscopy, ultrastructure research, membrane trafficking, endocytic pathways, nanomedicine, translational research, endothelial cells, nanoparticles, albumin, magnetic resonance imaging, fluorescence optical imaging, tissue barriers, systemic imaging, topical imaging, colon carcinoma

Research Focus

- Classical histological and cytological analyses through use of light- and scanning electron-microscopy with emphasis on clinically applied research topics (G. Klima)
- Ultrastructural investigation of subcellular constituents (organelles, cytoskeleton) in the context of intact cells and tissues (M. Hess)
- Imaging in cancer diagnosis (P. Debbage):
  - Interactions of albumin-based nanoparticles with tissues and cells
  - Magnetic Resonance Imaging by use of gadolinium-bearing albumin nanoparticles
  - Fluorescence Optical Imaging by use of fluorochrome-bearing albumin nanoparticles
  - Comparison of systemic and topical application of nanoparticles
  - Topical application of fluorochrome-bearing nanoparticles to image early cancer

Research

Clinical and Applied Histology and Cytology
Günter Klima

Long-term collaborations with Clinical Departments of the Innsbruck University Medical Center, i.e. Department of Visceral, Transplant and Thoracic Surgery, Department of Urology, Department of Plastic-, Reconstructive- and Aesthetic Surgery, Department of Anesthesiology and Critical Care Medicine, Center of Internal Medicine, Department of Cranio-maxillofacial and Oral Surgery.

Cellular Electron Microscopy
Michael W. Hess

Our cell biological research concentrates on ultrastructural aspects of intracellular membrane trafficking in eukaryotic cells and tissues, performed in close collaboration with the groups of L. A. Huber and D. Teis (Division of Cell Biology) as well as T. Müller and A. Janecke (Department of Paediatrics I). Cryo-based (immuno-) electron microscopy and 3D-modelling based on electron tomography are our preferred approaches for investigating mammalian cell cultures, (biopsy) samples from patients and various model organisms such as mice, yeast, flatworms and the freshwater polyp Hydra.
Membrane traffic is studied with special emphasis on endo/lysosomal pathways and intracellular signalling (Adell *et al.* 2014; Schiefermeier *et al.* 2014).
Furthermore, we are interested in the relationships between membrane traffic, cytoskeleton and loss of cellular polarity, as presented by Microvillus Inclusion Disease, a fatal hereditary enteropathy affecting neonates (Fig. 1; Wiegerinck *et al.*, 2014; Thoeni *et al.*, 2014). Finally, we perform methodological research on various organisms from all kingdoms of life, aiming at the improvement and development of advanced specimen preparation and labelling procedures for biomedical electron microscopy (Schmiedinger *et al.*, 2013).

Endothelial Biology Group
Paul Debbage

Nanomedicine aims to apply the advantages of nanoscale structured materials to enhance the targeting efficiency and reduce the toxicity of drug delivery, and to improve monitoring of therapeutic progress. Since 2004 our group has collaborated with other groups in the Medical University Innsbruck and the Leopold-Franzens-University in Innsbruck, and with partners elsewhere in Austria to carry out translational research in Nanomedicine. As a founder member of the

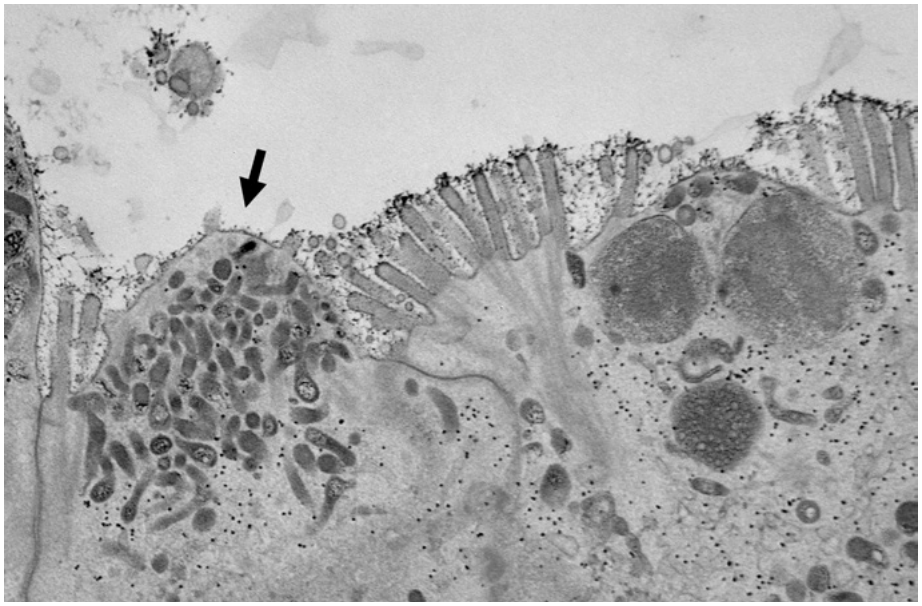

Fig. 1: Microvillus Inclusion Disease caused by homozygous truncating mutation in the apical t-SNARE protein syntaxin 3 (STX3). Electron micrograph from severely affected enterocytes (small intestine epithelial cells) showing characteristic atrophy and local loss of brush-border microvilli at the cell surface, associated with pathological accumulation of glycoprotein-rich, dark vermiform membrane vesicles (arrow) in the cell periphery.

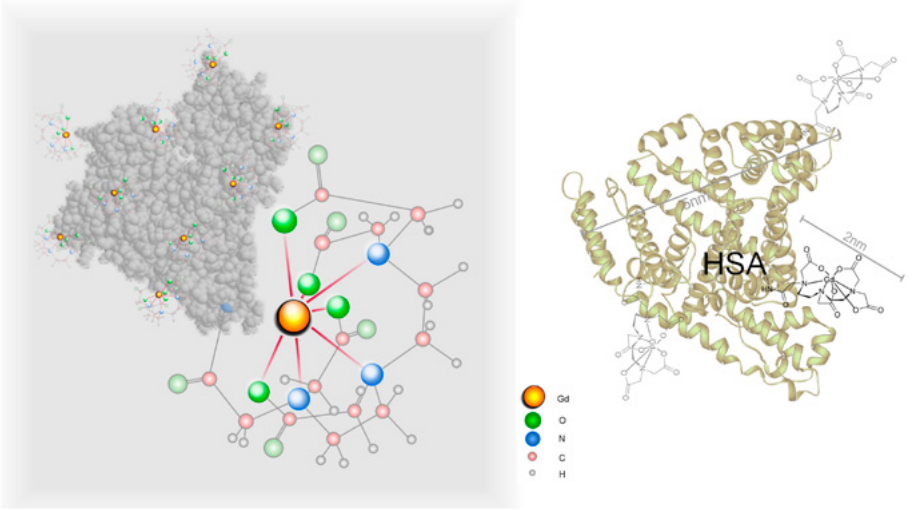

Fig. 2: at left, albumin in its native configuration as a heart shaped molecule. Each of the several linkers attached to it bears a single gadolinium atom (shown as a gold ball) which generates contrast in MRI. This principle of albumin with a linker bearing a signal-emitter is the basis of our translational research in the NanoEFEct project, but there the signal-emitter is a fluorochrome. At right, the dimensions of the albumin molecule are shown; we use these to plan quantitative aspects of the nanoparticles in the translational project. The image is taken from our publication Stollenwerk et al. (2010) Histochem Cell Biol. 133(4):375–404.

Austrian National Consortium "Nanohealth" we collaborated with teams in Vienna, Innsbruck and Graz, learning to design and synthesize protein-based nanoparticles of high quality (Figs. 2, 3): mechanically stable, of highly reproducible size, bearing standard numbers of both gadolinium tags and lectin targeting groups, and being non-cytotoxic according to OECD guidelines. However, after intravascular application they accumulated rapidly in the von Kupffer macrophages and in the endothelial cells lining the liver sinusoids, the gadolinium remaining in the liver (and kidneys and spleen) in large amounts for at least 2 weeks after application.

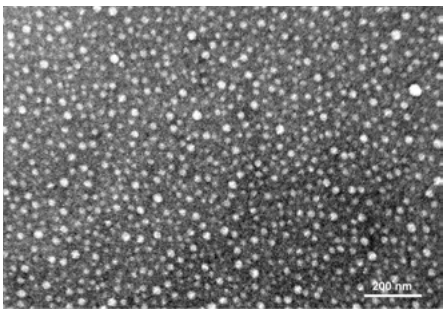

Fig. 3: A transmission electron microscope image of negatively contrasted nanoparticles (seen here as white spheroids). These high-quality particles do not aggregate, are highly uniform in size, and each contains approximately 10 of the albumin molecules shown in Fig. 2 (Abdelmoez, Thurner et al., 2010, Histochem Cell Biol. 134(2), 171–196).

This made us aware of how little we know of the potential tissue toxicity of nanoparticles bearing active substances, and of other potential toxicities not detected in cell-based assays. It prompted us to review the blood-tissue barriers which regulate the transfer of nanoscale objects across the vascular endothelial lining and thus control their distribution within the body. We found that systemic application of nanoparticles (e.g. by intravascular injection) faces multiple barriers maintained by the body between the blood and the internal compartments of almost all tissues (Debbage and Thurner, 2010, Pharmaceuticals 3 (11), 3371–3416). Once the nanoparticles have reached their targets within a tissue, high signalling and drug-release rates can be obtained exclusively within that tissue. To achieve that however, the nanoparticle requires 3–5 different targeting groups to "navigate" the barriers between the blood and the tissue cells. This raises significant regulatory hurdles.

We therefore considered topical application of nanoparticles. In this case, the blood-tissue barriers exclude the nanoparticles from the systemic circulation. Small amounts of nanoparticles could therefore be applied to achieve strong signalling, high local drug concentrations, and a minimum of material transfer into the systemic circulation, reducing side-effects potentially to extremely low levels.
As a consequence of these considerations, our group is now coordinating an EU ERA-Net Transcan project ("NanoEFEct") aimed at early diagnosis of colorectal carcinomas by nanoparticle-mediated fluorescence imaging (total funding volume slightly higher than € 1,000,000).

Future Goals: the translational research we presently carry out in the NanoEFEct project is aimed at early diagnosis of colon carcinomas, but the technology we are developing could also be applied to target any carcinomas arising in organs that can be accessed by endoscopy; these include other segments of the gastrointestinal tract, the genitourinary tract, the upper respiratory tract and the larger airways of the lungs. The technology can also be applied to target the earliest stages of inflammation, which underlies a range of diseases and is often associated with malignancies. In the 3–5 year term, we are also interested in learning to load the nanoparticles with drugs, aiming to achieve local treatment of tumours that cannot be excised.

Selected Publications

Coordinated binding of Vps4 to ESCRT-III drives membrane neck constriction during MVB vesicle formation. Adell MAY, Vogel GF, Pakdel M, Mueller M, Lindner H, Hess MW, Teis D.
JOURNAL OF CELL BIOLOGY. 2014; 205: p. 33–49.

The late endosomal p14-MP1 (LAMTOR2/3) complex regulates focal adhesion dynamics during cell migration.
Schiefermeier N, Scheffler JM, de Araujo MEG, Stasyk T, Yordanov T, Ebner HL, Offterdinger M, Munck S, Hess MW, Wickstroem SA, Lange A, Wunderlich W, Faessler R, Teis D, Huber LA.
JOURNAL OF CELL BIOLOGY. 2014; 205: p. 525–540.

Microvillus inclusion disease: loss of Myosin vb disrupts intracellular traffic and cell polarity. Thoeni CE, Vogel GF, Tancevski I, Geley S, Lechner S, Pfaller K, Hess MW, Müller T, Janecke AR, Avitzur Y, Muise A, Cutz E, Huber LA. TRAFFIC. 2014; 15: p. 22–42.

Loss of Syntaxin 3 Causes Variant Microvillus Inclusion Disease.
Wiegerinck CL, Janecke AR, Schneeberger K, Vogel GF, van Haaften-Visser DY, Escher JC, Adam R, Thoeni CE, Pfaller K, Jordan AJ, Weis CA, Nijman IJ, Monroe GR, van Hasselt PM, Cutz E, Klumperman J, Clevers H, Nieuwenhuis EES, Houwen RHJ, van Haaften G, Hess MW, Huber LA, Stapelbroek JM, Mueller T, Middendorp S.
GASTROENTEROLOGY. 2014; 147: p. 65–68.

Cryo-Immunoelectron Microscopy of Adherent Cells Improved by the Use of Electrospun Cell Culture Substrates.
Schmiedinger T, Vogel G F, Eiter OI, Pfaller K, Kaufmann WA, Floerl A, Gutleben K, Schoenherr S, Witting B, Lechleitner TW, Ebner H-L, Seppi T, Hess MW. TRAFFIC. 2013; 14: p. 886–894.

Proteomics of cancer stem cells. Skvortsov S, Debbage P, Skvortsova I. INT. JOURNAL OF RADIATION BIOLOGY. 2014. 90: p. 653–658.

Selected Funding

NanoEFEct, EU ERA-NET Transcan, Paul Debbage

Collaborations

- Institute of Cell Biology, Histology and Embryology, Medical Univ. of Graz, AT
- Centre for Medical Basic Research, Medical Univ. of Graz, AT
- Dept. of Pharmaceutical Technology, LFU Innsbruck, AT
- Medical Clinic 1 – Gastroenterology, Pneumology and Endocrinology, University Clinics Erlangen,Germany
- Inst. for Materials and Chemistry, SINTEF, Trondheim, Norway
- Faculty of Engineering. University of Porto, Portugal
- CESAR (Central European Society for Anticancer Research – EWIV), Vienna, AT

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Keywords

Infectious diseases, hygiene, infection, fungi, EHEC, HIV, dendritic cells, platelets, complement, N-chlorotaurine

Research Focus

Understanding Infections:
From Pathogenesis to Diagnosis

- The tasks of the Division of Hygiene and Medical Microbiology (HMM) comprise research, teaching, laboratory diagnosis of infectious diseases, environmental, hospital and technical hygiene.
- Scientific activities cover fungal pathogenicity and virulence factors, molecular mechanisms of host pathogen-interaction including the complement system, basic immunological research (interactions of dendritic cells/T-cells), antimicrobial agents (antimycotics and endogenous antiseptics), enterohemorrhagic E. coli and prevention of nosocomial infections.
- HMM seeks to prevent illness and death from targeted infectious disease threats through research and the translation of scientific information into real-world, practical applications, policies, and solutions (Fig. 1).

General Facts

Infectious diseases are turning into one of the most frequent causes of death in the world. Presently, bacteria and fungi are constantly developing resistance to antibiotics and antimycotics, resulting in an increase of emerging pathogens spread worldwide. Understanding the biological principles underlying the mechanisms by which infectious agents adapt, and undermining the defence mechanisms of a host is critical for fighting diseases.
HMM conducts basic and translational research into molecular mechanisms of pathogenesis of bacterial, viral, or fungal infections and different strategies for their prophylaxis and therapy. HMM's mission is to coordinate and strategically align translational infection research with the aim of developing new diagnostic, preventative and therapeutic methods for treating infectious diseases. To achieve this, HMM has formed thematic translational units of scientists, each dedicated to one specific pathogen or infectious disease. HMM is one of the largest microbiology diagnostic laboratories in Austria, with an average sample throughput of 250 000 specimens per year. (HMM is associated to all major hospitals in Tyrol,

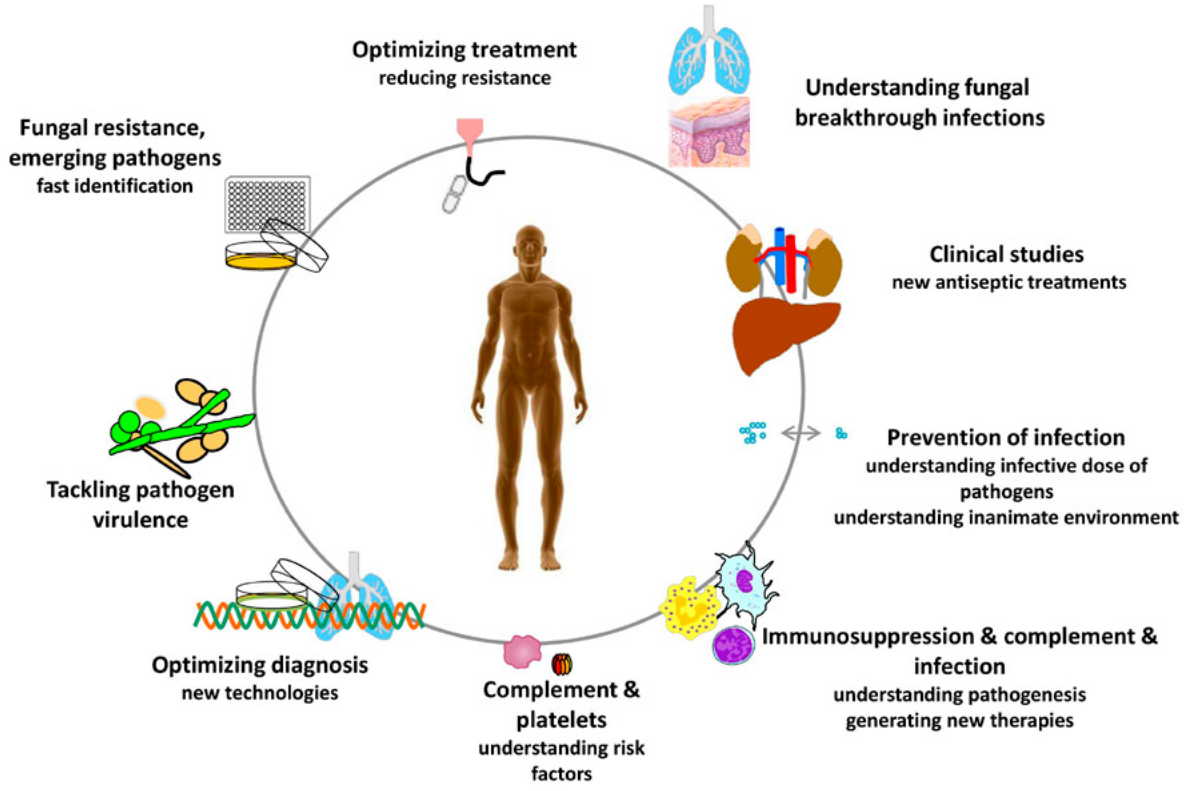

Fig. 1: Translation of in vitro to in vivo – overview of research questions targeted at HMM.

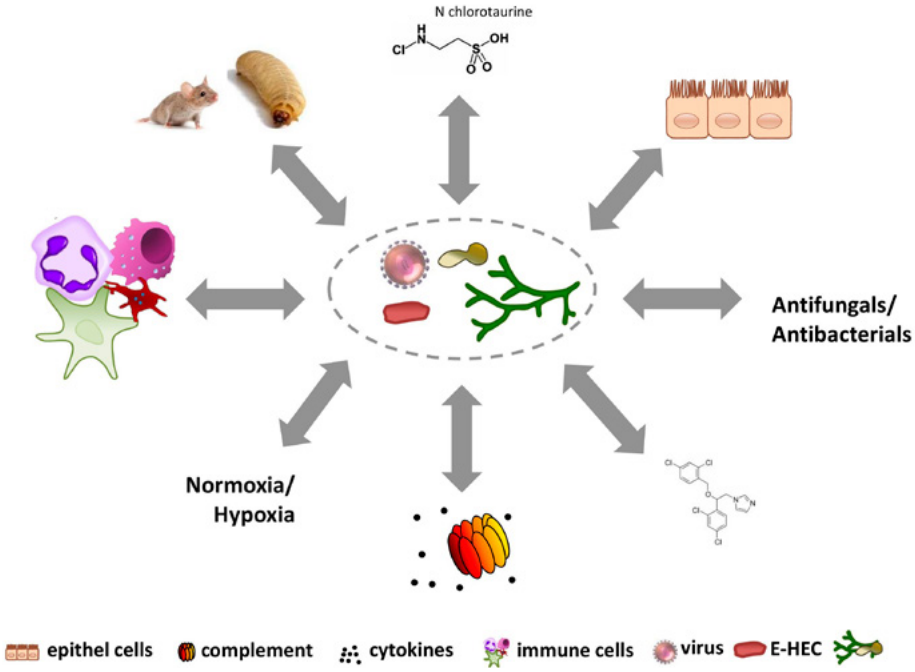

Fig. 2: Identifying underlying networks contributing to infectious diseases.

seeking it in a key position in the diagnostic laboratory landscape in Austria.)

Our research group consists of 6 Associate Professors, 5 Post-Docs, several PhD- and bachelor students and 7 technical assistants, the diagnostic of 9 medical doctors, 3 Post-Docs, and 26 technical assistants.
The mission of HMM is to bridge the gap between basic and translational research into microbial pathogenesis (Fig. 2).

Christian Doppler Forschungsgesellschaft

Christian-Doppler-Laboratory for Invasive Fungal Infections

In 2015 a "Christian-Doppler-Laboratory for Invasive Fungal Infections" was set up. Within the estimated 2 million fungal species on earth, about 600 cause diseases in humans, and the most important are Candida, Aspergillus, Mucorales, and Cryptococcus. Fungal infections are increasing and are associated with excessive morbidity and mortality (Fig. 3). Over 300 million people are acutely or chronically infected, leading to death, long term illness, and reduced work capacity. The reasons for emergence are likely multifactorial, e.g. the advent of medical progress, the successful application of immunosuppression in transplanted patients, and the use of immunomodulatory agents for treating various diseases from cancer to rheumatoid arthritis. Reducing the incidence relies on rapid and specific diagnostics, effective antifungal drugs, novel immunotherapeutic strategies, and adherence to infection control and sterility practices.

CD-Fungus deals with the following three main research questions: How to best find, treat and prevent mucor mycosis?

Tackling these key questions needs

1. recognising MM as such
2. identification of the source and type of infection
3. identification of the pathogen
4. understanding the underlying pathomechanisms
5. initiation of early targeted treatment and
6. providing a clean and safe hospital environment.

CD-Fungus attempts to unravel scientific questions raised by implementing 3 modules which will ultimately advance our understanding of fungal pathology, improve diagnosis and treatment of MM and enhance patients' outcome and safety in terms of prevention of nosocomial and hospital-associated infections.

Research

Emerging Infections with a Focus on Enterohemorrhagic Escherichia Coli (EHEC)-Induced Hemolytic Uremic Syndrome (HUS)

Experiences over the last decade clearly demonstrate the vulnerability of modern society due to emerging pathogens. Outbreaks and epidemics virtually affect all aspects of our lives, with constant threats to our health. A prompt health-care response is critical to prevent a rapid spread of infection. A thorough intensive knowledge of the pathogen, its reservoirs, its risk-factors as well as its associated broad-spectrum drugs is immensely important. Researchers (WG Orth-Höller & WG Würzner) investigate the interaction of EHEC virulence factors with the complement cascade and evaluate whether a transient complement blockade opens new therapeutic strategies. HMM will pursue immune modulation strategies focusing on the role of complement, and will provide genetic factors potentially responsible for disease development (Fig. 4).

Exploiting Immune Response to Infection

The human immune system is constantly active combating diseases. Researchers have developed novel methods for assessing the immune response in molecular detail focusing on HIV-1 and opportunistic fungal pathogens. During acute and chronic phase of infection, dendritic cells (DC), macrophages and platelets are of major interest. Various aspects of opsonization (complement, antibody) are considered in all *in vitro* experimental set-ups to mimic the *in vivo* situation close to reality. One focus is to study the

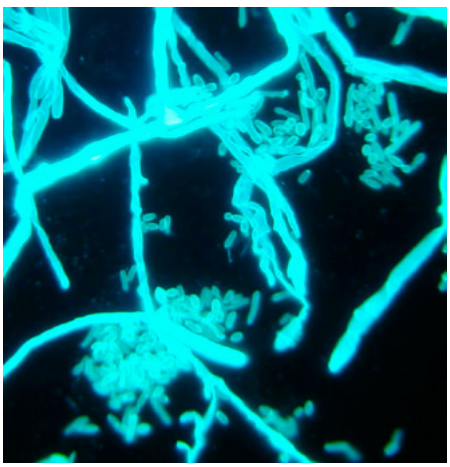

Fig. 3: Invasive fungal lung infection displaying hyphae (mucor species) and yeast cells.

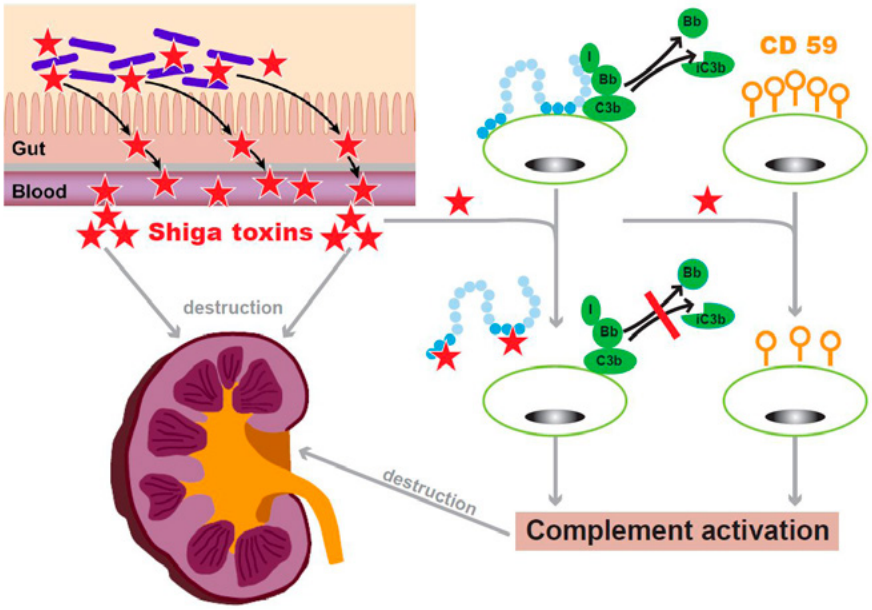

Fig. 4: Involvement of the complement system in the pathogenesis of EHEC-associated HUS.

impact of viral opsonization patterns on signalling pathways within DCs, on DC maturation, and on DC antigen presentation to CD4+ and CD8+ T cells (WG Wilflingseder & WG Posch; Fig. 5). Another goal is to evaluate the interaction of platelets and fungal pathogens. Such interplay might result in either mutual platelet activation or inhibition hence resulting in additive antifungal defence or excessive inflammation and thrombosis (WG Speth-Rambach). Another project aims at elucidating fungal proteins which allow pathogens to escape from complement interactions, subsequently protecting the fungus from the destructive action of an activated immune system (WG Würzner). This ground-breaking research is forming the basis for the development of novel treatment strategies and eventually of vaccines.

Fungal Infections of the Immunocompromised Patient

Our aging population and the growing prevalence of chronic diseases has forced modern medicine to use aggressive cancer therapies and organ or bone marrow transplantation, which result in or require immunosuppression. In immunocompromised patients, fungal pathogens, usually efficiently controlled by the immune system, can cause life-threatening diseases that may be difficult to treat with currently available anti-mycotics. While the degree of immune alteration is a major contributor to fungal diseases in immunocompromised patients, knowledge of other factors related to treatment failure is limited. Hence, researchers decipher the role of hypoxia in the onset of infections and various new *in vitro* and *in vivo* models will be applied (WG Binder-Lass-Flörl, WG Wilflingseder, WG Speth). HMM research intends to pursue immune modulation and new treatment strategies to provide promising options for the development of novel and more effective antifungal therapies. This topic is also dealt with in the FWF–funded doctoral programme of excellence, HOROS, for **HO**st **R**esponse in **O**pportunistic infection**S** and the Christian Doppler laboratory for invasive fungal infections.

Therapy-Resistant Fungal Infections

A disturbing and rapid increase in infections caused by antimycotic-resistant fungal pathogens is a big public health concern presently in the medical field. Most severe and fatal cases result from healthcare-associated fungal infections, which are increasingly caused by Candida, Aspergillus and Mucorales. Hence, a major focus is to investigate azole and echinocandin-resistance in yeasts and moulds and to discover new resistance mechanisms (WG Lackner-Lass-Flörl). Another main focus is to identify the underlying mode of amphotericin B resistance in Aspergillus terreus. In this context, we evaluate mitochondria as crucial modulator of polyene resistance (WG Wilflingseder-Blatzer-Jukic-Lass-Flörl). The mission of HMM is to bridge the translational gap between basic research and the development of novel antifungal drugs. HMM will support epidemiological, translational and clinical studies to improve the management of fungal diseases.

N-Chlorotaurine: Assessing of New Antiseptic Solutions and Antimicrobial Surfaces

N-chlorotaurine, a long-lived oxidant produced by activated human leukocytes has been synthesized as sodium salt in our division and is under clinical investigation for local treatment of infections of multiple body regions, including sensitive ones (Fig. 6). Basic research assesses its microbial activity against biofilms and investigates the activity against emerging pathogens (WG Nagl). While antibiotics are frequently considered the first line of containment for nosocomial infections, there is increasing effort being devoted to prevent infections. Researchers at the division are screening surface materials that prevent bacteria, viral and fungal contamination and persistence on medical surfaces (WG Mayr-Lass-Flörl).

Laboratory Diagnostics, Hospital and Technical Hygiene

The division HMM fulfils its tasks in detection and identification of pathogens causing infections. This covers bacteriology, parasitology, mycobacteriology and mycology. The diagnostic laboratories are certified according to ISO 9001:2009. Special parts are controlled by external audits in accordance to §67 Austrian Medicines Law and FDA, Division of Manufacturing and Product Quality. Within the sector of hospital and technical hygiene (accredited according to ISO/IEC 17025 and ISO/IEC 17020) guidelines for the prevention of infectious diseases are developed and controlled corresponding to the statutory pre-setting for technical facilities (e.g. disinfection machines).

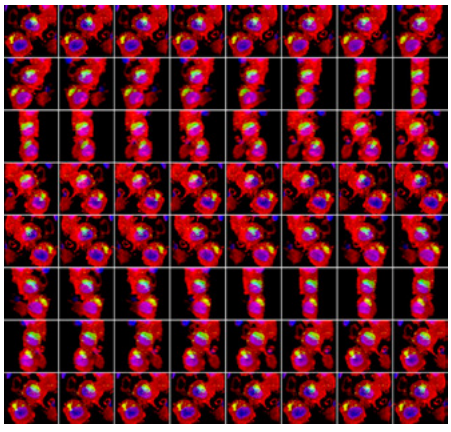

Fig. 5: Three-dimensional image of dendritic cells infected with HIV-1.

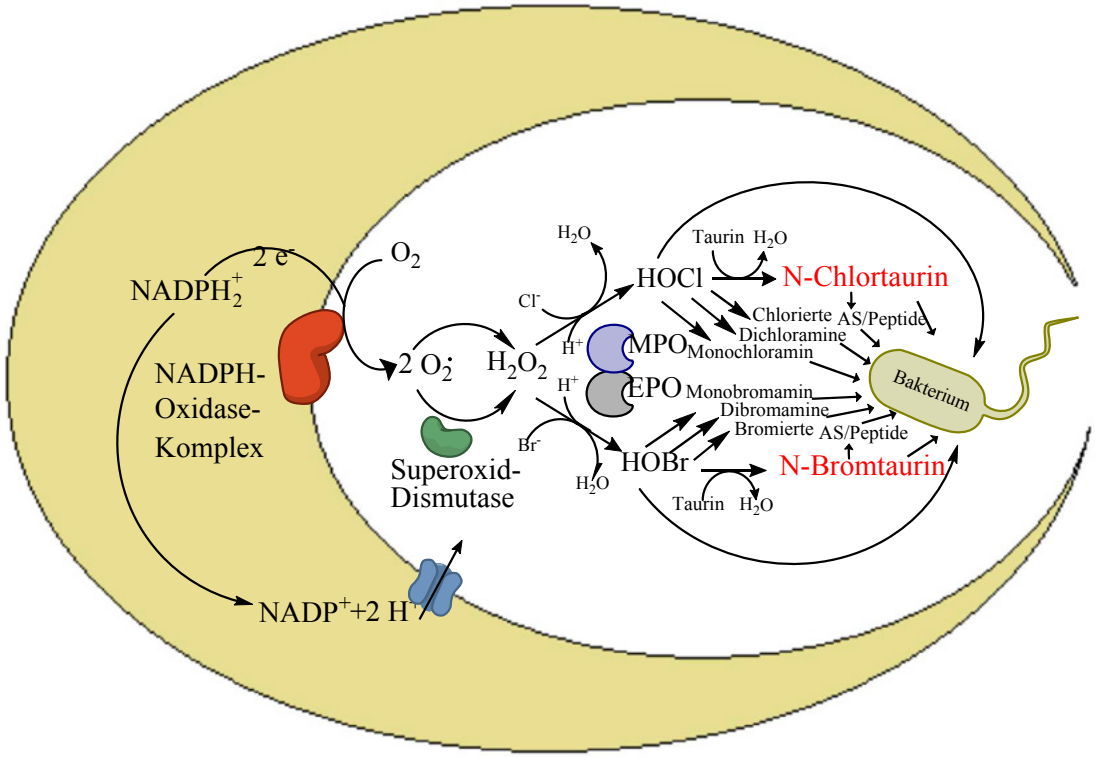

Fig. 6: Synthesis of N-chlorotaurine by human granulocytes.

Selected Publications

Bactericidal activity of N-chlorotaurine against biofilm forming bacteria grown on metal discs.
Coraca-Huber DC, Ammann C, Fille M, Hausdorfer J, Nogler M, Nagl M.
ANTIMICROB AGENTS CHEMOTHER. 2014;58:2235-2239.

Position and numbers of FKS mutations in C. albicans selectively influence *in vitro* and *in vivo* susceptibility to echinocandin treatment.
Lackner M, Tscherner M, Schaller M, Kuchler M, Mair C, Sartori B, Istel F, Cavling Arendrup M.
ANTIMICROB AGENTS CHEMOTHER. 2014;58:3626-3635.

Shiga toxin 2 reduces complement inhibitor CD59 expression on human renal tubular epithelial and glomerular endothelial cells.
Ehrlenbach S, Rosales A, Posch W, Wilflingseder D, Hermann M, Brockmeyer J, Karch H, Satchell SC, Würzner R, Orth-Höller D.
INFECT IMMUN. 2013;81:2678-2685.

Blocking Hsp70 enhances the efficiency of Amphotericin B treatment in resistant Aspergillus terreus strains.
Blatzer M, Blum G, Jukic E, Posch W, Gruber P, Nagl M, Binder U, Maurer E, Sarg B, Lindner H, Lass-Flörl C, Wilflingseder D.
ANTIMICROB AGENTS CHEMOTHER. 2015 [Epub ahead of print].

Identification of Aspergillus fumigatus surface components that mediate interaction of conidia and hyphae with human platelets.
Rambach G, Blum G, Latgé JP, Fontaine T, Heinekamp T, Hagleitner M, Jeckström H, Weigel G, Würtinger P, Pfaller K, Krappmann S, Löffler J, Lass-Flörl C, Speth C.
J INFECT DIS. 2015 [Epub ahead of print].

Immediate T-helper 17 polarization upon triggering CD11b/c on HIV-exposed dendritic cells.
Wilflingseder D, Schroll A, Hackl H, Gallasch R, Frampton D, Lass-Flörl C, Pancino G, Saez-Cirion A, Lambotte O, Weiss L, Kellam P, Trajanoski Z, Geijtenbeek T, Weiss G, Posch W.
J INFECT DIS. 2015 [Epub ahead of print].

Selected Funding

FWF I 661-B09: Oxystress and human fungal pathogens: clinical and applied aspects. 2011–2014

FWF I-656-B09: Biomarker and antifungal resistance in Aspergillus. 2011–2014

FWF W1253-B24: HOROS Doctoral Programme of Excellence "Wirtsabwehr bei opportunistischen Infektionen". 2014–2018

FWF KLI459: Tolerability of inhaled N-chlorotaurine in humans – a phase I clinical study. 2015–2016

FWF P22165-B13: DCs exposed to complement-opsonised HIV: A key to better vaccines? 2010–2013

FWF P24598-B13: HIV infection and transmission close to reality. 2012–2016

FWF W011010-21: DC-iphering complement- and Fc-receptor-mediated HIV-1 incorporation in and effects on DC function in search for novel therapeutical targets. 2015–2019

FWF P25389-B13: Deciphering the role of Th17 paradigm for viral infections. 2013–2016

FWF P26117-B20: Relevance of platelets and complement for the pathogenesis of invasive fungal infections 2014–2016

CD-Labor für Invasive Pilzinfektionen. 2015–2022 FP7-PEOPLE-2013-ITN:

ITN (Marie Sklodowska-Curie actions). From omics to patient improving diagnostics of pathogenic yeasts. 2015–2019

Collaborations

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sektion für hygiene und medizinische mikrobiologie

Christian Doppler Forschungsgesellschaft

HOROS

Virology

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Keywords

Virology, diagnostic of viral diseases, innate immunity, virotherapy, cancer immunotherapy

Research Focus

The major focus of the Division of Virology lies on the development of novel therapeutics and vaccines. This research spans from elucidating the modes of action of novel therapeutic strategies to the clinical translation and development in the spin-off biotech companies of the division. Specific foci are:

- Virus-based oncolytic cancer vaccine strategies and their mode of action.
- Viral vector-based vaccines primarily against HIV.
- Complement-enhanced vaccines and therapeutic antibodies.

General Facts

The Division of Virology has two professors: Dorothee von Laer, the director, and Heribert Stoiber, the deputy director.
In addition, there are three junior group leaders: Dr. Guido Wollmann, oncolytic viruses, Dr. Janine Kimpel, vector vaccines, associated with D. v. Laer, as well as Dr. Zoltán Banki, complement and dendritic cell vaccines, associated with H. Stoiber.

Around 30% of the employees work in the serological and virological diagnostics group, which services the university hospital Innsbruck (LKI), the regional hospitals and the medical practices in Tirol.

The division has developed an oncolytic viral cancer vaccine as well as complement enhanced therapeutic antibodies. To drive these two developments into clinical application, two companies were founded, ViraTherapeutics GmbH (founder D. v. Laer) and Lysovac (founder H. Stoiber), respectively. ViraTherapeutics has recently secured an investment that will cover the development up to early clinical phase II trials.

The division collaborates with several international groups and also with groups and clinics in Innsbruck: Hematology and Oncology (Gastl), Urology (Culig, Horninger), Gynaecology (Fiegl, Mart), Dermatology (Romani) a.o.

The division has established and is now in charge (Dr. Janine Kimpel) of the BSL2 and BSL3 animal facilities of Innsbruck Medical University.

Research

VSV-GP: a Viral Vaccine Vector and Oncolytic Cancer Vaccine
Dorothee von Laer

The vesicular stomatitis virus (VSV) is a negative strand RNA virus, with rapid replication and growth to high titres. It has proven to be a potent vaccine vector and oncolytic virus. However the neurotoxicity of VSV at higher doses and the rapid induction of neutralizing antibodies has limited the use of this virus in the clinic. The group of D. v. Laer abrogated both limitations, by substituting the VSV envelope protein G by the glycoprotein GP of the lymphocytic choriomeningitis virus, thus rendering a chimeric virus termed VSV-GP (Muik *et al.*, Journal of Virology, 2011).

VSV-GP-based Viral Vector Vaccines
Janine Kimpel

Funding: FFG Bridge

Using VSV-GP expressing the model antigen ova, we could show that VSV-GPova can boost the initially potent immune response to ova further upon repeated applications. In contrast, as already described previously by others, we found that other vector vaccine such as adenovirus and VSV wild-type did not boost the immune response induced by the first application any further upon additional injections (Tober *et al.*, 2014). VSV-GP is currently used as the basis for the development of a prophylactic HIV vaccine.

VSV-GP-based Oncolytic Cancer Vaccines
Guido Wollmann

Funding: FWF, FFG Research Studio Austria, ViraTherapeutics

Viruses that selectively replicate in cancer cells and thereby lyse cancer tissue are called oncolytic viruses. It is becoming more and more clear, that the therapeutic effects observed are not only achieved by direct viral destruction of cancer cells but also by a strong anti-cancer immune response. This is thought to be induced by the release of cancer antigens during oncolysis in the presence of the virus-induced inflammatory environment. VSV-GP was found to be safe and therapeutically effective in a broad range of cancer types in mouse models (Fig. 2, Muik *et al.*, 2014). In addition, we found strong synergism with a DC-based vaccine for melanoma in mice (co-supervised by Z. Banki). Currently clinical grade virus production and toxicology tests are under way to prepare for first-in-man studies.

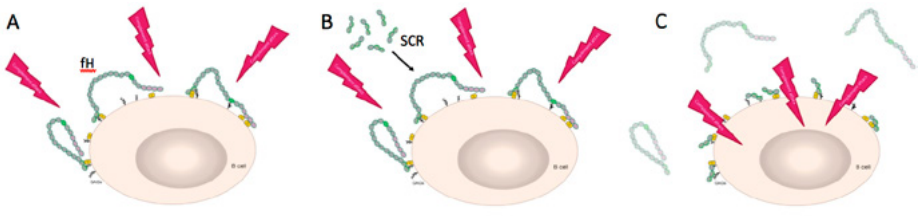

Fig. 1: Displacement of factor H (fH) to enhance complement-dependent cytotoxicity (CDC). (A) Binding of fH through short consensus repeats (SCR) 7 and 18-20 to the surface of tumor cells avoid CDC. (B) Addition of recombinant SCR7 or SCR18-20 removes fH from the cells and (C) makes them accessible to CDC.

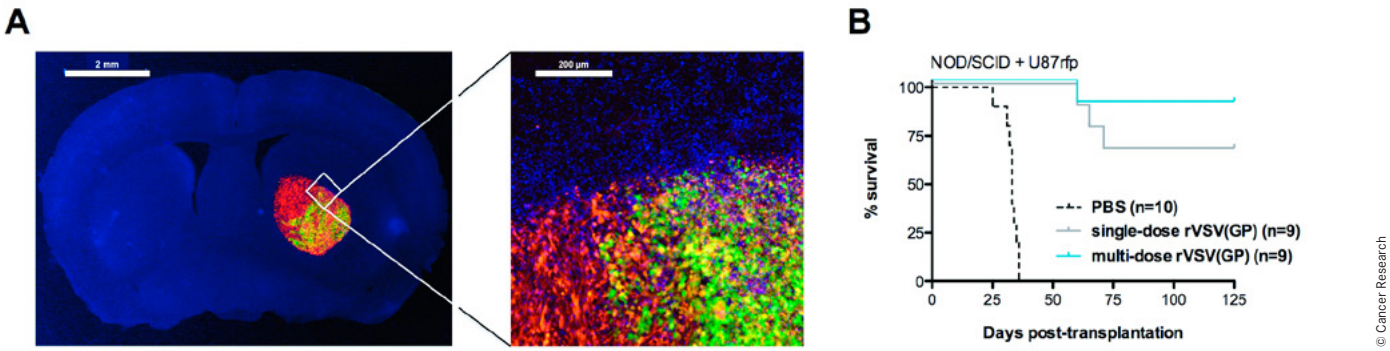

Fig. 2: rVSV(GP)-treatment led to long-term survival of both xenogeneic and syngeneic CNS-tumour bearing mice.
(A) N=3 U87-RFP orthotopic glioma-bearing NOD/SCID mice were treated i.v. with a single dose of 108 PFU rVSV(GP)-GFP at 10 days post-transplantation (dpt). Animals were sacrificed at 3 days post-injection and immunohistochemical analysis of coronal brain sections was performed with TO-PRO-3 iodide as nuclear counterstain (blue). A representative fluorescent micrograph is shown with an arrow indicating the area of progressing cellular disintegration. (B) Cohorts of n≥9 U87-RFP orthotopic glioma-bearing NOD/SCID mice were treated i.v. with either single or multiple doses of 108 PFU rVSV(GP)-GFP at 10 dpt or 10, 17 and 24 dpt, respectively. Control mice were injected with PBS. Animals were monitored for event-free survival over a period of 125 dpt.

HCV and Complement
Heribert Stoiber

Funding: FWF W1253 HOROS

The hepatitis C virus (HCV) specifically incorporates CD59 but not other regulators of complement activation (RCAs), such as CD46 or CD55, into the viral envelope (Ejaz, PLoS One, 2012). The incorporated CD59 protects HCV only partially against complement-mediated lysis. Thus an additional factor/RCA must be involved in the protection of the virus against complement. We aim to characterize additional RCA(s) that protect HCV against complement, which could be a potential therapeutic target.

Complement-Enhanced Therapeutic Antibodies
Heribert Stoiber, Zoltán Banki

The antitumor activity of monoclonal antibodies for the treatment of different cancers is mediated mainly by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Unfortunately, the efficacy of CDC is strongly impaired due to the expression and acquisition of regulators of complement activation (RCA) on tumor cells. A prominent RCA in fluid phase is factor H (fH), which was not investigated in this context so far. We found that abrogating fH function provides a novel approach to improve the CDC efficacy of therapeutic antibodies (Hörl, Leukemia, 2013; Hörl, Haematologica, 2013).

Complement and T Cell Responses in Retroviral Infections
Heribert Stoiber, Zoltán Banki

The implication of Tregs in viral infection was first described for mice persistently infected with Friend virus (FV), but Tregs also play a pathologic role in chronic viral infections like HIV and HCV (Chougnet, AIDS Res. Hum. Retroviruses, 2007; Manigold, Lancet Infect. Dis., 2007). We have found that the expansion of FV-induced Tregs is impaired in mice deficient for complement C3, suggesting that the complement system is involved in Treg responses. This exciting finding is the basis for a new project, which aims to define key molecules involved in the interaction between complement and Tregs during retroviral infections.

Memory Inflation
Zoltán Banki

Funding: FWF J3484

In recent years, accumulation of specific CD8+ memory T cells – termed memory inflation – has appeared to be one of the most important aspects of cytomegalovirus immunobiology. Dr. Z. Banki studied this phenomenon during his 12-months at Oxford University in the group of Paul Klenerman. He worked with a novel model of memory inflation that is based on replication-deficient adenovirus and characterized the role of latently infected non-hematopoietic cells in memory inflation.

Epidemiology of HPV Infection
Wegene Borena

The epidemiology of HPV infection is being studied in Austria, where hardly any data are available so far, and in different patient groups (Pichler *et al.* 2015).

Selected Publications

Type I interferons protect T cells against NK cell attack mediated by the activating receptor NCR1.
Crouse J, Bedenikovic G, Wiesel M, Ibberson M, Xenarios I, Von Laer D, Kalinke U, Vivier E, Jonjic S, Oxenius A.
IMMUNITY. 2014; 19;40(6): p. 961–973.

Re-engineering vesicular stomatitis virus to abrogate neurotoxicity, circumvent humoral immunity, and enhance oncolytic potency.
Muik A, Stubbert LJ, Jahedi RZ, Geiß Y, Kimpel J, Dold C, Tober R, Volk A, Klein S, Dietrich U, Yadollahi B, Falls T, Miletic H, Stojdl D, Bell J C, von Laer D.
JOURNAL OF CANCER RESEARCH. 2014; 1;74(13): S 3567–3578.

VSV-GP: a potent viral vaccine vector that boosts the immune response upon repeated applications.
Tober R, Banki Z, Egerer L, Muik A, Behmüller S, Kreppel F, Greczmiel U, Oxenius A, von Laer D, Kimpel J.
JOURNAL OF VIROLOGY. 2014; 88(9): S 4897–4907.

Reduction of complement factor H binding to CLL cells improves the induction of rituximab-mediated complement-dependent cytotoxicity.
Hörl S, Bánki Z, Huber G, Ejaz A, Windisch D, Muellauer B, Willenbacher E, Steurer M, Stoiber H.
LEUKEMIA. 2013; 27(11): S 2200–2208.

Complement factor H-derived short consensus repeat 18-20 enhanced complement-dependent cytotoxicity of ofatumumab on chronic lymphocytic leukemia cells.
Hörl S, Banki Z, Huber G, Ejaz A, Müllauer B, Willenbacher E, Steurer M, Stoiber H.
HAEMATOLOGICA. 2013; 98(12): S 1939–1947.

Low prevalence of HPV detection and genotyping in non-muscle invasive bladder cancer using single-step PCR followed by reverse line blot.
Pichler R, Borena W, Schäfer G, Manzl C, Culig Z, List S, Neururer S, Von Laer D, Heidegger I, Klocker H, Horninger W, Steiner H, Brunner A.
WOLRD JOURNAL OF UROLOGY. 2015; Epub ahead of print.

Selected Funding

- A chimeric oncolytic rhabdovirus for the treatment of melanoma, FWF - P 25499-B13, Univ.-Prof. Dr. Dorothee von Laer
- Evaluation of a semi-replication competent VSV system as HIV vaccine, FFG-Bridge, Univ.-Prof. Dr. Dorothee von Laer
- AWS Pre-Seed, Univ.-Prof. Dr. Dorothee von Laer
- HOROS – Host response in opportunistic infections, FWF-W1253, Univ.-Prof. Dr. Heribert Stoiber

Collaborations

- J. Schmitz, B. Haynes; Harvard Medical School, Boston, USA
- A. van den Pol; Yale University, New Haven, USA
- A. Oxenius; ETH Zürich, Zürich, Switzerland
- HP Kiem; Fred Hutchinson Cancer Research Center, Seattle, USA
- J. Bell; CICR – Centre for Innovative Cancer Research, Ottawa, USA
- H. Miletic; University of Bergen, Bergen, Norway
- L. Hansmann, S. Newrzela; Johann-Wolfgang-Goethe University, Frankfurt a. M., Germany
- F. Kreppel; University Ulm, Ulm, Germany
- L. Lehmann; Ludwigs-Maximilian-Univeristy, Munich, Germany

Facilities

BSL-2 and BSL-3 mouse facility

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Head of Division (interim):
ao. Univ.-Prof. Dr. Peter Lercher

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Keywords

Environmental and social epidemiology, Environmental health impact assessment, Combined effects, Transportation Noise & vibration & air pollution, Psychoacoustics, Soundscape research, Public health, Health related quality of life

Research Focus

- Integrated environmental health impact assessment
- Cardiovascular effects of environmental noise exposure
- Effects of environmental noise & air pollution on HRQoL
- Air pollution, social factors and respiratory health
- Dispositional factors, coping styles as effect modifiers in environmental health studies
- Combined effects of noise, vibration and air pollution exposure on annoyance and health
- Effects of quiet areas and other restorative residential neighbourhoods on health & well-being

General Facts

The division has a strong focus on teaching public health to medical students complemented by in-depth practica on a wide range of health related themes.
The current head of the division was the responsible module organiser (2.31: Humans, family, society and the environment) for the medical curriculum (6. to 7. Semester).
Members of the division are further involved in teaching public health doctors in environmental health.
The division supports governments in environmental health impact assessments at larger scales and more focused health impact assessments at the community and smaller regional levels.
One member of the division is supporting the regional government and communities in providing restorative options and facilities for handicapped persons (wheel chair routes, handbike-routes, barrier-free tourist destinations etc.)

Research

Sound Exposure and Health: Our Research Perspective

Empirical research on the health impacts of environmental noise has focused mainly on the critical question of whether certain intensities of sound exposure can harm or threaten human health and well being. This main effect or direct effects model has a certain weakness, however.
Human reactions to environmental conditions occur within an ecological context that shapes their responses. One key element of such a contextualised research orientation is that individual, social and other factors of the natural and built environment can substantially alter the direct noise response function (see Fig. 1).

Soundscape and Blood Pressure in Schoolchildren

Peter Lercher

Most research on the effects of noise on blood pressure in children has focused on a direct effects model using sound levels as indicator. We published such a well-cited analysis in 2001 (Evans *et al.*). A re-analysis of the data set was conducted within the EU-funded 7th Framework project ENNAH and the COST-Soundscape project with a contextual perspective on effect modification by dispositional (low birth weight) and contextual (Housing, soundscape assessment, chronic stress) factors.

We found children with premature births and elevated chronic stress (i.e. overnight cortisol) more susceptible to adverse blood pressure responses to road traffic noise. Furthermore, residence in a multi-dwelling

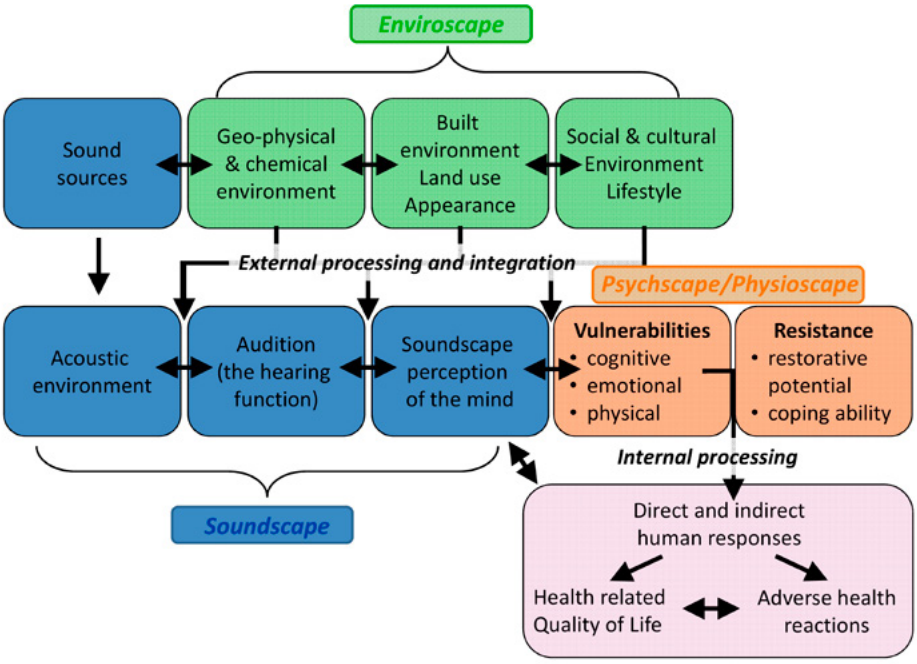

Fig. 1: Block diagram outlining the soundscape perception process and its moderation by context leading to direct and indirect human responses (Lercher & Schulte-Fortkamp 2013)..

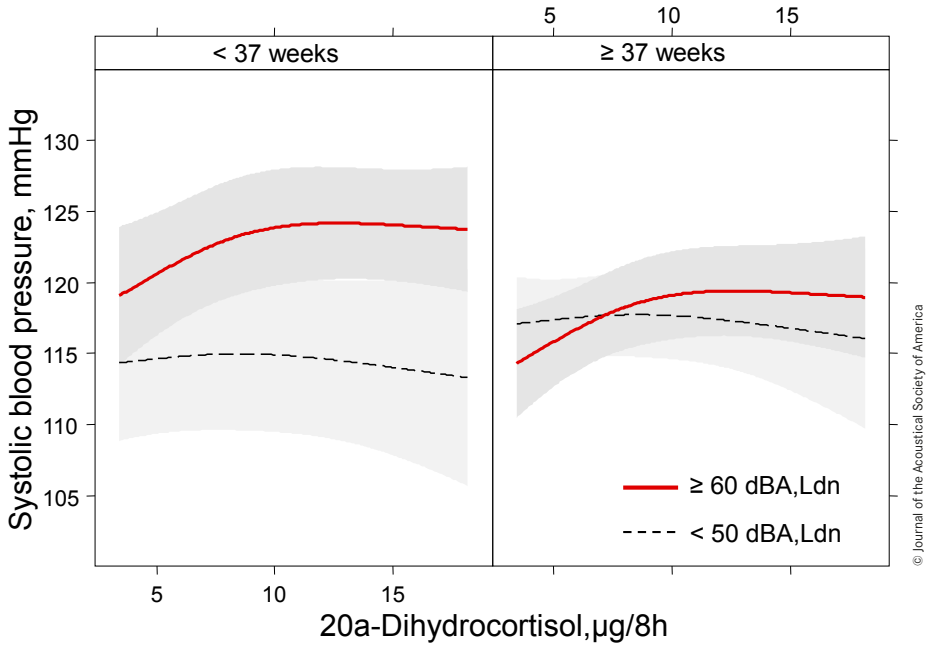

*Fig. 2: Systolic blood pressure by gestational age and urine cortisol, adjusted for BMI, sex, family history, education, house type, area quiet, sound*gestation*

unit, as well as perceived quietness of the area, did not modify the traffic noise impacts: rather, each factor had its own, independent effect on resting blood pressure. These results complement earlier findings (Lercher *et al.* 2002), where we showed an effect modification in children with low birth-weight/premature birth on mental health.

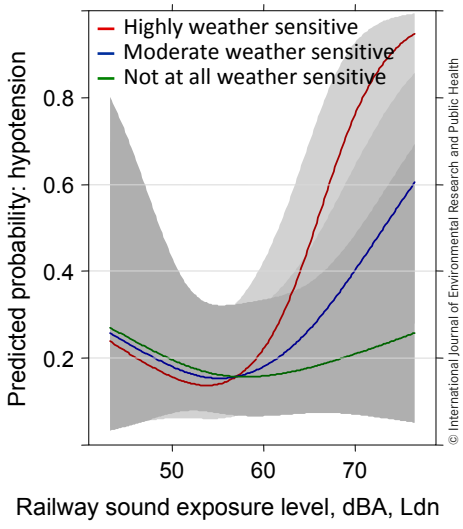

Fig. 3: Predicted probability of reported hypotension past year with rail sound level exposure by weather sensitivity. Adjusted for 16 potential confounders and interaction terms

Noise and hypotension in adults: A novel relationship?
Peter Lercher

Although earlier short-term experimental studies showed not only increases but also decreases in blood pressure after noise exposure, this fact has been neglected in research during the past 25 years. We had posed questions about hypotension and hypotension medication in two surveys and wanted to test whether hypotension is a potential health outcome of chronic noise exposure.

In the first survey (N=1989), self-reported hypotension was associated non-linearly with noise exposure (P=0.044) in the presence of a strong sex × age effect modification (P<0.0001). A further significant modification by noise was observed with reported symptoms of exhaustion (P=0.03). Weather sensitivity showed a significant interaction with noise sensitivity (P=0.02) and also a non-linear interaction with age (P=0.02). The results remained stable after adjustment for variables known to be associated with constitutional hypotension. Low blood pressure readings were not associated (too small N).

In the second survey we conducted a replication analysis on two samples (N=800 & N=567). The smaller sample was an intensive study with anthropometric and blood pressure readings and more in depth health assessments with slightly different instruments. In addition the noise exposure assessment was improved.

We found reported hypotension to be significantly associated with rail and total noise exposure and strongly modified by weather sensitivity. Reported hypotension medication showed associations of similar size with rail and total noise exposure – but without effect modification by weather sensitivity. This replication study showed also that the noise effect varies significantly by sex, age and body mass index and is moderated by adjacent main roads and related annoyance but not by highways.

Stress, Meditation and Blood Pressure
Harald Hörmann
(PhD in preparation)

Selected Publications

Association and moderation of self-reported hypotension with traffic noise exposure: A neglected relationship. Lercher Peter, Widmann Ulrich. NOISE HEALTH. 2013; 15(65): p. 205–216.

The ecological context of soundscapes for children's blood pressure. Lercher Peter, Evans Gary, Widmann Ulrich. JOURNAL OF THE ACOUSTICAL SOCIETY OF AMERICA. 2013; 134(1): p. 773–781.

Hypotension and environmental noise: a replication study. Lercher Peter, Widmann Ulrich, Thudium Jürg. INTERNATIONAL JOURNAL OF ENVIRONMENTAL RESEARCH AND PUBLIC HEALTH. 2014; 11(9): p. 8661–8688.

Soundscape of European Cities and Landscapes–Harmonising. Lercher Peter, Schulte-Fortkamp Brigitte. In AIA/DAGA CONFERENCE, 40th Italian (AIA) Annual Conference on Acoustics and the 39th German Annual Conference on Acoustics (DAGA). 2013; p. 8–21.

Collaborations

- Gary W. Evans, Cornell University, Ithaca, USA
- Jürg Thudium, Oekoscience-Institute, CH-7000 Chur, Switzerland
- Ulrich Widmann, AUDI AG, I/ET, D-85045 Ingolstadt, Germany
- Andre Fiebig, HEAD acoustics GmbH, D-52134 Herzogenrath, Germany
- Dietrich Kühner, Independent noise consultant, D-51519 Odenthal, Germany
- Helen Lin, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
- Dick Botteldooren, Acoustics Research Group, Ghent University, B-9000 Ghent, Belgium
- Brigitte Schulte-Fortkamp, TU Berlin, Berlin, Germany
- Michael Cik, TU-Graz, 8010 Graz, Austria
- Mark Brink, Federal Office for the Environment & ETH Zurich, Switzerland
- Terry Hartig, Uppsala University, Sweden

Pharmacology

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Keywords

Neuropeptides, metabotropic glutamate receptors, opioid receptors, neuropeptide Y receptors, fear learning, anxiety disorders, epileptogenesis

Research Focus

- Characterization of the neural networks underlying physiological and pathological fear/anxiety and identification of novel treatment strategies.
- Etiology and novel treatments of temporal lobe epilepsy.

General Facts

The Department of Pharmacology, established in 1886, is a centre of excellence in Neuropharmacology, and uses a variety of cutting-edge experimental approaches to address fundamental research questions related to the identification of novel molecular targets and the development of new therapeutic concepts for neuropsychiatric disorders.
The Department provides training in pharmacology to both medical undergraduate and graduate students. An additional task of the Institute is to contribute within national and international societies to the promotion of Pharmacology. This is done through the board functions (R. Fischer-Colbrie, Secretary) in the Austrian Pharmacological Society (APHAR) and the organization of the Annual Meeting of the APHAR every 3 years in Innsbruck.
Furthermore, the Department of Pharmacology provides independent drug and therapeutic information to doctors through the "Pharmainformation" bulletin and contributes to a variety of public bodies (e.g. Ethic Committee of the Medical University of Innsbruck) involved in the evaluation of drug safety and development.

Research

Neural Circuits Underlying Fear and Anxiety – Francesco Ferraguti

The laboratory is primarily interested in understanding the neural mechanisms mediating emotional information processing in the amygdala, and the role that classical neurotransmitters have, e.g. glutamate and GABA, on the acquisition, storage and inhibition of fear memories.
Although a large body of *in vivo* work has suggested that fear and extinction of fear are encoded by specific neuronal activity patterns with characteristic temporal dynamics, neuroanatomical information on the underlying neural networks activated during a particular behavioural task is still largely lacking. A first step in understanding these networks is the characterization of the main cell types of the amygdala and the identification of their participation in intrinsic and extrinsic circuitries of this region.
Our work in recent years involved primarily the anatomical, pharmacological and physiological characterization of different GABAergic cell types of the basolateral complex and of the intercalated cell masses of the rodent amygdala. Currently, taking advantage of recent developments in molecular genetics, viral trans-synaptic tracing and novel ultrastructural techniques (e.g. SDS-digested freeze-fracture replica immunogold labelling), we investigate long-range connections between amygdala GABAergic neurons and cortical or subcortical brain structures as well as structural synaptic plasticity of amygdala inhibitory networks.
Moreover, we examine the pharmacological and anatomical bases of anxiety disorders in models of Parkinson's disease. In particular, we seek to determine whether dopamine-depletion of the amygdala elicits pathological anxiety in mice.
Major Achievements: Identification of novel cell types of the intercalated cell masses of the amygdala and their participation in amygdala neural circuits processing sensory stimuli.
Future Goals: Characterization of the long-range connections of amygdala GABAergic neurons and their behaviourally-relevant plasticity.

Neuropeptides in Fear and Anxiety – Ramon Tasan

The laboratory investigates the role of neuropeptides in modulating emotional behaviours that are related to fear and hunger. A further aim is to unravel the underlying synaptic correlates of these emotional responses. Avoiding danger and finding food are two intimately associated, life-sustaining behaviors that are organized in survival circuits and strongly modulated by emotions. Maladaptation within such survival circuits can induce dysregulated, pathological behavior, resulting in the development of feeding- or anxiety-disorders. Interestingly, neuropeptides are essential modulators of both, energy homeostasis and anxiety-related behaviors. For instance, PP-fold peptides, including neuropeptide Y (NPY), peptide YY (PYY) and pancreatic polypeptide (PP) are released during states of hunger or acute danger. While the anxiolytic and fear-reducing properties of these neuropeptides are increasingly evident, a potential interaction of feeding and fear has not been elucidated so far.
Neuropeptides are highly enriched in the amygdala and hippocampus, two brain regions that are fundamentally involved in controlling emotional behaviors. There, they are considered to act as essential mediators significantly shaping synaptic functioning. Through a multidisciplinary approach, which involved immunohistochemistry, neuronal tract tracing, *ex vivo* slice electrophysiology with pharmaco- and optogenetic approaches in different transgenic mouse lines, we have demonstrated that several neuropeptides of the gut-brain axis are fundamentally involved in the modulation of

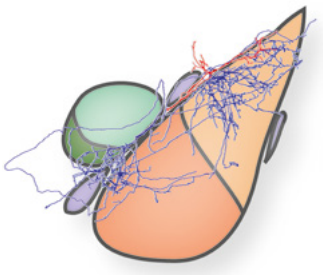

Fig. 1: Axonal projections (shown in blue) of a large intercalated neuron (shown in red) of the amygdala located in the intermediate capsule.

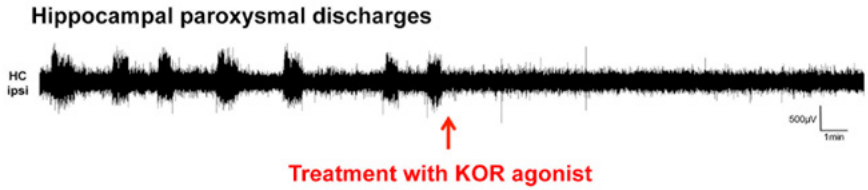

Fig. 2: EEG depth electrode recording from the ipsilateral hippocampus of an epileptic mouse before and after KOR agonist treatment.

fear and fear extinction behaviour, an effect that highly depends on the homeostatic situation of the individual, emphasizing a mutual interaction of survival circuits for fear and hunger.
Major Achievements: Identification of neuropeptides of the gut-brain axis that are also fundamentally involved in the modulation of fear and fear extinction behavior.
Future Goals: Characterization of peripheral modulators of hunger and satiety which could also affect fear learning, closing the loop of the gut-brain axis in controlling emotionally driven behaviors.

Opioid Systems in Epilepsy and Emotional Control – Christoph Schwarzer

The laboratory investigates the role of the endogenous dynorphin/kappa opioid receptor (KOR) system in epilepsy and epileptogenesis. Moreover, by gaining insight into the functional neuroanatomy of the dynorphin/KOR in emotional control, a further aim is to minimize potential side-effects of KOR agonist treatment.
Epilepsy is one of the most frequent neurological diseases, which presently cannot be cured. A high number of patients are refractory to pharmacological treatment, rendering surgical removal of parts of the brain as the ultimate solution.
In recent years, we provided evidence, that the activation of KOR plays an important role in epileptogenesis. Thus, dynorphin deficient mice display faster progression and more neurodegeneration in models of epileptogenesis than wild-type animals. Application of a KOR agonist during epileptogenesis reduces neurodenegeration and neurochemical alterations. On the other hand, activation of KOR is known to induce dysphoria in humans. In male mice, endogenous dynorphin acting on KOR exerts anxiogenic effects. In female mice, anxiogenic effects of dynorphin may depend on an interplay with the estrogen system. Based on these findings, we presently investigate the potential of G-protein biased KOR agonists in epilepsy. In order to do so, we apply 4 channel *in vivo* EEG in the kainic acid model of temporal lobe epilepsy with behavioral testing.
Major Achievements: Established that the activation of KOR plays an important role in epileptogenesis.
Future Goals: Investigate the potential of G-protein biased KOR agonists in epilepsy.

Neuronal Circuitries of the Subiculum in Epileptogenesis
Meinrad Drexel and Günther Sperk

The group currently investigates the role of GABAergic interneurons of the subiculum in the generation of epileptic seizures. Epileptic seizures are generated by abnormal, excessive or synchronous neuronal activity. Malfunctioning of microcircuits of the hippocampus, thalamus or cortex may be causative. Neurophysiological information formed in the hippocampus is processed and transmitted to multiple brain areas.
Recently, we obtained evidence that malfunctioning of the subiculum, the main output area of the hippocampus, is crucially involved in the generation of epileptic seizures in animal models of temporal lobe epilepsy. In particular GABA/somatostatin and GABA/parvalbumin neurons targeting the dendritic trees and the somata of pyramidal neurons, respectively, as well as afferent glutamate/calretinin neurons originating in the nucleus reuniens thalami may be impaired in their function.
We use transgenic mice that allow cell-specific overexpression of tetanus toxin introduced by stereotactic injections of a respective viral vector into the subiculum or nucleus reuniens thalami. Tetanus toxin is then selectively expressed in GABA/somatostain, GABA/parvalbumin or glutamate/calretinin neurons at the site of injection and impairs neurotransmitter release from these neurons. We are then monitoring EEG activity in these mice for one month and probe development of epilepsy. So far, we have demonstrated that selective silencing of GABA/parvalbumin neurons in the subiculum leads to spontaneous limbic seizures and highlighted the crucial role of these neurons in the manifestation of temporal lobe epilepsy.
Major Achievements: Identification that selective silencing of GABA/parvalbumin interneurons in the subiculum leads to spontaneous limbic seizures.
Future Goals: Investigate the role of GABAergic interneurons of the subiculum in the generation of epileptic seizures.

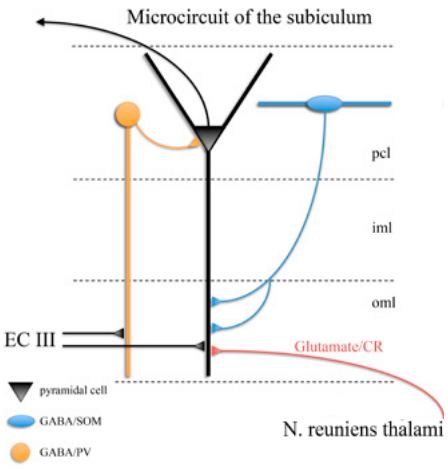

Fig. 3: Microcircuits of the subiculum.

Selected Publications

Large intercalated neurons of amygdala relay noxious sensory information. Bienvenu TCM, Busti D, Micklem BR, Mansouri M, Magill PJ, Ferraguti F, Capogna M.
JOURNAL OF NEUROSCIENCE. 2015; 35:5. 2044–57.

Sensory inputs to intercalated cells provide fear-learning modulated inhibition to the basolateral amygdala. Asede D, Bosch D, Lüthi A, Ferraguti F, Ehrlich I. NEURON. 2015; 86:2. 541–54.

Expression of GABA receptor subunits in the hippocampus and thalamus after experimental traumatic brain injury.
Drexel M, Puhakka N, Kirchmair E, Hörtnagl H, Pitkänen A, Sperk G. NEUROPHARMACOLOGY. 2015; 88. 122–33

Maternal inheritance of the Gnas cluster mutation Ex1A-T affects size, implicating NESP55 in growth. Eaton SA, Hough T, Fischer-Colbrie R, Peters J.
MAMMALIAN GENOME. 2013; 24:7–8. 276–85.

GPER1 (GPR30) knockout mice display reduced anxiety and altered stress response in a sex and paradigm dependent manner. Kastenberger I, Schwarzer C.
HORMONES AND BEHAVIOR. 2014; 66. 628–36.

Selected Funding

- Signaling in neurons, Austrian Science Fund (FWF) Doctoral college Program no. W12060, F. Ferraguti & C. Schwarzer.
- Cell signaling in chronic CNS disorders, FWF Spezialforschungsbereich Program no. F44-17, F. Ferraguti.
- NPY in adult neurogenesis and hippocampus-dependent fear learning, FWF grant no. P25851, R. Tasan.
- Gene therapy in temporal lobe epilepsy, FWF, grant no. I977, C. Schwarzer.
- Neuronal circuitries of the subiculum in epileptogenesis, FWF grant no. P26680, G. Sperk.

Collaborations

Prof. Aiba A., the University of Tokyo, Tokyo, Japan. Prof. Becker A., Dept. Neuropathology, University of Bonn, Bonn, Germany. Prof. Beck-Sickinger A., University of Leipzig, Leipzig, Germany. Dr. Bonaventure P., Johnson & Johnson Pharmaceutical Research & Development, USA. Prof. Capogna M., Oxford University, Oxford, UK. Prof. Colmers W., Dept. Pharmacology, University of Alberta, Edmonton, Canada. Dr. Ehrlich I., University of Tübingen, Tübingen, Germany. Prof. Heilbronn R., Dept. Virology, Campus Benjamin Franklin, Charité – Medical School, Berlin , Germany. Prof. Herzog H., Garvan Institute of Medical Research, Australia. Prof. Lüthi A., Friedrich Miescher Institute, Basel, Switzerland. Prof. Pape H.C., Westfälische Wilhelms-Universität, Münster, Germany.

Core Facilities

- Neurolucida (in collaboration with the Biooptics facility)

Medical Statistics and Informatics

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Keywords

Medical statistics, biostatistics, statistical methods, epidemiology, medical informatics, medical documentation, clinical trials, registries, risk prediction, prevention

Research Focus

Cancer Epidemiology

In cancer epidemiology, we investigate metabolic and lifestyle factors as potential risk factors for cancer incidence and mortality.

Statistical and Epidemiological Methods

The focus of the division lies in the development and application of statistical and epidemiological methods for modelling complex associations in the framework of classification and regression analysis.

Medical Informatics and Documentation

Medical informatics, which is a multidisciplinary research field, targets the use of information technology in order to improve health care.

Biobanking and BioMolecular Resources Research Infrastructure (BBMRI.MUI)

BBMRI.MUI aims to establish a state-of-the-art biobanking infrastructure at the Medical University of Innsbruck and to increase close cooperation between and harmonization of local, national and international biobanks.

General Facts

The Division of Medical Statistics and Informatics provides a major contribution to the teaching of medical students. Besides offering obligatory lectures in semesters 1, 5 and 8, we focus on teaching diploma and PhD students. Students who are working on their diploma and PhD theses are advised on the use of appropriate statistical methods.

Additionally, we provide statistical consultations to all researchers of MUI with a focus on clinical studies. We support clinical researchers in all aspects of statistical study planning, protocol writing, applications for ethical review, data management, statistical analysis and publication. We provide expertise regarding the usage of statistical (SAS, Stata, SPSS, etc.) and data management software (REDCap). Lalit Kaltenbach has developed an e-CRF system for the international, multicentre LEVOREP trial.

Other multi-centre trials with major participation of our division are the EU-funded Gannet53 randomized controlled trial, as well as other studies such as the PLATA, VITRIS, AFREEZE, ForaC and FlinTIC trials.

The division with Lalit Kaltenbach, as responsible IT manager, runs five Austria-wide registries: the HIR (heart failure) registry, the PTCA (percutane coronary intervention) registry, the IIK (invasive interventional cardiology) registry, the Ablation registry, and the Parkinson registry. The Austrian societies of Cardiology and Neurology are partners in these projects.

The statistical consulting and the participation in these projects are fundamental for the strong publication record of the division. In relation to the number of employees, the division has a top rank within MUI in recent years regarding total number of publications. In the years 2013 to 2014, a total of 76 original research papers were published by researchers of the division

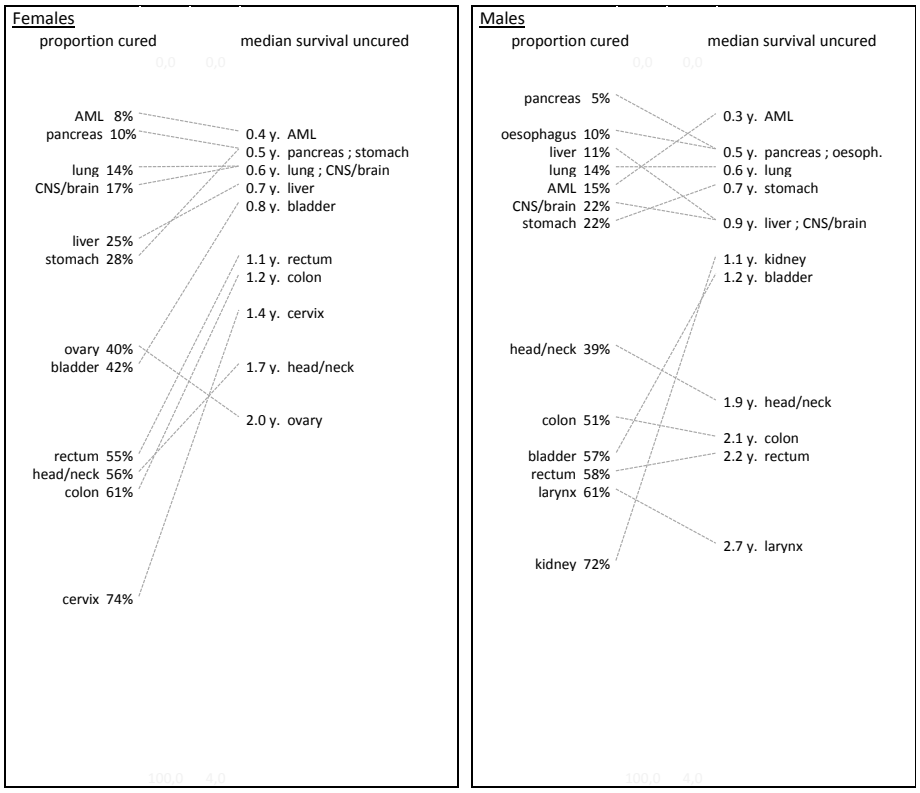

Fig. 1: Estimated levels of the proportion cured (left, in %) compared to levels of the median survival time of the uncured (right, in years) in Tyrol during 2005–2009 by cancer site, stratified by sex.

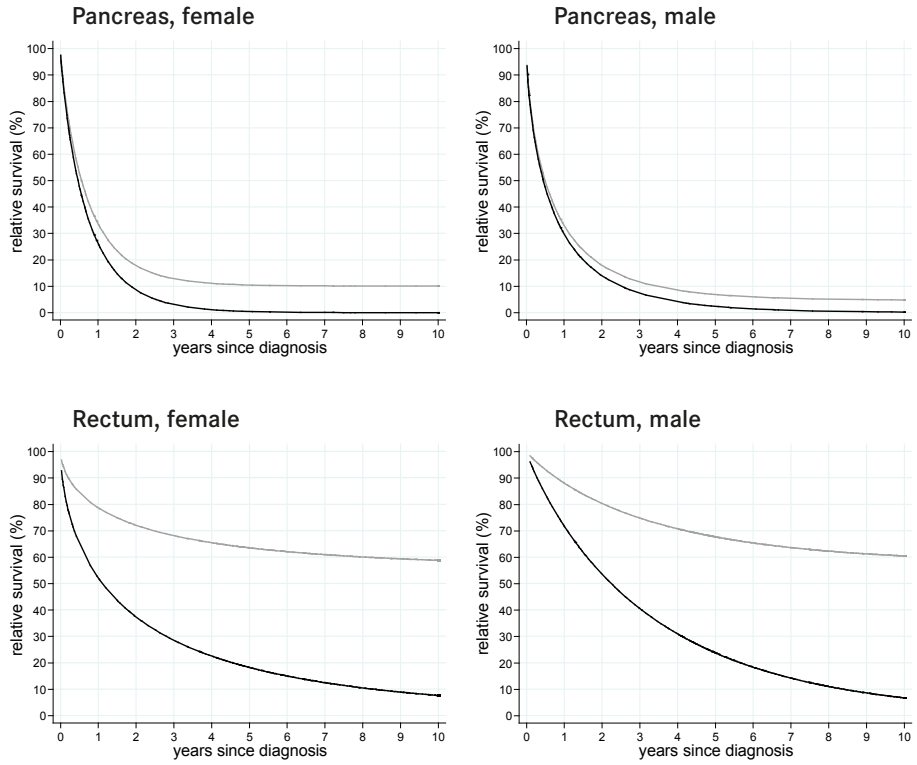

Fig. 2: Estimated relative survival, overall (upper curve, gray) and of the uncured (lower curve, black), for pancreas and rectum cancer according to duration since diagnosis in Tyrol during 2005–2009, stratified by sex.

(mostly co-authorships). In order to support researchers with submitting their PhD and habilitation theses, Joachim Masser developed the SCORE program. It enables the administration of the personal publication record of MUI researchers, including impact factors, citations and journal rankings.

Sabrina Neururer (chair of the organizing committee) and Hanno Ulmer (president of the society, chair of the scientific committee) organised the 2013 Conference of the Austro-Swiss Region of the International Biometric Society.

Research

Cancer Epidemiology
Hanno Ulmer, Michael Edlinger

In cancer epidemiology, we investigate metabolic and lifestyle factors as potential risk factors for cancer incidence and mortality. Metabolic syndrome is a cluster of factors characterized by obesity, hypertension, dyslipidemia and high blood glucose. The prevalence of metabolic syndrome is rising worldwide. Individuals with metabolic syndrome have a higher risk of cardiovascular diseases and diabetes, but less is known about the association with cancer.

We participated in the Me-Can project, containing a large database with health examination data from about 570 000 individuals from Sweden, Norway and Austria. Measurements such as height, weight, blood pressure, blood glucose, triglycerides and total cholesterol were recorded between 1972 and 2004.
Individuals in the database have been followed until their death, emigration or the end of follow-up, according to the principles of epidemiological cohort studies. To obtain cause of death and cancer incidence information, the database was linked to cancer registries in each country.

The division is a key partner in the Me-Can project. Susanne Strohmaier, Wegene Borena, and Michael Edlinger published papers regarding the association of metabolic factors with liver, gall-bladder and brain cancer, as well as the associations of total cholesterol and triglycerides with cancer incidence and mortality.

Besides our international collaborations, we cooperate locally with the TILAK Institute of Epidemiology (Willi Oberaigner). In 2014, a paper applying proportion cured models to Tyrolean cancer data was published by Michael Edlinger. Currently, he is also involved in a large clinical cohort study (CARDIIGAN) in association with the University Hospital for Internal Medicine III (Cardiology and Angiology) at MUI.

Using data from the Vorarlberg health examination database (VHM&PP), we investigated the role of elevated gamma-glutamyltransferase in endometrial cancer survival. This is, so far, the most recent publication regarding gamma-glutamyltransferase, finishing up a series of top publications in journals such as Circulation, Arteriosclerosis, thrombosis, and vascular biology, Cancer research and International journal of cancer.

More recently, we have set up a case-control study to investigate the association of aluminium exposure and breast cancer. Caroline Linhart is working on this study in cooperation with MUI scientists from the Department of Gynaecology, the University Hospital for Plastic, Reconstructive and Aesthetic Surgery and the Division of Clinical Biochemistry at MUI.

Statistical and Epidemiological Methods
Hanno Ulmer

Classification and regression trees are commonly applied for exploration and modelling of complex data. They are able to handle strongly non-linear relationships with high order interactions and different variable types.

Thomas Grubinger developed a new R package “evtree”, available from the Com-

prehensive R Archive Network at http://CRAN.R-project.org/package=evtree, providing evolutionary methods for learning globally optimal classification and regression trees.

More recently, this research group has set a new focus on causal inference, applying mediation analysis to epidemiologic research problems. Josef Fritz is currently working on the contribution of cardiovascular risk factors to the gender gap in mortality from coronary heart disease.

Medical Informatics and Documentation
Georg Göbel

In the division of Medical Statistics and Informatics, we have a strong focus on the use of semantic web technology in order to integrate data repositories and to support medical documentation. Formal, semantically enriched knowledge representation by means of ontologies provides a powerful solution to facilitate semantic interoperability and knowledge sharing within the scope of e-health, medical documentation, or biobanking. An ontology represents classes of entities of the real world and focuses on the definition of concepts and relations between them. They offer a good solution for addressing the challenge of machine-readable concepts in order to support health care providers and researchers with their daily work.

Sabrina Neururer developed ontologized versions of classification systems for health care, especially the Austrian procedure catalogue (Österreichischer Leistungskatalog) for procedure coding. A four-step approach (comparative analysis, definition analysis, typological analysis, ontology implementation) for formalizing the Austrian procedure catalogue is proposed, which provides a novel, systematically developed, strong framework to semantically enrich procedure classifications.

Philipp Hofer is currently working on the evaluation of ontologies in order to represent biosample collections and the usage of ontologies for automated data integration. This includes semantic equivalences between different data model representations. In this context, we developed a novel approach that combines competency evaluation and query expansion to assess the usefulness of existing ontologies for the biobanking domain.

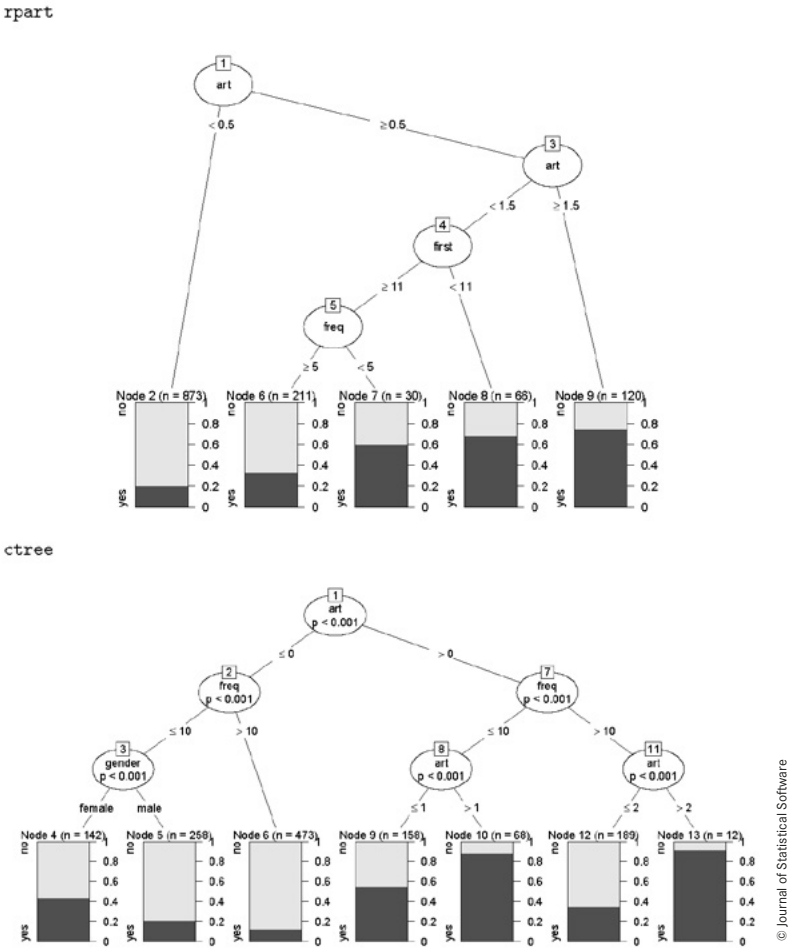

Fig. 3: Trees for customer targeting constructed by rpart (upper panel) and ctree (lower panel). The target variable is the customer's choice of buying the book. The variables used for splitting are the number of art books purchased previously (art), the number of months since the first purchase (first), the frequency of previous purchases at the Bookbinder's Book Club (freq), and the customer's gender.

Biobanking and BioMolecular Resources Research Infrastructure (BBMRI.MUI)
Georg Göbel

BBMRI.MUI is a part of the Austrian BBMRI.at project, which aims to develop a biobanking infrastructure in Austria in order to increase cooperation and harmonization between biobanks. Since 2014, the local BBMRI.MUI research team, consisting of Georg Göbel, Sabrina Neururer, Philipp Hofer, Thomas Insam, Anette Zeilner and Helga Hauffe, has worked on establishing common guidelines for the collection of human biosamples and on data management in order to implement a university-wide state-of-the-art biobanking infrastructure at the Medical University of Innsbruck. Currently, several independent decentralized collections of human biomaterials are located at different MUI divisions. Based on the approval of the local ethics committee, most of these separate sample collections are linked to pseudonymized, detailed clinical data. The project aims at integrating archived biospecimens with clinical and molecular data in a collaborative environment that emphasizes scientific insights, while ensuring security and compliance. As a preliminary result, a university-wide biobank registry based on international standards was implemented and it will be linked with the European-wide BBMRI registry.

In the future, these projects will go beyond the sample-centric workflows of conventional biobanks by integrating patient materials, clinical, specimen, genetic and molecular assay data, to deliver a holistic, unified view, enabling researchers to facilitate data exploration and hypotheses driven research

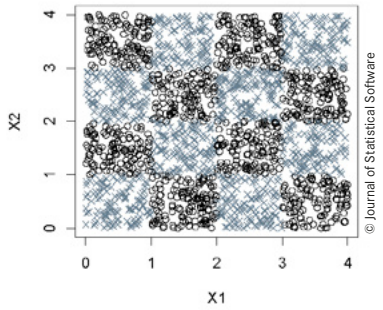

Fig. 4: Class distribution of the simulated 4 × 4 chessboard problem with zero noise, plotted on the (X1, X2)-plane. The two classes are indicated by black circles and gray crosses, respectively.

without extra programming or IT support. Multi-level user access control ensures that all collaborators can work effectively while ensuring compliance with patient consent and maintaining regulatory guidelines.

Selected Publications

A prospective study on metabolic risk factors and gallbladder cancer in the metabolic syndrome and cancer (Me-Can) collaborative study.
Borena W, Edlinger M, Bjørge T, Häggström C, Lindkvist B, Nagel G, Engeland A, Stocks T, Strohmaier S, Manjer J, Selmer R, Tretli S, Concin H, Hallmans G, Jonsson H, Stattin P, Ulmer H.
PLoS One. 2014 Feb 21;9(2):e89368.

Site-specific proportion cured models applied to cancer registry data.
Edlinger M, Ulmer H, Cvancarova M, Oberaigner W.
Cancer Causes & Control. 2014 Mar;25(3):365–73.

evtree: Evolutionary Learning of Globally Optimal Classification and Regression Trees in R.
Grubinger T, Zeileis A, Pfeiffer KP.
JOURNAL OF STATISTICAL SOFTWARE. 2014; 16: p. 1–29.

A concept of a MIABIS based register of biosample collections at the Medical University of Innsbruck.
Hofer P, Fiegl H, Angerer J, Mueller-Holzner E, Chamson M, Klocker H, Steiner E, Hauffe H, Zschocke J, Goebel G.
STUDIES IN HEALTH TECHNOLOGY AND INFORMATICS. 2014; 205: p. 293–297.

Total Serum Cholesterol and Cancer Incidence in the Metabolic Syndrome and Cancer Project (Me-Can).
Strohmaier S, Edlinger M, Manjer J, Stocks T, Bjorge T, Borena W, Haggstrom C, Engeland A, Nagel G, Almquist M, Selmer R, Tretli S, Concin H, Hallmans G, Jonsson H, Stattin P, Ulmer H.
PLoS One. 2013; 8: p. e54242.

Selected Funding

- BBMRI.MUI, Austrian BMWFW (GZ 10.470/0016-II/3/2013), Georg Göbel

Collaborations

- Odd Aalen, University of Oslo, Oslo, Norway
- Tone Bjørge, Bergen University, Bergen, Norway
- Larry Brant, National Institute on Aging, Baltimore MD, USA
- Hans Concin, Arbeitskreis für Vorsorge- und Sozialmedizin, Bregenz, Austria
- John Danesh, University of Cambridge, Cambridge, UK
- Rick Grobbee, University Medical Centre Utrecht, Utrecht, the Netherlands
- Leo Held, University of Zurich, Zurich, Switzerland
- Cecily Kelleher, University College Dublin, Dublin, Ireland
- Yuan Lu, Harvard University, Cambridge MA, USA
- Anna Lukanova, German Cancer Research Centre, Heidelberg, Germany
- Jonas Manjer, Lund University, Malmö, Sweden
- Gabriele Nagel, University of Ulm, Ulm, Germany,
- Petra Peeters, Imperial College, London, UK
- Ruth Pfeiffer, National Cancer Institute, Bethesda MD, USA
- Pär Stattin, Umeå University, Umeå, Sweden
- Ewout Steyerberg, Erasmus MC University Medical Centre Rotterdam, Rotterdam, the Netherlands
- Reinhild Strauss, Medical University of Vienna, Vienna, Austria
- Jaakko Tuomilehto, University of Helsinki, Helsinki, Finland
- Christopher Wild, International Agency on Research of Cancer, Lyon, France
- Kurt Zatloukal, Medizinische Universität Graz, Austria

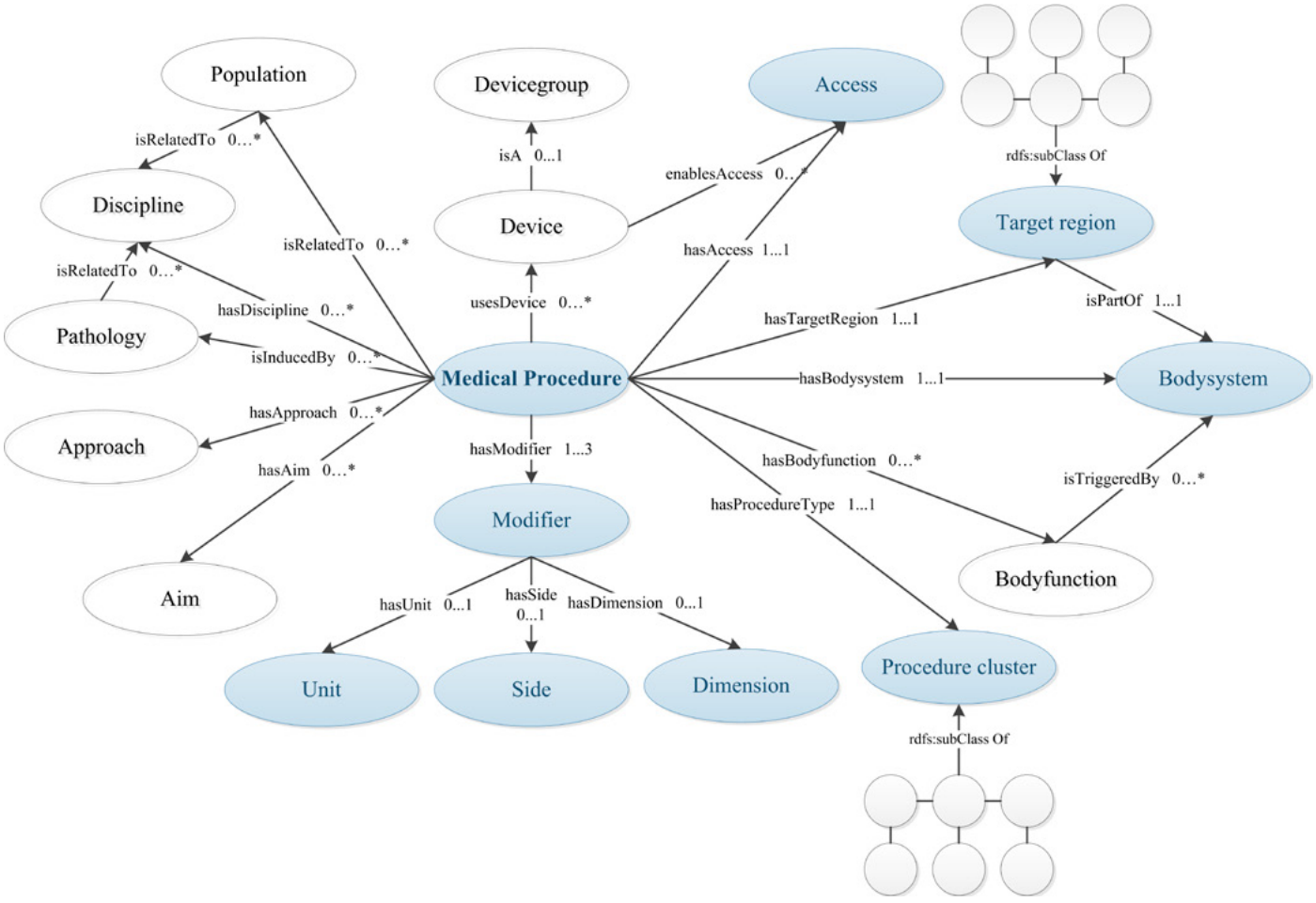

Fig. 5: Core concepts and relations of the Austrian procedure catalogue ontology. Blue concepts represent static information from the initial procedure catalogue.

Health Economics

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Keywords

Diagnosis related groups (DRGs), patient classification, cost analyses, length of stay analyses, hospital cost accounting, hospital quality, hospital efficiency, hospital performance, hospital payment

Research Focus

Development and improvement of hospital financing systems based on diagnosis related groups (DRGs)

General Facts

The Division of Health Economics has a long tradition regarding the development and improvement of the Austrian hospital financing system (Leistungsorientierte Krankenanstaltenfinanzierung, LKF).
It was established in 2004 on the initiative of Professor Karl Peter Pfeiffer, following the former Ludwig-Boltzmann-Institute of Epidemiology and Health System Research. In 2009, the division joined the European Union funded EuroDRG (diagnosis related groups in Europe: towards efficiency and quality) project. Karl Peter Pfeiffer, Conrad Kobel and Caroline Linhart were the core researchers in this project.

Research

DRGs in Austria and Europe
Conrad Kobel

Payment mechanisms represent one of the fundamental building blocks of any health system, introducing powerful incentives for actors in the system and fierce technical design complexities. Inpatient case payments, mainly referred to as diagnosis related groups (DRGs), are nowadays used as a payment mechanism with ambitious aims: they seek to reimburse providers fairly for the work they undertake. Moreover, they intend to encourage efficient delivery and to discourage the provision of unnecessary services, i.e. to overcome some of the drawbacks of more traditional hospital reimbursement systems. A case payment system that fulfils these hopes requires carefully balanced incentives as well as a methodologically sound system. Especially, DRGs need to accurately reflect the resources and costs of treating a group of similar patients.
Case-based hospital financing systems have been adopted in an increasingly large number of countries around the world.

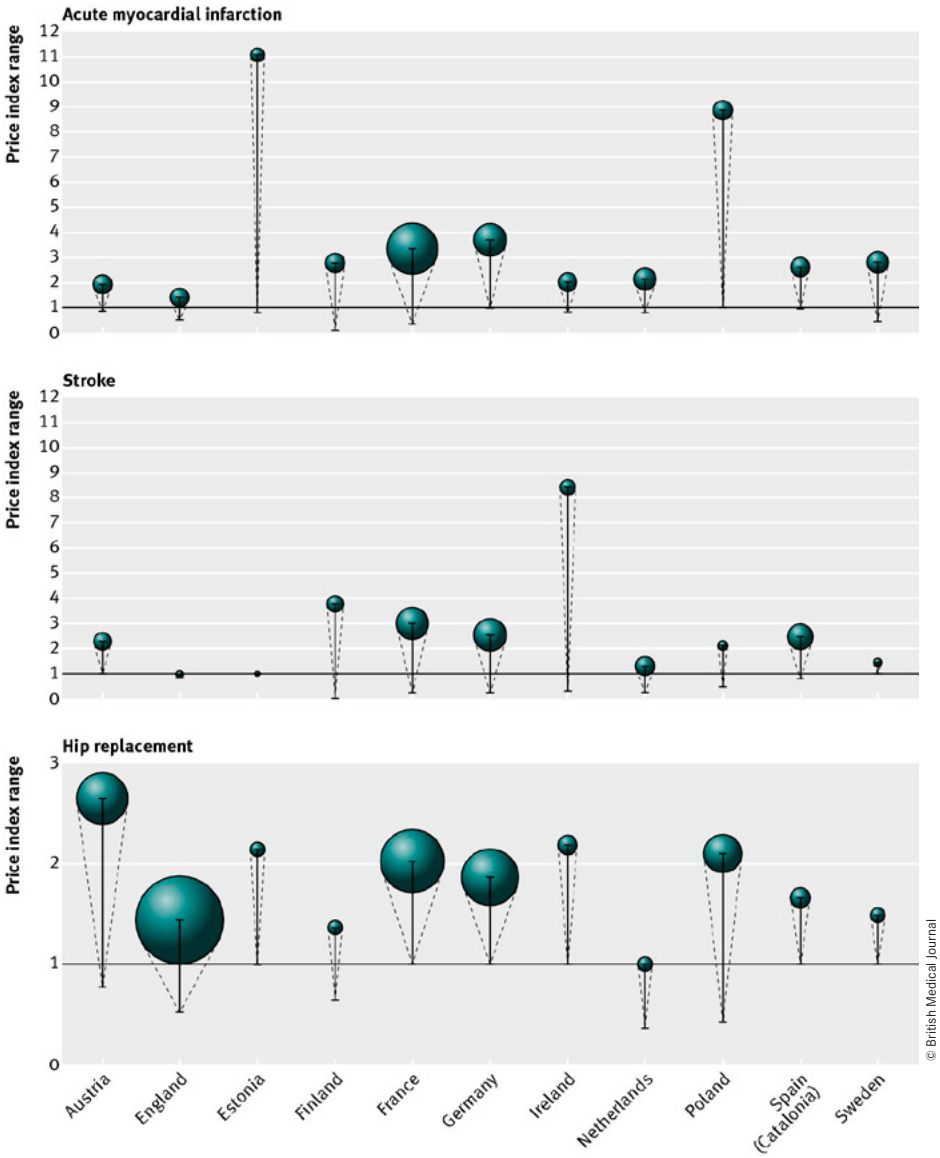

Fig. 1: Number of DRGs and relative price range for three episodes of care in 11 countries. The length of the bars indicates the range of the price index, which compares country specific DRG weights (relative weights, tariffs, or scores) with the weight of an index DRG (price index = 1) for the episode of care (into which a standard case without complications would be classified). The size of the circles represents the number of DRGs used to classify patients.

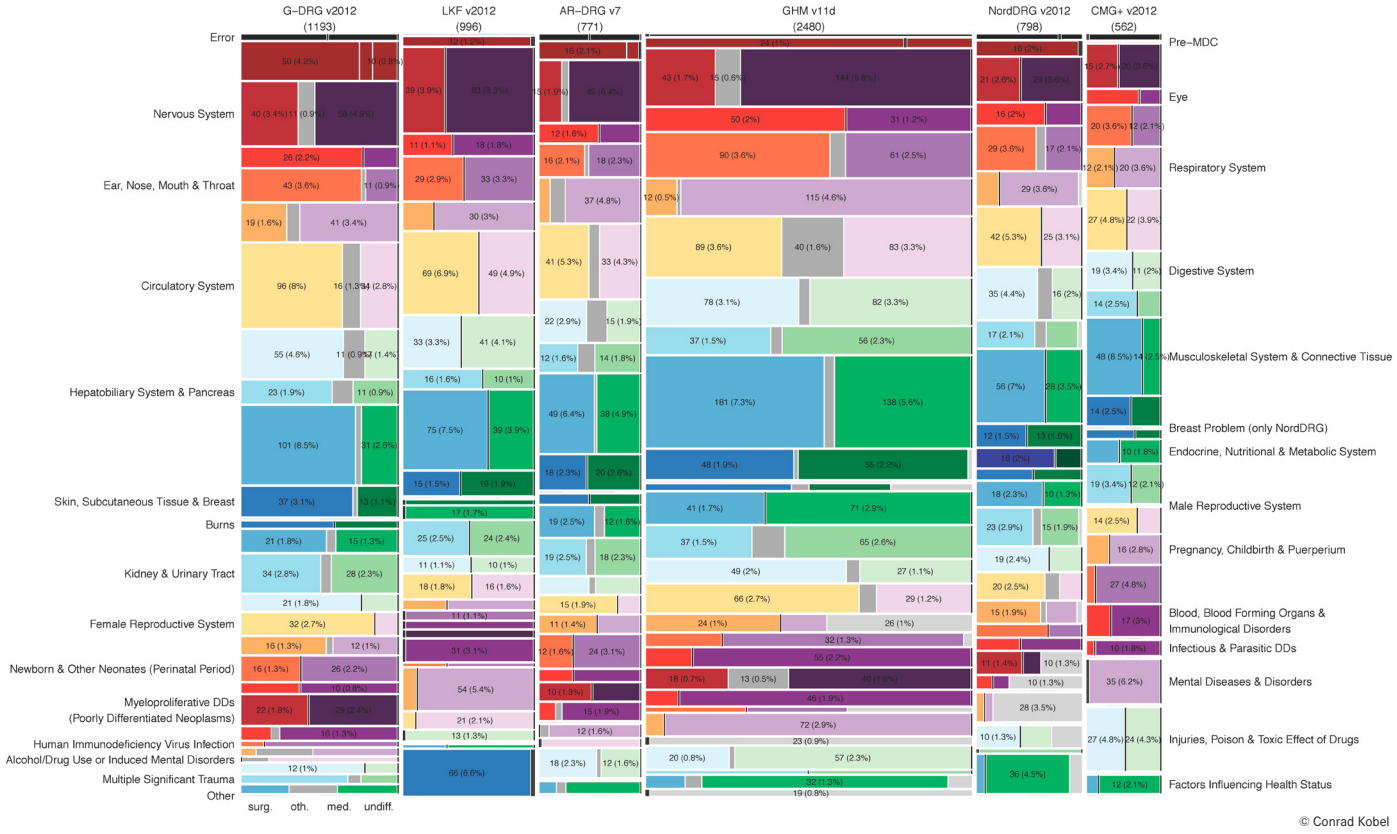

Fig. 2: Graphical illustration of the distribution of DRGs into MDCs and partitions in different systems. The columns represent the DRG systems. The wider a column, the higher the total number of groups of this DRG system is in comparison to the others. The rows represent the MDCs, labelled alternately on both sides of the figure. Medicare Severity (MS)-DRGs served as the reference for this comparison. The higher a cell, the higher the share of groups in this system's MDC is. For example, the column representing the GHM system is more than three times wider than the column representing the AR-DRG system. In addition, the differently coloured parts within MDCs of every system show the distribution of cases into medical, surgical and other partitions.

They are built around patient classification systems, i.e. DRG systems, which classify hospital cases into DRGs on the basis of classification variables such as diagnoses, treatments, and demographic characteristics. DRGs condense the confusingly large number of different patients treated in hospitals into a manageable number of (a) clinically meaningful and (b) economically homogenous groups.

In all systems, DRGs are organized into Major Diagnostic Categories (MDCs) or similar categories, and a distinction is made between surgical and medical cases, which are again separated into different partitions. In addition, most systems attempt to distinguish between patients with different levels of complexity or severity by further subdividing (splitting) DRGs. However, the specific design features of different countries' systems as well as the dynamics of change remain relatively poorly understood. Refinement of DRG systems over the past decade or so has led to DRG systems with more DRGs, better distinction between complex and less complex cases, and a slightly higher proportion of surgical DRGs.

Our research focus was to compare similarities and differences across systems in Europe in comparison to the Austrian LKF system. We aim to provide the scientific foundation for the further development of the LKF system, delivering empircal research results on the consequences of certain system characteristics.

Selected Publications

Diagnosis related groups in Europe: moving towards transparency, efficiency, and quality in hospitals?
Busse R, Geissler A, Aaviksoo A, Cots F, Häkkinen U, Kobel C, Mateus C, Or Z, O'Reilly J, Serdén L, Street A, Tan SS, Quentin W. BMJ. 2013;346:f3197.

Coronary artery bypass grafts and diagnosis related groups: patient classification and hospital reimbursement in 10 European countries.
Gaughan J, Kobel C. Health Econ Rev. 2014;4:4.

Why do patients having coronary artery bypass grafts have different costs or length of stay? An analysis across 10 European countries.
Gaughan J, Kobel C, Linhart C, Mason A, Street A, Ward P, EuroDRG group. Health Econ. 2013; Suppl 2:77–88.

Selected Funding

EuroDRG, Diagnosis related groups in Europe: towards efficiency and quality, EC, Contract/Grant agreement number: 223300, Karl Peter Pfeiffer

Collaborations

- Andrew Street, Anne Mason, Padraic Ward, James Gaughan, Silvio Daidone, Centre for Health Economics, University of York, York, England
- Mona Heurgren, Lisbeth Serdén, Mats Talbäck, National Board of Health and Welfare, Stockholm, Sweden
- Martine Bellanger, Josselin Thuilliez, National School of Public Health, Paris, France
- Siok Swan Tan, Leona Hakkaart-van Roijen, Ken Redekop, Institute for Health Policy & Management, Erasmus Universitair Medisch Centrum Rotterdam, The Netherlands
- Francesc Cots, Pietro Chiarello, Xavier Salvador, Xavier Castells, Parc de Salut Mar, Barcelona, Spain
- Zeynep Or, Thomas Renaud, Institute of Research and Information on Health Economics, Paris, France
- Maria Swiderek, Katarzyna Czach, Katarzyna Wiktorzak, Agata Szymczak, Katarzyna Klonowska, Paweł Sakowski, National Health Fund, Warsaw, Poland
- Unto Häkkinen, Mikko Peltola, Hanna Ratto, Kirsi Vitikainen, National Institute for Health and Welfare, Helsinki, Finland
- Jeni Bremner, Paul Giepmans, European Health Management Association, Brussels, Belgium
- Reinhard Busse, Alexander Geissler, David Scheller-Kreinsen, Wilm Quentin, Department of Health Care Management, Berlin University of Technology, Germany
- Jacqueline O'Reilly, Brian McCarthy, Economic and Social Research Institute Dublin, Ireland

General Pathology

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Keywords

Oncology, uropathology, hematopathology, gastrointestinal pathology, oropharyngeal pathology, endocrine pathology, pathology of infections, immunology, transplantation

Research Focus

- oncology
- immunology and transplantation pathology

General Facts

The Division of General Pathology focusses on diagnostic clinical pathology and is responsible for the routine pathological diagnosis of biopsies and surgical specimens obtained from most of the Clinical Departments of the Medical University of Innsbruck, with an emphasis on oncology, especially of the lymphatic tissue, the urogenital tract and oropharyngeal tumors. A biobank consisting of formalin-fixed paraffin-embedded material is located at our division, thus making us an important connecting link between basic science and clinical research. This translational research is reflected by a close cooperation with clinicians and researchers in the fields of oncology, surgery, radiology, nuclear medicine, head & neck as well as cranio-maxillofacial surgery, dermatology and other departments.

Research

Oncology

Main topics are the diagnosis of rare tumor entities, tumor biology and mechanisms of treatment resistance, evaluation of biomarkers to predict individual risk and prognosis, support diagnosis and assist in treatment allocation as well as identification of potential therapeutic targets using molecular pathological methods. Current projects deal with the early detection of lung cancer, the role of molecular pathology for therapy in lung cancer patients and potential prognostic markers in pancreatic carcinoma.

The research groups for uropathology, hematopathology and cranio-maxillofacial surgery represent a particular field of interest at our division and are therefore highlighted separately.

<u>Uropathology</u>

The main topic in the field of uropathology is prostate cancer focusing on tumor biology (Fig. 1), mechanisms of treatment resistance, evaluation of biomarkers for diagnosis, risk prognosis and therapy allocation as well as potential therapeutic targets. Furthermore the function of the androgen receptor and the role of stem cells, cytokines and inflammation in tumor progression and treatment resistance are evaluated in close cooperation with the Department of Urology. Another field of interest is bladder cancer currently concentrating on biomarkers for risk, prognosis, resistance to BCG-therapy and the prevalence of HPV infection in superficial bladder cancer.

In addition the biobank for frozen tissue located at our division includes tissue samples from prostate cancer and other urological tumors (kidney cancer, bladder cancer). For research purposes, samples of other malignancies, such as breast cancer, are also stored there.

<u>Hematopathology</u>

The main field of interest is the pathology of malignant lymphomas, focusing on the microenvironment and the role of autophagy in multiple myeloma as part of the European Union Seventh Framework Programme (FP7/2007–2013 OPTATIO under grant agreement no. 278570), the expression of PD1 and PDL1 in multiple myeloma (Fig. 2) and the morphology, immune phenotype and molecular pathology (MYD88 and CXCR4 mutations) of lymphoplasmacytic/plasmacytoid lymphomas.

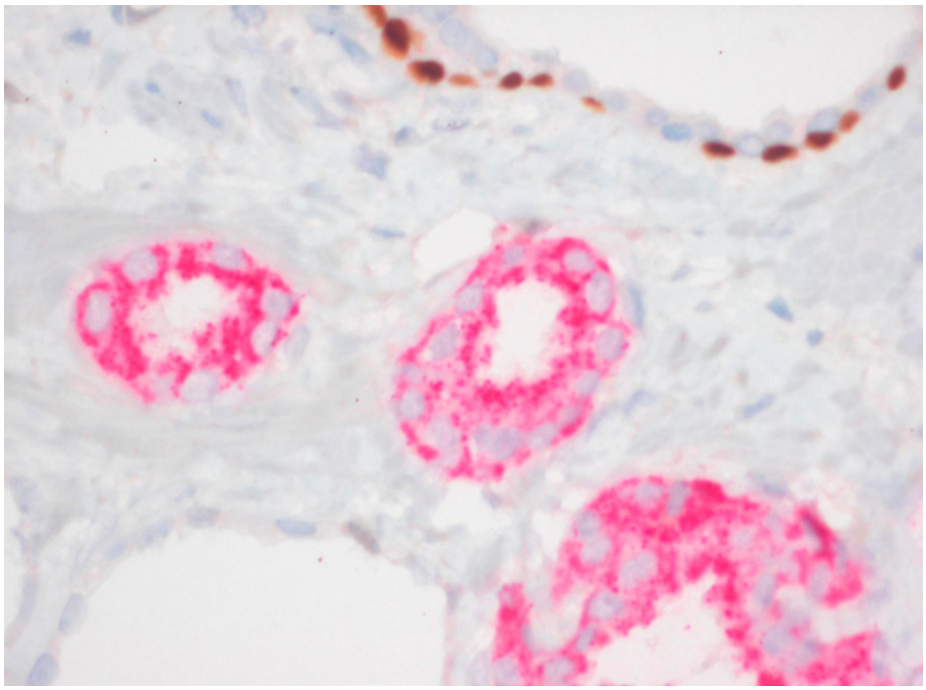


Fig. 1: Prostate cancer with loss of basal cells and expression of AMACR as well as a normal prostate gland (double staining immunohistochemistry for p63 (brown) and AMACR (red); 40x)

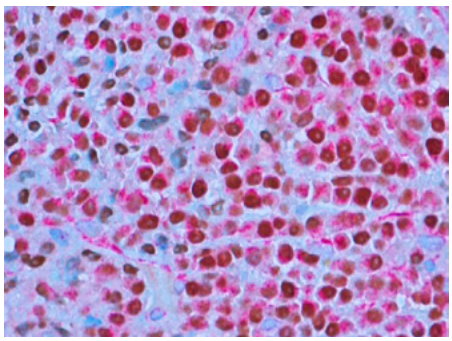


Fig. 2: Bone marrow with multiple myeloma and expression of PDL1 (double staining immunohistochemistry for MUM1 (brown) and PDL1 (red); 40x).

Current projects also deal with aggressive B-cell-lymphomas including microenvironment, potential prognostic biomarkers such as C-MYC translocations, and therapeutic targets such as PD1 and PDL1.

In addition, a wide number of clinical studies are provided with tumor samples from our bio-bank of paraffin-embedded tissue specimens.

Cranio-Maxillofacial Pathology

This project aims at the application and integration of clinical, molecular pathological, molecular imaging (MALDI-IMS, FTIR imaging and µCT), bioinformatics and protein identification technologies to identify molecular signatures allowing the stratification of patients who are susceptible to curative treatment of oral squamous cell carcinoma. Patient samples that have been and are still being collected at the Department for Cranio-Maxillofacial and Oral Surgery and at the Department for Pathology (biobank) will be systematically collected, dissected, and prepared to be accessible for this study.

Infectiology, Immunology and Transplantation

The main topics include composite allograft transplantations, limb transplantation in animal experiments, hand transplantations of patients at the Innsbruck Medical University with a special emphasis on morphology and standardized diagnosis, immune phenotype of the inflammatory infiltrate and therapeutic approaches resulting from this knowledge. Also samples from human and animal tissue (rat and mouse models) will be stored for future research.

Further fields of attention are the immunology and new therapeutic approaches in chronic inflammatory bowel disease in close cooperation with the Department of Endocrinology, Gastroenterology and Metabolic Diseases and the evaluation of new methods of detection of Mycoses from blood and tissue using PCR based methods and molecular imaging techniques (MALDI-MS) in cooperation with the Department of Hygiene, Microbiology and Social Medicine as well as the Institute of Forensic Medicine.

Neuropathology

The Division of Neuropathology is currently vacant. Routine diagnosis of neurological diseases and specific tumors in tissue specimens of human brain are currently made in close cooperation with Prof. J. Hainfellner, Institute of Neurology, Medical University of Vienna (MUV).
Latest research projects in cooperation with the Department of Neurology and Neurosurgery focusing on the morphological and immunohistochemical evaluation of the infiltrative zone of brain metastases, the consequences of anterior cervical discectomy on patients with cervical herniation and the expression of somatostatin receptor in meningioma are supervised at the Division of General Pathology.

Selected Publications

ERG rearrangement prevalence in prostate cancer: higher frequency in young age and in low PSA prostate cancer. Schaefer G, Mosquera JM, Ramoner R, Park K, Romanel A, Steiner E, Horninger W, Bektic J, Ladurner-Rennau M, Rubin MA, Demichelis F, Klocker H. DISTINCT PROSTATA CANCER AND PROSTATIC DISEASES. 2013;16:132–138.

Clinical presentation of cutaneous adnexal tumors. Zelger B, Kazakov DV, Zelger BG. PATHOLOGE. 2014;35(5):487–96.

Loss of membranous expression of the intracellular domain of EpCAM is a frequent event and predicts poor survival in patients with pancreatic cancer. Fong D, Moser P, Kasal A, Seeber A, Gastl G, Martowicz A, Wurm M, Mian C, Obrist P, Mazzoleni G, Spizzo G. HISTOPATHOLOGY. 2014;64(5):683–692.

Improved accuracy of discrimination between IgM Multiple Myeloma (MM) and Waldenstroem's Macroglobulinaemia (WM) by testing for MYD88 L265P mutations. Willenbacher W, Willenbacher E, Brunner A, Manzl C. BR J HAEMATOL. 2013;161(6):902–904.

The immunology of fibrosis. Wick G, Grundtman C, Mayerl C, Wimpissinger TF, Feichtinger J, Zelger B, Sgonc R, Wolfram D. ANNU REV IMMUNOL. 2013;31:107–135.

Selected Funding

The spectrum of B-cell-neoplasias with plasmacytic/plasmacytoid differentiation in bone marrow: Diagnostic workup for rational treatment allocation; Medizinischer Forschungsfond Tirol (MFF); Dr. Ella Willenbacher (Hematology)/Ass. Prof. PD Dr. Andrea Brunner-Véber (Pathology)

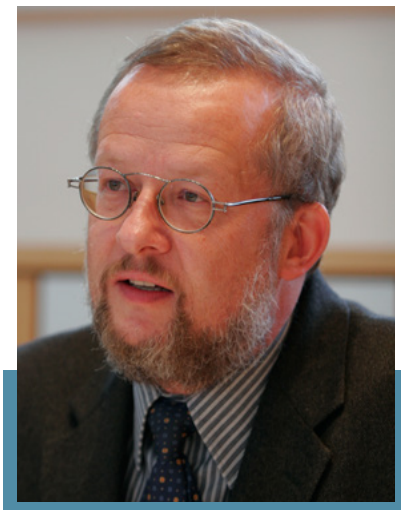
The Role of HPV infection regarding non-muscle invasive bladder cancer; Medizinischer Forschungsfond Tirol (MFF); Dr. Renate Pichler (Urology), Ass. Prof. PD. Dr. Andrea Brunner Véber (Pathology)

Multidimensional Approach of Spectra and Morphology of Oral Squamous Cell Carcinoma; Land Tirol; Prof. Christian Huck (Analytische Chemie, Leopold Franzens Universität)/ao. Univ.-Prof. Dr. Bettina Zelger (Pathology)

Collaborations

- Prof. Dr. Martina Prelog, Department of Pediatrics, University of Würzburg, Würzburg, Germany
- Prof. Hainfellner/Dr. A. Wöhrer- Klinisches Institut für Neurologie, AKH Wien, AT

Legal Medicine



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Keywords

Forensic medicine, human identification, mitochondrial DNA, EMPOP, Y-STR, pharmacogenetics, drug monitoring, spectrometry

Research Focus

- Analysis of Short Tandem Repeat (STR) loci, mitochondrial and Y-chromosomal DNA on archaeological samples. Development of molecular photo fitting for prediction of the geographical source as well as physical traits of an individual.
- Qualitative and quantitative analysis of small bioorganic molecules. Common targets are drugs, pharmaceuticals, endogenous compounds, and metabolites thereof included in all kinds of biological samples (e.g. biofluids, cells, tissues).

Research

Forensic Molecular Biology
Walther Parson

International Mitochondrial DNA Reference Laboratory
EMPOP (European forensic mtDNA population database)

In the past 20 years forensic molecular biology has faced substantial technological developments. Short Tandem Repeat (STR) loci have become the golden standard for (human) identification in crime case, ID and paternity case work. Major developments have been witnessed in the field of the uniparentally inherited genomes mitochondrial and Y-chromosomal DNA. Also, the application of X-chromosomal markers has found a vital niche in forensic DNA analysis. The Innsbruck Institute of Legal Medicine took responsibility in setting up the "EDNAP forensic mtDNA population database" (EMPOP), a new concept that addresses the necessary quality standards criteria for data generation, analysis and transfer quality control. Mitochondrial DNA (mtDNA) has the appealing characteristics of a multicopy target molecule under strict maternal inheritance that makes it an informative marker for forensic, population and medical genetic investigations. Research on mtDNA at the Institute of Legal Medicine Innsbruck goes back to the mid-nineties, where basic protocols and population studies in the human field and species-specific identification methods were introduced. Reference mtDNA database is used by international laboratories for forensic and population/medical genetic research. In addition it is used by international police organizations and judicial systems (e.g. FBI) to generate forensic evidence and to serve as a basis for internal recommendations.

mtDNA Next Generation Sequencing

Nuclear DNA (nDNA) analysis on the human remains of the 43 Mexican students missing resulted in only one identification that was reported in December 2014. The remaining 16 specimens did not contain enough intact nDNA to allow further identification. Mitochondrial DNA (mtDNA) analysis is often applied in cases where nDNA fails to provide results. But in this specific case quantification of mtDNA in the 16 unidentified remains was also negative. The results suggest that the excessive heat has destroyed the nuclear and mitochondrial DNA in the remains at least to an extent, that the conventional methods applied so far cannot be used for successful analysis. A novel technology termed "Massively Parallel Sequencing" (MPS) could serve as a useful tool to further investigate these remains. MPS has a couple of advantages over conventional DNA methods, including an increased success rate when analysing severely degraded DNA. This technology is currently evaluated for its application in forensics to identify further remains. The Institute of Legal Medicine at the Medical University of Innsbruck, has over three years of experience and is therefore pioneering research with MPS technology. Experimental data on test samples demonstrate that the new sequencing method produces useful results. In a case, where conventional DNA analysis failed, application of MPS technology would be a last attempt.

Fig. 1: Eric Pokorak (Unit Chief, Mitochondrial DNA Unit, FBI) & Douglas Hares (Custodian of the US National DNA Database, FBI) visit the Institute of Legal Medicine (Prof. Richard Scheithauer, Prof. Walther Parson) for collaboration on mtDNA interpretation.

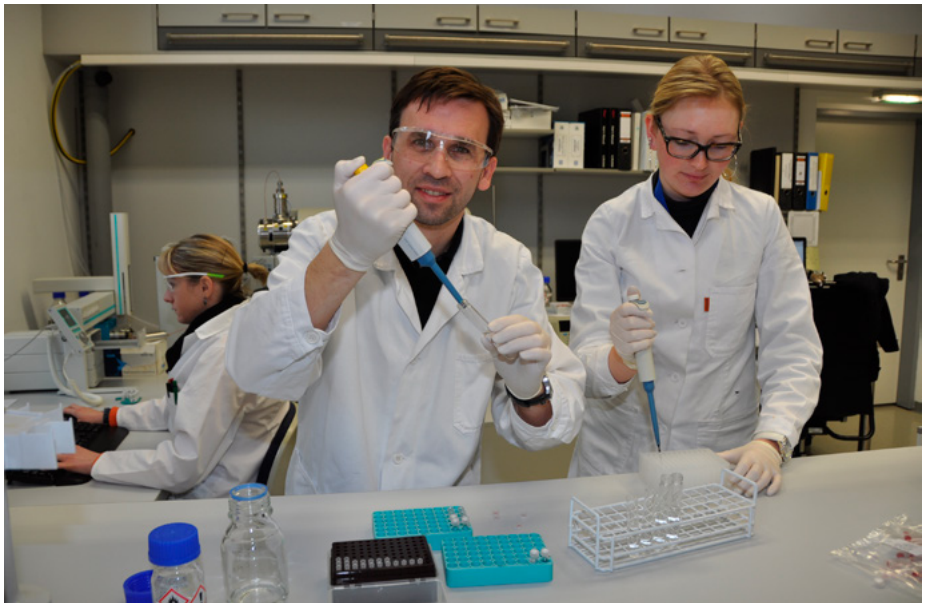

Fig. 2: Dipl-Ing.(FH) Kathrin Arnhard, Prof. Herbert Oberacher and Julia Steger at the lab of the core facility.

Forensic Archaeology
The institute has a long standing tradition in being repeatedly consigned to handle international requests on DNA fingerprinting such as the DNA identification of the Asian Tsunami-victims, the remains of the Russian Tsar family or historical cases such as the putative Mozart skull and the remains of Friedrich Schiller. Recently, Walther Parson has been invited to join the King Richard III identification research group as an expert in mitochondrial DNA analysis. In this specific case reference samples were available from two living individuals: Michael Ibsen and Wendy Duldig, who are 19 and 21 generations removed from King Richard III, respectively. Using genetic and non-genetic evidence thus strongly supporting, beyond reasonable doubt, that the skeleton is Richard III, which represents the eldest human identification case known to date.

Bioanalytical Mass Spectrometry Group and Core Facility Metabolomics
Herbert Oberacher
Our research is interdisciplinary, focusing on different aspects of bioanalytical chemistry and its application in metabolomics, forensic science, medical and pharmaceutical research, as well as pharmacogenetics.
The analytical methods, on which our research is mainly focused, are high-resolution bioorganic mass spectrometry, separation techniques as well as different kinds sample preparation techniques, such as extraction, polymerase chain reaction or electrochemistry. Furthermore, we spend much effort on the development of cutting-edge algorithms and software tools for small molecular identification via automated interpretation of tandem mass spectral data. Developed and validated assays find applicability in the comprehensive analysis of complex biological samples as part of the service provided by the Core Facility Metabolomics.
The mission of the Core Facility Metabolomics is to serve as an enabling resource for research and development programs at the Medical University of Innsbruck. We aim to provide expertise and state-of-the-art technologies for the qualitative and quantitative analysis of small bioorganic molecules. Common targets are drugs, pharmaceuticals, endogenous compounds, and metabolites thereof included in all kinds of biological samples (e.g. biofluids, cells, tissues).

Selected Publications

DNA Commission of the International Society for Forensic Genetics: revised and extended guidelines for mitochondrial DNA typing.
Parson W, Gusmao L, Hares DR, Irwin JA, Mayr WR, Morling N, Pokorak E, Prinz M, Salas A, Schneider P M, Parsons TJ.
FORENSIC SCI INT GENT. 2014; 13: 134–142.

Evaluation of next generation mtGenome sequencing using the Ion Torrent Personal Genome Machine (PGM).
Parson W, Strobl C, Huber G, Zimmermann B, Gomes SM, Souto L, Fendt L, Delport R, Langit R, Wootton S, Lagace R, Irwin J.
FORENSIC SCI INT GENT. 2013; 7(5): 543–549.

Identification of the remains of King Richard III.
King TE, Fortes GG, Balaresque P, Thomas MG, Balding D, Delser PM, Neumann R, Parson W, Knapp M, Walsh S, Tonasso L, Holt J, Kayser M, Appleby J, Forster P, Ekserdjian D, Hofreiter M, Schurer K. NAT COMMUN. 2014; 5: 5631.

Evaluation of the Sensitivity of the "Wiley Registry of Tandem Mass Spectral Data, MSforID" with the "NIST/NIH/EPA Mass Spectral Library".
Oberacher H, Whitley G, Berger B.
JOURNAL OF MASS SPECTROMETRY. 2013; 48: 487–496.

Studying the Reducing Potencies of Antioxidants with the Electrochemistry Inherently Present in Electrospray Ionization-Mass Spectrometry. Plattner S, Erb R, Chervet J-P, Oberacher H.
ANALYTICAL AND BIOANALYTICAL CHEMISTRY. 2014; 406: 213–224.

Concept for estimating mitochondrial DNA haplogroups using a maximum likelihood approach (EMMA).
Röck AW, Dür A, van Oven M, Parson W.
FORENSIC SCI INT GENT. 2013; 7(6): 601–609.

Comparison of morphological and molecular genetic sex-typing on mediaeval human skeletal remains.
Bauer CM, Niederstatter H, McGlynn G, Stadler H, Parson W.
FORENSIC SCI INT GENT. 2013; 7(6): 581–586.

Getting the Whole Picture: Adding Patient-Reported Outcomes to Adjuvant Endocrine Treatment Evaluation in Premenopausal Breast Cancer Patients.
Oberguggenberger A, Goebel G, Beer B, Oberacher H, Meraner V, Sztankay M, Sperner-Unterweger B, Zeimet AG, Marth C, Hubalek M, Holzner B. BREAST JOURNAL. 2014; 20: 555–557.

Selected Funding

- Maximizing mtDNA Testing Potential with the Generation of High-Quality mtGenome Reference Data, NIJ mtDNA WGS 2011-MU-MU-K402
- European Forensic Genetics – Network of Excellence, EUROFORGEN FP7-SEC-2011-285487
- Application of forensic DNA fingerprinting for the investigation of archaeological and modern human migration patterns in a geographically defined Alpine population, FWF, Volders P22880-B12
- Simulation of redox processes involving nucleic acids, FWF, Projekt P 22526-B11, 2010–2013

Collaborations

- Institute of Mathematics, University Innsbruck, Innsbruck, Austria
- Institut Geschichtswissenschaften / Europäische Ethnologie, University Innsbruck, Innsbruck, Austria
- Zentralinstitut für Bluttransfusion und Immunologische Abteilung, Tirol Kliniken, Innsbruck, Austria
- Armed Forces DNA Identification Laboratory, Rockville, USA
- Bundeskriminalamt Wiesbaden, Wiesbaden, Germany
- Institut für Veterinärpathologie, University Giessen, Giessen, Germany
- Department of Internal Medicine, Innsbruck Medical University, Innsbruck, Austria
- Department of Gynecology and Obstetrics, Innsbruck Medical University, Innsbruck, Austria
- Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Core Facilities

- Metabolomics


G12
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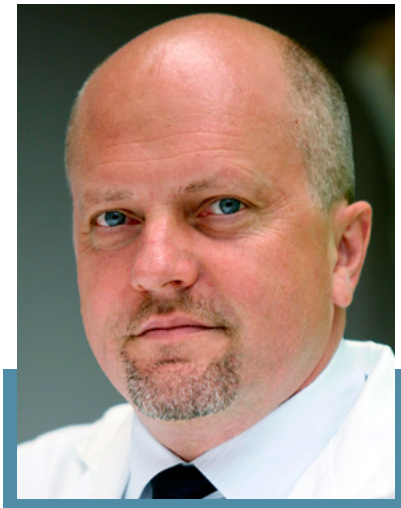
Clinical Research Units

Center of Operative Medicine

Visceral, Transplant and Thoracic Surgery



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Keywords

Metastatic surgery, ischemia-reperfusion injury, sepsis

Research Focus

Oncology – Metastatic Disease
- Clinical studies on surgical oncology including both retrospective single center studies and prospective international studies, according to the affected organs
- Clinical and experimental studies on peritoneal carcinomatosis and metastatic disease

Ischemia-Reperfusion Injury in Organ Transplantation
One main focus of our research is to gain a better understanding of the pathophysiological mechanisms underlying ischemia-reperfusion (I/R) injury. I/R injury represents a threat, to which all transplanted organs are subjected in the process of transplantation and which is known to crucially influence graft and patient long-term survival. Identification of the mechanisms involved would not only help to better understand this process but also to identify new treatment targets.

Sepsis
Treatment of abdominal sepsis with open abdomen treatment and negative pressure.

General Facts

The Department of Visceral, Transplant, and Thoracic Surgery maintains not only an internationally established high volume transplant program with transplantation of all solid organs (kidney, liver, pancreas, small bowel, cluster and in cooperation with the Department of Cardiac Surgery heart and lung), as well as vascularised composite allografts, but also covers as a Central Hospital with tertiary patient care the entire field of general, visceral and thoracic surgery in adults and children.

Translational research takes place at the Department of Visceral, Transplant, and Thoracic Surgery with its associated **Daniel Swarovski Research Laboratory**. Work is proceeding along three main axes, which cover the fields of main interest in transplantation, surgical oncology and infectiology, namely ischemia-reperfusion injury, sepsis and metastatic disease. In parallel to patient care with an extended quality assurance program and risk management, the Daniel Swarovski Research Laboratory (DSL) represents a high-end research unit which creates a perfect symbiosis between clinicians and basic scientists. In a "bed to bench and back" approach: complex treatment regimes and clinical trials can be further enhanced by molecular in-depth analysis. Furthermore, the research line is supplemented by development of proof of concept trials employing a large variety of micro-surgically most challenging organ and limb transplantation models in small as well as large animals.

Together with Prof. Jakob Troppmair as head of the DSL research laboratory, senior staff surgeons and/or senior surgical residents investigate infectious, oncological and transplantation-related topics in cell culture, small animal models and specimens from clinical trials in collaboration with regional or international research colleagues. Within a project, group leaders usually mentor diploma students, who hereby have the unique opportunity to develop not only basic science but also (micro)surgical skills.

Research

Oncology – Metastatic Disease
Priv.-Doz. Dr. Alexander Perathoner, Ass.-Prof. Dr. Florian Augustin
Oncological science is one of the most important and dynamic areas of surgical science. The Department of Visceral, Transplant and Thoracic Surgery is able to

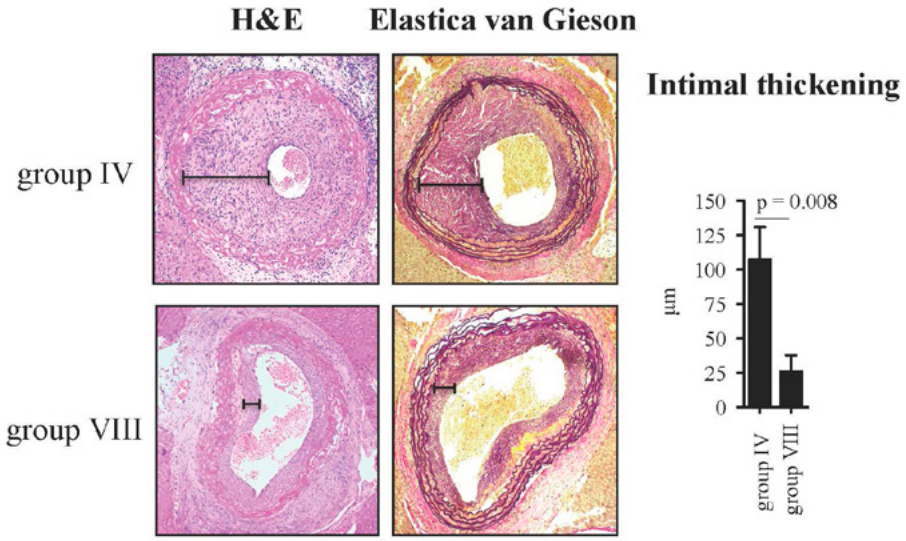

Fig. 1: Development of transplant vasculopathy. Aortic grafts taken from a tetrahydrobiopterin-treated (group VIII) or untreated donors (IV), subjected to 24h cold ischemia time (CIT), and reperfused for 4 weeks. H&E (left column) and Elastica van Gieson (right column) staining. (a+b) untreated with cold ischemia time, (c+d) tetrahydrobiopterin-treated with cold ischemia time, (e) intimal thickening (µm). Results are expressed as mean ± SEM.

offer complete surgical management of the whole spectrum of surgical malignancies from very frequent tumors such as colon cancer to very rare tumors such as peritoneal malignancies. Therefore, oncological research at the Department of Visceral, Transplant and Thoracic Surgery is also characterized by a broad field of variegated research topics according to the different affected organs (e.g. thyroid cancer, gastric cancer, lung cancer). Surgical science is typically dominated by clinical research: all patients with a malignant disease are registered in databases (e.g. Austrian HIPEC Registry) to allow periodic retrospective and prospective analyses. The ongoing surveillance of oncological patients also enables the Department to participate in important national (e.g. ABCSG 16/SALSA Study and ABCSG 26/SOLE Study on extended endocrine therapy in breast cancer patients) and international studies (e.g. international multicenter study on surgical morbidity in lung cancer patients with VATS-lobectomy). The clinical research includes diagnostic tools (e.g. the diagnostic value of ultrasound in thyroid cancer) as well as new treatment options (e.g. hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis). Of course, experimental projects also play a very important role in oncological research at the Department of Visceral, Transplant and Thoracic Surgery: scientists in our own or in cooperating laboratories (e.g. Daniel Swarovski Laboratory) work on various projects, including studies on transcription factors (e.g. STAT-1 in gastric cancer and colorectal cancer), adhesion molecules (e.g. CD44v6 in patients with non small cell lung cancer), cytokines (e.g. in peritoneal carcinomatosis) and numerous other proteins (e.g. lipocalin 2 in colon cancer patients).

Given that the treatment of patients with metastatic disease has changed significantly in the last years due to development of multimodal therapies, the Department of Visceral, Transplant and Thoracic Surgery intends to establish this topic as a new focus in surgical oncological science. The aim of the Metastasis Research Group in the future will be to combine clinical and experimental scientific projects in order to improve understanding of metastatic disease and treatment of patients with metastases.

The following list of different exemplary clinical and experimental studies displays the broad spectrum of oncological research

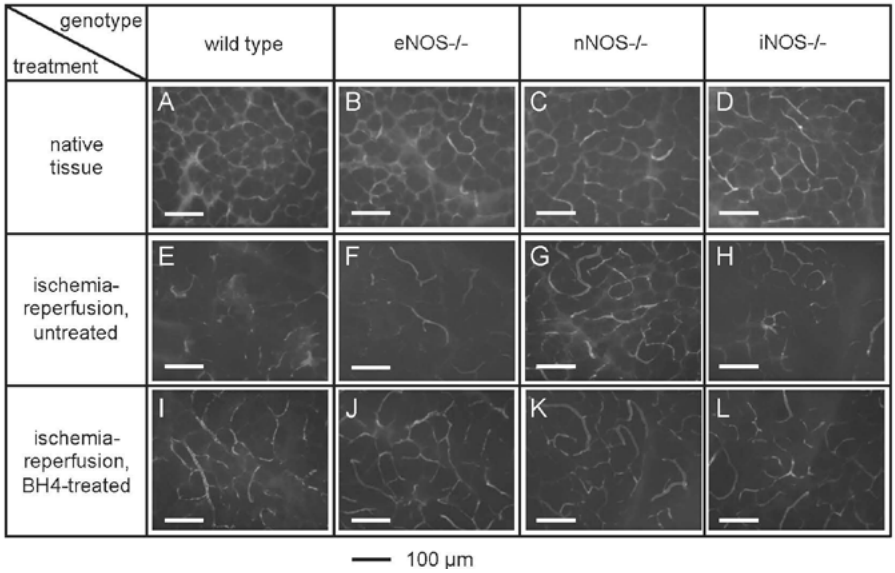

Fig. 2: Capillary mesh of pancreata in dependence of donor treatment and donor genotype. Pancreata were taken from tetrahydrobiopterin-treated or untreated donors with the indicated genotypes, subjected to ischemia, and transplanted to wild type recipients of the same background as the knockouts (n = 5 per group). The capillary mesh was stained by infusion with fluorescein labelled dextran and observed by confocal intravital fluorescence microscopy. A–D: nontransplanted organs of wild type, eNOS -/-, nNOS -/- and iNOS -/-. E–H: organs of untreated donors (wild type, eNOS -/-, nNOS -/- and iNOS -/-, respectively), transplanted to wild type recipients, 4 h after reperfusion. I–L: organs of donors treated with BH4 (wild type, eNOS -/-, nNOS -/- and iNOS -/-, respectively), transplanted to wild type recipients, 4 h after reperfusion.

at the Department of Visceral, Transplant and Thoracic Surgery according to the primary affected organs:

Elastography predicts thyroid cancer: comparison of two methods (compression ultrasound elastography vs. acoustic radiation force ultrasound elastography) with respect to diagnostic value and feasibility. (Research Group Thyroid Cancer)

ABCSG Study 16/SALSA (Prospective, randomized, open-label, multi-center, phase-II-study evaluating the effect of a secondary adjuvant endocrine therapy with anastrozole for 2 years vs. 5 years in patients with hormone-receptor-positive breast cancer after 5 years prior adjuvant endocrine therapy.) (Research Group Breast Cancer)

Nation wide survey in Austria: Is laparoscopic adjustable gastric banding an underestimated risk factor for developing esophageal cancer? (Research Group Esophageal and Gastric Cancer)

Expression of neutrophil gelatinase-associated lipocalin in colorectal cancer (Research Group Colorectal Cancer)

Single center prospective analysis of cancer-associated cytokines in serum and peritoneal fluid of patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal surface malignancies as a potential tool for perioperative therapy monitoring. (Research Group Peritoneal Carcinomatosis)

Study on volatile organic compounds in non-small cell lung cancer tumor tissue, aiming to define tumor markers for monitoring of therapy and for early detection of recurrent disease. (Research Group Lung Cancer)

Ischemia-Reperfusion Injury
ao. Univ.-Prof. Dr. Stefan Schneeberger, Ass.-Prof. Priv.-Doz. Dr. Manuel Maglione
Major advances in surgical techniques, antibiotic prophylaxes, preservation solutions and immunosuppressive therapy, have elevated solid organ transplantation to the treatment of choice in patients suffering from irreversible organ failure.

Currently, organ shortage as well as chronic allograft loss represent two major hurdles to further enhancing the success of solid organ transplantation. For both, the limited

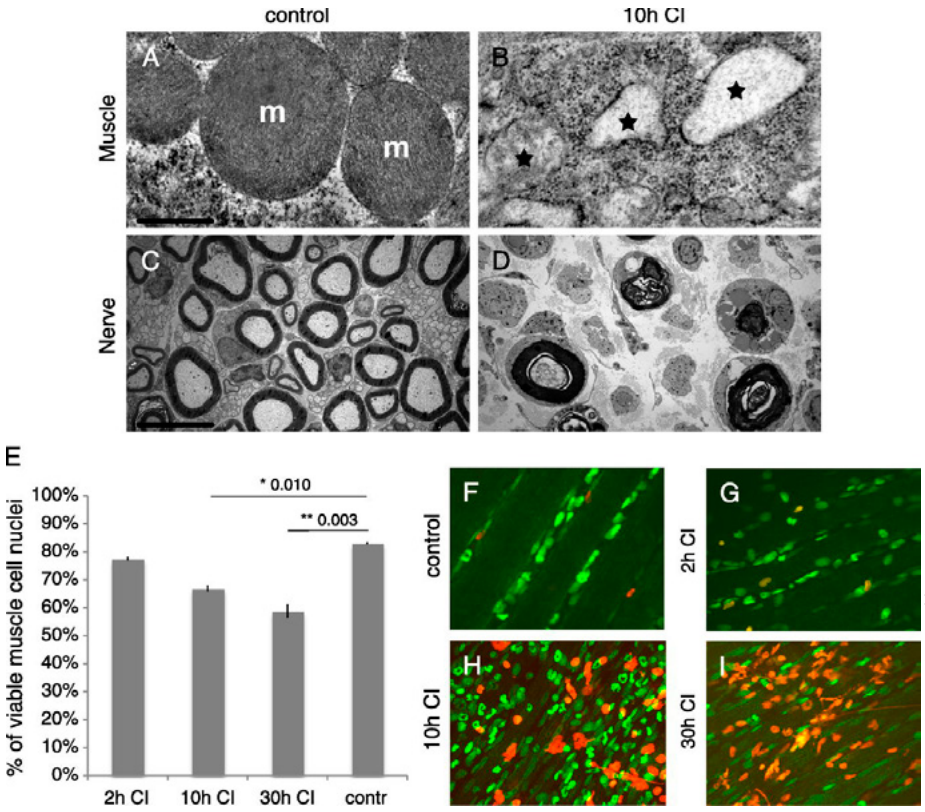

Fig. 3: A-D, TEM observations of the skeletal muscle and the sciatic nerve in saline-treated limbs on POD 10. Muscle (A, B): A, The ultrastructure of the muscle mitochondria (m) is well preserved in both the controls and the 2-hr CI limbs, B, whereas in the 10-hr and 30-hr CI group, a large fraction of the mitochondria is degenerated (asterisks). A and B: same magnification. Scale bar=0.5 µm. Nerve C and D: C, In the control, nerve fibers display a compact arrangement of their myelin lamellae around the axon. D, In all CI groups, however, either vacuolization of the myelin sheath is seen or the myelin sheath has completely disappeared. C and D: same magnification. Scale bar=10 Km. µ-I, Confocal microscopy of the skeletal muscle in saline-treated animals on POD 10. Staining of viable (green, SYTO 16) and avital (red, PI) muscle cell nuclei was performed to further detect damage to skeletal muscle. E, Although only a slight loss of viable cell nuclei was observed in the anterior tibial muscle of 2 hr CI animals, compared to nontransplanted controls, viable muscle cell nuclei were significantly diminished in 10 hr (P=0.01) and 30 hr (P=0.003) CI animals. F and G, In nontransplanted controls and 2 hr CI animals, the majority of cell nuclei were vital (green). H and I, Prolonged CI (10 hr and 30 hr) led to a high number of avital cell nuclei in skeletal muscle, detected by PI staining (red). TEM, transmission-electron microscopy; CI, cold ischemia; POD, postoperative days; PI, propidium iodide.

potential use of available organs and long-term graft failure, I/R injury plays an important role.

Increasing both donor age and the incidence of extended criteria donors (ECDs) provides us with organs which are more prone to develop significant injury through I/R. As a consequence, and in order to avoid severe, irreversible I/R injury, these organs are more likely to be declined if a prolonged cold ischemia time is foreseen. Further, I/R injury is known to crucially influence the development of chronic allograft rejection. Hence, prevention of I/R injury is probably one of the most important goals in solid organ transplantation. One of the long-standing points of interest of our research aims is to investigate ischemia/reperfusion injury following organ transplantation as well as its long-term consequences. While the phenotype of I/R injury has been quite well established in solid organ transplantation, no such detailed analysis is available for transplantation of vascularized composite tissue allografts such as the hand or the face. While this field is relatively new, in the past 15 years vascularized composite tissue allotransplantation (VCA) has become a rapidly advancing field with more than 100 hand/forearm transplantations and 20 face transplantations carried out in transplant centres all over the world. We have recently established the first in-depth analysis of the tissue damage induced by I/R injury in rodent models. Employing electron microscopy, confocal microscopy and molecular analysis of tissue-infiltrating inflammatory cells and markers for tissue damage, we have identified the injury to individual tissues as well as the architecture of the graft. Further, novel solutions and techniques for rinsing and storage of the tissue are currently being tested in order to enhance tissue conservation during the process of transplantation and to allow for prolongation of the ischemia time. Particular attention is paid towards preserving nerves and muscle, where the most significant damage has been established to occur: in Schwann cells and in subcellular components such as mitochondria. Building on the experience from findings in organ transplantation, mechanisms proven to be relevant in preventing I/R injury may also be tested in VCA models.

Another topic in our research unit is the analysis of the immunomodulatory properties of tetrahydrobiopterin, a naturally occurring essential co-factor structurally related to the vitamins folate and riboflavin. We could show in a pancreas transplantation model in mice that treating the donor with exogenous tetrahydrobiopterin could effectively prevent lethal I/R injury in the transplanted recipient. In addition to its potent antioxidative properties, tetrahydrobiopterin is also known as an essential co-factor for a set of 8 different enzymes, including the three nitric oxide synthase (NOS) isoforms (neuronal, endothelial, and inducible). We have identified neuronal nitric oxide synthase as a target for tetrahydrobiopterin treatment in the prevention of I/R injury. Whether the other tetrahydrobiopterin-dependent enzymes play immunomodulatory roles will be the focus of future studies. Based on these observations, current projects in this field focus on (1) prevention of severe I/R injury in a brain death mouse model, aiming to simulate the clinical situation of cadaveric organ donation; (2) the triggering mechanisms of I/R injury in inducing transplant vasculopathy and the potential role of tetrahydrobiopterin in preventing it, and (3) simvastatin, which is hypothesised to prevent I/R injury by a tetrahydrobiopterin-mediated process.

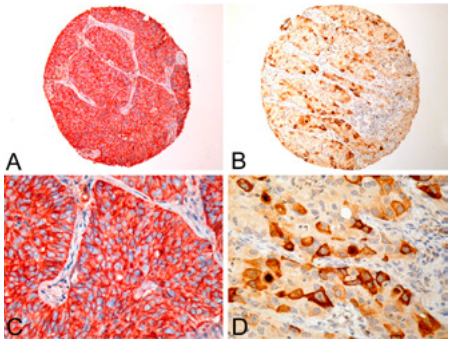

Fig. 4: (A) Expression of CD44v6 in a squamous cell carcinoma (SCC); tissue microarray (TMA) core overview, 80x magnification. (B) Expression of the receptor of hyaluronic acid-mediated motility (RHAMM) in a large-cell carcinoma (LCC); TMA core overview, 80x magnification. (C) Expression of CD44v6 in the above SCC case; 320x magnification. (D) Expression of RHAMM in the above LCC case; 320x magnification.

A further topic in our research unit is the protective role of hemeoxygenase-1 (HO-1) and biliverdin. HO-1 is the rate-limiting step in conversion of heme into biliverdin, carbon monoxide and free iron (Fe^{2+}). Up-regulation of HO-1 has been described during acute and chronic rejection as well as I/R injury, and has been considered to act as a cytoprotective enzyme. HO-1 heme degradation products act strongly anti-oxidatively, and this seems to be the crucial aspect in prevention of I/R injury by HO-1 induction. Hence, activating this pathway early after organ transplantation or even during organ recovery might protect transplanted grafts from ischemia reperfusion injury. Considering future clinical applications, current projects aim to target the HO-1 pathway in different small animal models by (1) application of nutraceuticals such as Ginseng and Resveratrol, which are known to induce HO-1, and by (2) administration of the bile pigment biliverdin, the degradation product of heme, which is known to have important anti-oxidative properties.

Clearly, the backbone of the transplant research unit consists of the various established animal models, which closely resemble clinical everyday life. The experimental setting is completed by morphological analysis, comprising intravital confocal fluorescence microscopy, histopathology and immunohistochemistry, electron microscopy, and also by biomolecular methods including amongst others western blots, enzyme activity assays, RTqPCR, proteomics and gene chip analysis, mediating the ultimate goal of eventually translating results into clinical reality.

Research Focus Sepsis
Priv.-Doz. Dr. Reinhold Kafka-Ritsch

The research on abdominal sepsis is integrated into the clinical routine of the department; the main focus is on development of new strategies for the treatment of abdominal sepsis. The ongoing prospective randomized study is administered by our study coordination office.

Abdominal sepsis with generalized peritonitis is a life-threatening condition requiring immediate surgical intervention. Despite intervention, a high percentage of these patients develop severe septic shock with multi-organ dysfunction. At the time of emergency laparotomy, patient recovery is uncertain and stabilization of the patient in the intensive care unit is recommended. We have developed a damage control concept using abdominal vacuum therapy to treat patients' abdominal sepsis. The primary aim of this concept is to enhance recovery and allow bowel reconstruction in a second-look operation.

To prevent retraction of the fascia and enhance the possibility of direct closure of the abdominal wall, we combine use of negative-pressure therapy with dynamic sutures to the fascia. Moreover, our studies aim to investigate the long-term outcome of this patient population with special interest in incisional hernia development.

At present we are performing a prospective randomized study on the surgical treatment of patients with colonic perforation and peritonitis, treating with a damage control strategy and application of abdominal vacuum therapy.

The aim of the study is to demonstrate that by using a damage control strategy with topical negative pressure in patients with peritonitis caused by colonic perforation, a faster recovery from sepsis and a higher rate of colonic reconstruction can be achieved. Based on our published experience with this damage control concept and a reconstruction rate of 80% in this life threatening situation, we want to test this concept in a prospective randomized trial.
Primary Endpoint: Rate of patients having a reconstructed colon at discharge from the hospital and at 6 months after emergency operation.
Secondary Endpoints: 30 day hospital mortality rate, ICU Stay , Hospital stay, VAC associated complications and overall complication rate.

The study is approved by the local ethics committee and was initiated as a single center trial at the University Hospital Innsbruck, but is further planned to become a multicenter trial with the surrounding secondary hospitals.

Selected Publications

Incisional hernia rate after open abdomen treatment with negative pressure and delayed primary fascia closure. Brandl A, Laimer E, Perathoner A, Zitt M, Pratschke J, Kafka-Ritsch R.
HERNIA. 2014; 18: p. 105–111.

Therapeutic Management and Outcome of Locoregional Recurrence After Curative Colorectal Cancer Therapy-a Single-Center Analysis. Kogler P, Kafka-Ritsch R, Sieb M, Sztankay A, Pratschke J, Zitt M. JOURNAL OF GASTROINTESTINAL SURGERY. 2014; 18: p. 2026–2033.

Up-regulation of Neutrophil Gelatinase-Associated Lipocalin in Colorectal Cancer Predicts Poor Patient Survival. Maier HT, Aigner F, Trenkwalder B, Zitt M, Vallant N, Perathoner A, Margreiter C, Moser P, Pratschke J, Amberger A.
WORLD JOURNAL OF SURGERY. 2014; 38: p. 2160–2167.

Crucial role for neuronal nitric oxide synthase in early microcirculatory derangement and recipient survival following murine pancreas transplantation. Cardini B, Watschinger K, Hermann M, Obrist P, Oberhuber R, Brandacher G, Chuaiphichai S, Channon KM, Pratschke J, Maglione M, Werner ER.
PLOS ONE. 2014; 9: p. e112570.

Histomorphometric Evaluation of Ischemia-Reperfusion Injury and the Effect of Preservation Solutions Histidine-Tryptophan-Ketoglutarate and University of Wisconsin in Limb Transplantation. Hautz T, Hickethier T, Blumer MJF, Bitsche M, Grahammer J, Hermann M, Zelger B, Messner F, Pechriggl EJ, Krapf C, Kimelman M, Brandacher G, Lee WPA, Margreiter R, Pratschke J, Schneeberger S.
TRANSPLANTATION. 2014; 98: p. 713–720.

Selected Funding

- RAF and BCL-2 in the regulation of cell death under oxidative stress; Der Wissenschaftsfonds (FWF); MCBO -W01101; 2005–2015; € 600,000; Univ.-Prof. Dr. Jakob Troppmair
- Deutsche Forschungsgemeinaschaft (DFG); Auswirkung und Therapieversuche des Hirntodes in experimentellen und klinischen Modellen; 2010–2014; € 399,398.06; Univ.-Prof. Dr. Katja Kotsch
- Tiroler Zukunftsstiftung; MitoCom Tyrol; 2011–2014; € 169,943.50; ao.Univ.-Prof. Dr. Erich Gnaiger
- Houskapreis B&C Privatstiftung; Houska-Preis 2011; MitoCom Netzwerk; 2012–2017; € 120,000; ao.Univ.-Prof. Dr. Erich Gnaiger
- Der Wissenschaftsfonds (FWF); Die Rolle von Lipocalin-2 als Marker und therapeutisches Target in der Nierentransplantation; 2011–2014; € 165,350.20; ao. Univ.-Prof. Dr. Felix Aigner

Collaborations

- Peter J. Friend, Rutger Ploegh, University of Oxford, Nuffield Department of Surgical Scieces, Oxford, UK
- Keith M. Channon, University of Oxford, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, Wellcome Trust Centre forHuman Genetics, Oxford, UK
- Darius Mirza, University Hospitals Birmingham, Liver and Hepato-Pancreato-Biliary (HPB) Unit, Birmingham, UK
- Gerald Brandacher, Andrew WP Lee, Johns Hopkins Medical University, Department of Plastic Surgery, Baltimore, USA
- University of Pittsburgh Medical Center (UPMC), Division of-Plastic and Reconstructive Surgery, Department of Surgery, Pittsburgh, USA
- Hans Schlitt, Universitätsklinikum Regensburg, Klinik und Poliklinik für Chirurgie, Regensburg, GER
- Kurt Werner Schmid, Universitätsklinikum Essen, Institut für Pathologie, Essen, GER
- Emmanuel Morelon, Hospices Civils de Lyon, Hospital Edouard Herriot – Transplantation, néphrologie et immunologie, Lyon, FR

Cardiac Surgery

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Keywords

Myocardial infarction, hypoxia, angiogenesis, bypass graft biology, thoracic aortic aneurysm, stem cells, pharmacotherapy, prevention, aging, risk factors

Research Focus

The research strategy of the University Clinic for Cardiac Surgery is split into two main concepts and generally covers central aspects of cardiovascular surgery, medicine, and biology. With application-oriented projects we seek i) to improve myocardial protection and regeneration after infarction, ii) to increase durability of coronary bypass grafts, and iii) to develop new tests allowing for the early diagnosis of and screening for thoracic aortic aneurysms in blood samples. Several of these studies are done in cooperation with companies. With basic science projects we seek to define fundamental molecular and cellular pathophysiological processes leading to cardiovascular diseases, allowing for a later application in diagnosis, prevention and treatment of patients. Techniques cover areas of analytical chemistry, molecular and cellular biology, primary human cell culture, tissue and organ culture studies, as well as patient-based studies.

General Facts

The University Clinic for Cardiac Surgery aims to act as a modern cardiosurgical unit with focus on surgical outcome, quality control, and development of modern surgical strategies combined with patient well-being, and advanced training of staff. Permanent improvement in all areas of activity of our department is our maxim. Activities in our department include patient care, academic teaching, education, and research. Core expertises of our clinic are:

i) coronary bypass surgery with focus on aggressive use of bilateral mammary arteries, and minimally invasive robotic coronary surgery

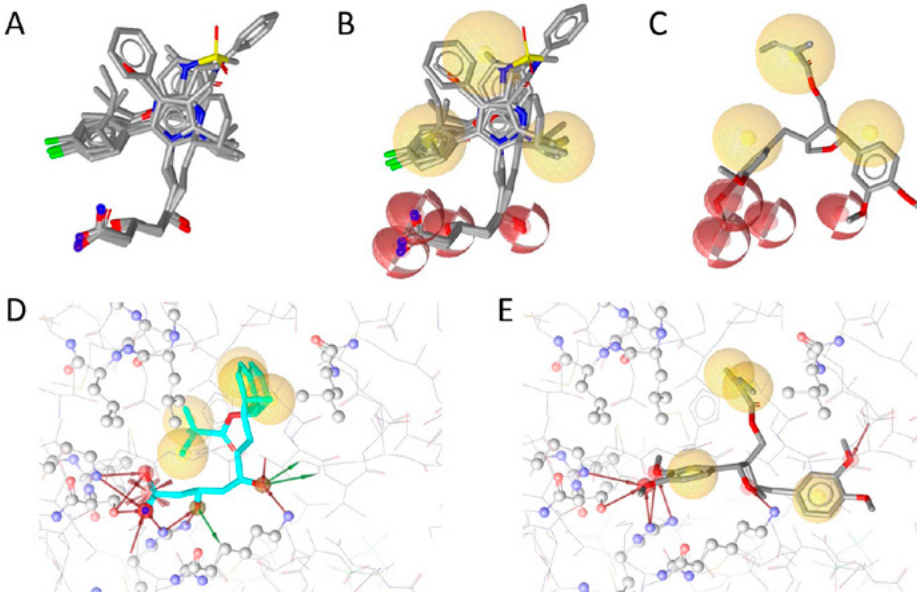

Fig. 1: Molecular modelling and docking of leoligin (isolated from Edelweiss) with HMG-CoA-reductase suggests an unconventional binding mode. Alignment of bioactive conformations of statin molecules bound to HMG-CoA-reductase (A). Chemical functionalities shared by statins (B). Leoligin mapped to the common feature statin model. All but two chemical features (red spheres) were mapped by the ligand, suggesting similar protein-ligand interaction profiles to those of the currently used statins (C). Simvastatin bound to HMG-CoA-reductase in the PDB entry 1hw9 (D). The statin forms hydrophobic contacts, hydrogen bond acceptors and donors, and a charged interaction with Arg590. Suggested binding orientation of leoligin within the HMG-CoA-reductase active site (E). Similar to simvastatin, hydrophobic contacts and hydrogen bond networks also including Arg590 are formed. Interaction types are color-coded: red – hydrogen bond acceptor, green – hydrogen bond donor, yellow – hydrophobic, red star – negative charge. Cooperation with Dr. Daniela Schuster, University of Innsbruck.

ii) valve surgery is performed – 85% of all solated procedures – with minimally invasive access without compromise in outcome quality (evaluated by contribution to international multicenter studies). The use of transcatheter valves (TAVI) is successfully implemented (in high-risk patients we have an overall mortality of 6% – the calculated risk is 29% (logistic EuroScore)).

The program on minimally invasive mitral valve repair via anterolateral thoracotomy has a very strong position in our unit. This program is not only the biggest in Austria, but also gives Innsbruck a strong international reputation. Approximately 80% of all suitable mitral repair procedures are performed using this technique. About 95% of these specific patients received successful repair of the native valve, which is remarkably high. The annual surgical training course "Focus Valve" is held in Innsbruck and has become the most important meeting on advanced techniques in minimally invasive valve surgery in Europe, with surgeons from more than 30 countries attending.

iii) In advanced life support, Innsbruck has established a local network for mechanical circulatory support and in acute cardiogenic shock ECMO has become the primary care for these patients.

iv) Being the second largest program in Austria, we also run a heart and lung transplantation program with excellent outcome (1-year survival rates above 90% in heart and above 80% in lung transplantation). Currently we offer various types of mechanical circulatory assist devices to our patients (HeartMate II, Heartware; for BiVentricular Support: Thoratec, Berlin Heart (pediatrics), and Total Artificial Heart (SynCardia)).

v) With our complete spectrum of child heart surgery, in recent years we have treated more children with congenital heart disease than ever before, and with excellent results. In years 2008 to 2012 we carried out 364 cases with cardio-pulmonary bypass and more than 200 without. The complexity (defined by Aristotle score) of our cases is gradually increasing, with very low mortality.

vi) In the thoracic aortic aneurysm program we offer a full spectrum of modern aortic surgery. Central to this are the weekly aneurysm clinics for thoracic aortic aneurysm held by our unit. Here we see about 500 patients a year, predominantly originating from Western Austria.

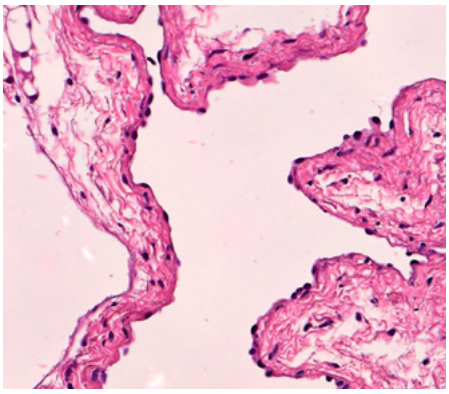

Fig. 2: Histological state of a venous bypass graft prior to implantation into the arterial system (mouse model). We are currently running a study on the pathophysiology of vein graft intimal hyperplasia. First results indicate that the current view on the genesis of intimal hyperplasia may be wrong – our results may open totally new treatment options.

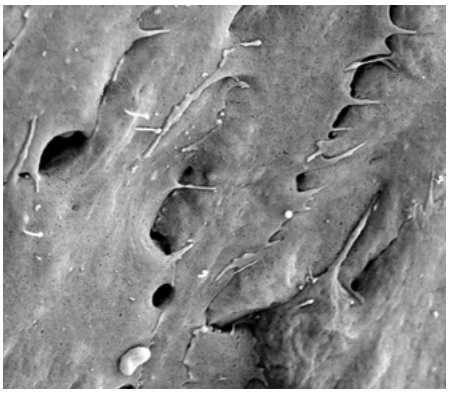

Fig. 3: This electron microscopic image shows events occuring on the endothelial surface of an atherosclerotic plaque in the mouse aorta in reponse to cadmium exposure. A clear retraction of endothelial cells can be observed, which leads to the opening of gaps between these cells, resulting in a loss of endothelial barrier function. A significant acceleration of plaque development and rupture is the consequence.

vii) Our research laboratory team is multidisciplinary and in close contact with the clinical team. Regular meetings allow for a perfect communication and exchange of knowledge between the laboratory and clinics. Our work is published in the top journals of the field, and our science has led to company cooperation and consultation support to the Austrian Ministry of Health and the World Health Organisation.

Research

As a central part of the Department of Cardiac Surgery, the Cardiac Surgery Research Laboratory covers: scientific consulting and analytics for clinical trials, scientific education of surgical assistants, PhD and medical PhD projects, application-oriented research and basic research. Since 2007, the laboratory has been headed by a biologist and pathophysiologist (Ass-Prof. PD. Dr. David Bernhard) (with a 3 year break during which he headed the Cardiac Surgery Research Laboratory of the Medical University of Vienna), and includes three teams (i.e. work groups Bernhard, Holfeld, and Bonaros). The goal of the Department of Cardiac Surgery is to mirror clinical projects and studies by laboratory based projects and *vice versa*, to cover the full spectrum of bench-to-bed side and bed side-to-bench options.

Application-Oriented Science

The central task in this field of research is the improvement of current surgical treatments as well as the development of novel treatment options.

Myocardial Protection and Regeneration

The induction of regenerative processes and angiogenesis after myocardial infarction (MI) is the central goal of most experimental approaches aiming to improve the treatment of MI patients. To achieve this goal the Cardiac Surgery Research Laboratory follows three major strategies: i) pharmacological, ii) physical, and iii) biological stimulation of regeneration.

Many years of research in all of the above areas have led to significant pre-clinical success. One major innovative approach, which was discovered and established in the Cardiac Surgery Research Laboratory, is a classical bench-to-bed side approach. The basis of this **approach i) (team Bernhard)** was laid by a cooperation with the Department of Pharmacy of the University of Innsbruck, which set out to find compounds that stimulate angiogenesis. 5-Methoxyleoligin, a compound isolated from the roots of Edelweiss, showed potent effects *in vitro*. *In vivo* the effects were even more surprising, as the compound not only stimulated angiogenesis, but also arteriogenesis (formation of larger blood vessels), and rescued myocardial muscle mass in the infarction area, altogether increasing cardiac performance by + 21%EF (ejection fraction) in pre-clinical trials.

Approach ii) (team Holfeld) applies shock waves to the infarcted area of the heart. Shock wave therapy improved cardiac performance (left ventricular ejection fraction) by + 18 % EF (ejection fraction). This effect is mediated by the induction of angiogenesis and other regenerative processes. The major advantage of shock waves, compared to all other kinds of treatments, and due to its focused mode of application, is that it is almost free of side effects; it is cheap, and easy to apply.

Approach iii) (team Bonaros) seeks to stimulate myocardial regeneration by stem cell therapy. As studies in the past showed only a minor effect of stem cell therapy in human myocardial infarction, due to the rapid disappearance of stem cells from the infarction zone (hours), the core and focus of this approach is to increase the duration of residence and survival of stem cells in the infarction area.

Importantly, the above strategies can also be combined. Approaches i) and ii) are protected by patents, large animal studies have been conducted for ii) and are planned in the near future for i) and iii). Toxicological studies for i) have been performed and did not show toxicity. The compound for i) is now available in a synthetic form (cooperation with the Technical University of Vienna). For ii) and iii), initial clinical trials have been performed.

Bypass Surgery (Team Bernhard)
The Vena saphena is used as blood vessel in about 50 % of all cases of bypass surgery. However, the patency of the saphenous veins is significantly lower e.g. compared to internal mammary arteries. However, due to its good availability the saphenous vein will remain an important option in bypass surgery. In order to increase saphenous vein patency the team of the Cardiac Surgery Research Laboratory has in the past conducted a study aiming to find compounds that reduce intimal hyperplasia (the first pathobiological step leading to loss of patency) in saphenous veins in organ culture. The compound found, Leoligin, not only inhibited intimal hyperplasia *in vitro*, but also potently increased patency *in vivo* (pre-clinically), without toxicity.

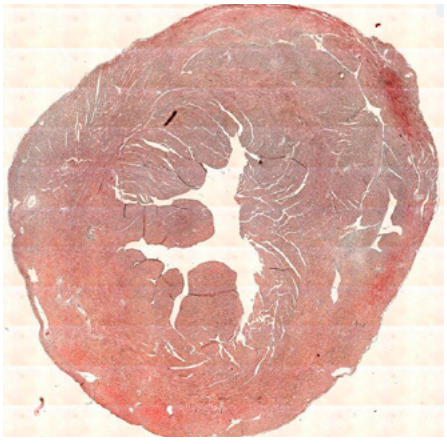

Fig. 4: A histological section of Apo E mouse heart, stained with Masson Trichrome Goldner. Animals were exposed to high cholesterol for 12 weeks. Blue color indicates fibrotic tissue/collagen, red is muscle, and brown-black indicates nuclei.

Importantly, a single intra-operative application of the drug was sufficient to block intimal hyperplasia. Large animal models are currently running and the laboratory is currently starting cooperation with a company to develop an intra-operative storage solution (medical device) for venous grafts, which allows for the extracorporeal treatment of venous bypass grafts. This approach is protected by a patent. The next goal is to apply this new drug in the form of drug eluting stents.

Basic Science
Apart from the goal of science in general, to aquire and gain knowledge, the basic science projects of the Cardiac Surgery Research Laboratory also aim to establish scientific based knowledge for future application-oriented studies and the development of novel therapies.

Thoracic Aortic Aneurysms
Team Dumfarth/Schachner/Bernhard
As a laboratory-based mirror of the clinical Aortic Competence Center of the Departments of Cardiac Surgery, Vascular Surgery and Radiology, the Cardiac Surgery Research Laboratory has a major focus on studies of the thoracic aortic aneurysm (TAA). The primary goal is to understand the pathogenesis of the TAA. In the past many studies have been undertaken to address this issue. However, up to now, TAA pathophysiology remains largely enigmatic.

A major problem in this field of research is the lack of proper *in vivo* models, as well as of human samples showing early stages of the diseases. Further, almost all studies in the past worked with total aortic wall tissue (protein and nucleic acid studies, as well as histo- and immunohistology). The Cardiac Surgery Research Laboratory is one of the very few teams in the world to have expanded the study of TAA to include its basis in cell biology. To do so, cell isolation and culture methods were established, and cell populations were expanded and analyzed.

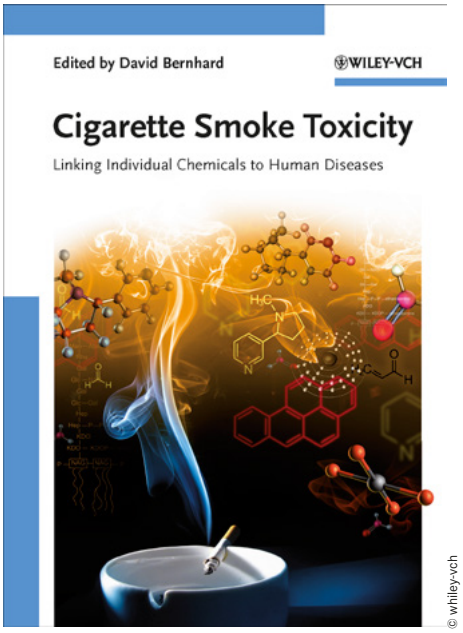

Fig. 5: Cover of a book on cigarette smoke toxicity, a core expertise of the research team. Knowledge about cigarette smoke toxicity is mainly used for disease prevention issues. This expertise is also supplied to the Austrian Ministry of Health and the World Health Organisation. Currently the team is investigating e-cigarette toxicity on the cardiovascular system.

One of the most significant findings, presented in the first published study of the team, was that smooth muscle cells in the TAA aorta are aged cells, with significantly shortened telomeres, and with reduced metabolism, proliferation, and migration rates. As these cells are generally difficult to expand, due to their aged phenotype, it is planned to set up a bio-bank, allowing us to continually acquire cells.

Future research will include studies of smooth muscle cells, fibroblasts, endothelial cells, other cell types in the TAA vessel wall, and patient serum. Major areas of study include: aging processes, and the correlation of cell culture findings with histo- and immunohistology, and evaluation of patient data on progression and outcome. The goal: to reveal the driving forces in TAA formation and progression and to use this new knowledge for disease detection and to monitor progression (biomarker), and for prognosis and treatment.

Search for Unknown Risk Factors for Cardiovascular Diseases
Team Bernhard

Based on solid estimates the reason (risk factors) for about 25 – 50 % of cardiovascular diseases are unknown to date. In order to define such unknown risk factors the team of the Cardiac Surgery Research Laboratory conducted studies in the past, and was able to define two totally novel risk factors, which are relevant to the general population. In several studies we could show that even slightly increased levels of serum cadmium increase the risk for cardiovascular diseases (early atherosclerosis).

Our team was the first to show this interrelation in a small human study (cooperation with the Department of Neurology, Medical University of Innsbruck). Further, the pathobiology of cadmium-induced atherosclerosis could largely be elucidated. In recent years, large epidemiological studies (up to 10,000 individuals), as well as prospective cohort studies, confirmed our finding. Currently, two cadmium studies are ongoing. Ultimately, we hope that our results will contribute to a reduction in acceptable exposure levels for humans. The second risk factor that could be defined is lead (Pb). Similarly to cadmium, slightly increased serum levels of Pb also increase the risk for early atherosclerosis.

Pathophysiology of Cardiovascular Disease Risk Factors
Team Bernhard

Another major area of research during the past years was analysis of the pathobiology of the cardiovascular disease risk factor smoking. Despite its extremely high relevance for diseases such as cancer, chronic obstructive pulmonary disease, and cardiovascular diseases, the pathophysiological processes induced and aggravated by cigarette smoke were hardly understood. The team of the Cardiac Surgery Research Laboratory investigated cigarette smoke-induced atherosclerosis in a large number of studies. A published book, and recent invitations to contribute reviews in cardiovascular top journals on this issue, highlight the significant contribution of the team. Currently, the team is analyzing potential toxic effects of e-cigarettes.

Physiological Regeneration after Myocardial Infarction
Team Bonaros/Bernhard

A major task for the future of the Cardiac Surgery Research Laboratory is to study and elucidate physiological processes that occur after myocardial infarction. The intention is to define more precisely the physiological response in the area affected by myocardial infarction, and to define adverse and beneficial effects. The major focus will be on mitochondrial metabolism, a key factor in the redox state (mitochondria make up 1/3 of the total mass of a cardiomyocyte), the relevance of inflammation (physiological intensity of inflammation, and pharmacological modulation), as well as differentiation and dedifferentiation processes occurring after myocardial infarction. The first planned step is to identify the physiological processes and later to interfere with them and to analyse the signaling transduction pathways involved. The techniques used will involve high resolution respirometry, and histological, immunohistological, and molecular biological techniques. The results may form the basis for novel therapeutic strategies. Finally, it is important for us to mention that almost all of the above projects are not seen in an isolated manner but form a unit. A good example for this statement is the fact that cigarette smoking is the major source of cadmium uptake by humans, and is one of only two well defined risk factors for the thoracic aortic aneurysm. The connected scientific projects should – in our view – connect molecules to cells, to tissues, to organs, to the organism, and ultimately to the healing of patients.

Selected Publications

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Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Messner B, Bernhard D.
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Shockwave therapy differentially stimulates endothelial cells: implications on the control of inflammation via toll-Like receptor 3. Holfeld J, Tepeköylü C, Kozaryn R, Urbschat A, Zacharowski K, Grimm M, Paulus P.
Inflammation. 2014 Feb;37(1):65-70. doi: 10.1007/s10753-013-9712-1.

Impact of cold ischemia on mitochondrial function in porcine hearts and blood vessels. Wiedemann D, Schachner T, Bonaros N, Dorn M, Andreas M, Kocher A, Kuznetsov AV.
Int J Mol Sci. 2013 Nov 7;14(11):22042-51. doi: 10.3390/ijms141122042.

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- Dr. Alexander Egger, Austria Drug Screening Institute, Innsbruck, Austria
- Prof. Christian Hartinger, Oragnic Chemistry, Auckland University, New Zealand
- Dr. P. Paulus, Department of Anesthesiology, Goethe-University Frankfurt, Germany
- Prof. Hermann Stuppner, Institute of Pharmacy, University of Innsbruck
- Prof. Xing Li Wang, Texas Heart Institute, Houston, Texas, USA

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Keywords

Peripheral arterial disease, cerebrovascular disease, aortic aneurysm, aortic dissection, vascular trauma, venous disease, arterial and venous thrombosis

Research Focus

- Treatment of patients with symptomatic stenosis of the internal carotid artery (comparison of carotid artery stenting (CAS) and carotid endarterectomy (CEA), investigation of the influence of timing on the outcome after CEA and CAS);
- Risk factor assessment in patients with peripheral arterial disease and investigation of cardiovascular complication rates;
- Vascular trauma including early and long-term outcome, functional analysis and quality of life;
- Aortic dissection and factors associated with prognosis and outcome;
- Perioperative anticoagulation management including novel oral inhibitors (NOACs).

General Facts

At the Department of Vascular Surgery we are especially interested in atherosclerosis and its different clinical manifestations: peripheral arterial disease, cerebrovascular disease and aortic aneurysms.

Another research focus is carotid artery disease, its optimal treatment and novel diagnostic techniques. For many years now we have participated in this field in international trials comparing carotid artery stenting and carotid endarterectomy.

In addition, we elaborate on the optimal treatment of aortic dissection and on the natural course of this degenerative disease.

Furthermore we focus on all forms of vascular trauma and their optimal therapy. We assess the functional capacity of patients following a vascular trauma and whether the outcome can be positively influenced.

In the last years a variety of new anticoagulants have appeared and we now evaluate these in daily clinical routine.

We are especially interested in testing these novel anticoagulants in perioperative management. We focus on advantages and possible dangers in surgical patients and attach special importance to surgeries in emergency situations.

Research

Carotid Artery Disease
We study the influence of timing on the outcome of carotid endarterectomy and carotid artery stenting in symptomatic patients. Historically it was recommended to postpone carotid surgery in symptomatic patients for at least four to six weeks after the qualifying neurological event, to prevent cerebral bleeding. However, results from the recent literature indicate that carotid endarterectomy is most effective when performed earlier, to be precise: within two weeks. The rationale for the diminishing benefit of surgery in the latter period is that the first days after an initial neurological event carry the highest risk of stroke recurrence due to plaque embolization. For over a decade now, we have been following the question whether CEA can be performed safely in the early days after stroke onset, and conclude that CEA is safe and most effective when carried out rapidly after the onset of symptoms.

Carotid artery stenting (CAS) appeared as an alternative treatment technique in the early 1990s. So far the safety and efficacy of CAS in comparison with CEA has not been proven in patients with symptomatic stenosis of the internal carotid artery. In addition, the influence of timing on the outcome of CAS is not fully understood. Using the pooled analysis of all three

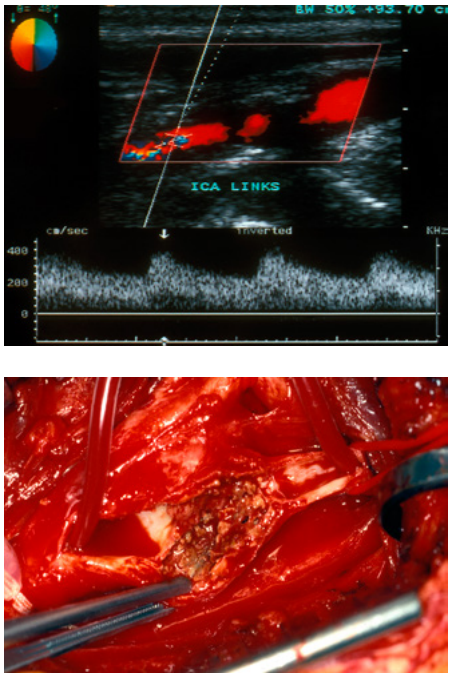

Fig. 1: Sonography and intraoperative view of a symptomatic carotid stenosis

European trials (Carotid Stenting Trialists' Collaboration, CSTC) which compared CAS and CEA, we could demonstrate that CAS is especially harmful in the early days after a qualifying neurological event. During the first 7 days CAS carries a fourfold risk of periprocedural complication compared to CEA (Fig. 2).

Perspectives: The pooled analysis of the CSTC and CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) data concerning the influence of the timing of treatment is ongoing. The results are expected during for the next few weeks.

Peripheral Arterial Disease (PAD), the CAVASIC Study

The CAVASIC study (Cardiovascular risk factors in patients with intermittent claudication) was initiated in 2002 to carry out prospective investigation of patients with intermittent claudication and to assess their cardiovascular morbidity and mortality rates. The follow-up examinations were finished in 2011, and since then different analyses on cardiovascular risk factors have been completed; once again we could demonstrate that patients with PAD carry a significant risk of cardiovascular complications. The number of cardiovascular complications has not significantly decreased over the last years despite intensive medical treatment. Survival following a myocardial infarction, however, is much better; PAD patients most frequently die from malignancy.

Vascular Trauma

Institutional characteristics (diagnosis data registry back to 1989; big Trauma Center) allowed analysis of various aspects of the repair of arterial and venous trauma: perioperative mortality and analysis of factors associated with early limb loss, early and long-term outcome including patency of the repaired vessel, long-term functional analysis and quality of life. In our institution, trauma mechanisms most frequently include blunt injuries, in contrast to other centres which have a majority of penetrating traumata (e.g. stab- and gunshot injuries). In blunt injuries, vascular injuries are regularly associated with bone and nerve injuries, which lead to a worse functional outcome in the long term.

This is particularly important in the upper limb. Our research group analysed factors associated with poor functional outcome, by use of standardised questionnaires to report on long-term quality of life, limb function and cold intolerance, which is another common finding in this setting. Furthermore, iatrogenic injuries were analysed, with special interest in access site complications occurring during vascular interventional procedures. Access site complications are uncommon in institutions with large numbers of invasive vascular procedures, however they represent an important issue. We were interested in strategies to reduce such complications, such as the use of local compression and the additional use of Vascular Closure Devices (VCDs), and in techniques and outcome of surgical repair of access site complications.

Aortic Dissection

Multicentric analysis of data including patients with Type B Aortic Dissection aimed to evaluate risk factors for planning of individual treatment. In addition, patients with complicated dissections were analysed with special attention to limb revascularisation and to renal and visceral malperfusion. Patients who were treated with Stentgrafts were evaluated with respect to the consequences of coverage of the left subclavian artery, such as neurological complications including stroke and spinal cord ischemia, and ischemic complications of the left upper limb. In addition, we compared outcome parameters in patients with aortic dissection to data from patients with thoracic aortic aneurysms and traumatic aortic injuries.

Selected Publications

The risk of carotid artery stenting compared with carotid endarterectomy is greatest in patients treated within 7 days of symptoms. Rantner B, Goebel G, Bonati LH, Ringleb PA, Mas JL, Fraedrich G, Carotid Stenting Trialists' Collaboration.
J Vasc Surg. 2013 Mar;57(3):619-626.

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Atherosclerosis. 2014 Dec;237(2):711-7.

Outcome after interposition of vein grafts for arterial repair of extremity injuries in civilians. Klocker J, Bertoldi A, Benda B, Pellegrini L, Gorny O, Fraedrich G.
J Vasc Surg. 2014; 59(6): 1633-1637.

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J Thorac Cardiovasc Surg. 2014; 148(5): 2155-2160.

Ischemia and functional status of the left arm and quality of life after left subclavian artery coverage during stent-grafting of thoracic aortic pathologies. Klocker J, Koell A, Erlmeier M, Goebel G, Jaschke W, Fraedrich G.
J Vasc Surg. 2014; 60(1): 64-69.

Collaborations

- Carotid Stenting Trialists' Collaboration
- Dr. Peter Klein-Weigel, Klinik für Angiologie, Klinikum Berlin-Buch,Germany
- PD Dr. Jochen Grommes,Department of Vascular Surgery, RWTH Aachen/Maastricht
- Prof. Dr. A Greiner, Department of Vascular Surgery, Charité Berlin

	CEA, No. (%)	*CAS, No. (%)*	*Crude RR (95% CI)*	*P value*
Stroke or death				
0-7 days	3 (2.8%)	13 (9.4%)	3.79 (1.1-13.1)	.03
8-14 days	7 (3.4%)	19 (8.1%)	2.42 (1.0-5.7)	.04
>14 days	44 (4.0%)	78 (7.3%)	1.82 (1.3-2.6)	.001
Disabling stroke or death				
0-7 days	1 (0.9%)	7 (5.1%)	6.40 (0.8-51.0)	.08
8-14 days	3 (1.4%)	7 (3.0%)	2.28 (0.6-8.7)	.23
>14 days	28 (2.6%)	34 (3.5%)	1.35 (0.8-2.2)	.22
Any stroke				
0-7 days	3 (2.8%)	13 (9.4%)	3.79 (1.1-13.1)	.03
8-14 days	7 (3.4%)	18 (7.7%)	2.27 (1.0-5.4)	.06
>14 days	41 (3.8%)	74 (7.0%)	1.86 (1.3-2.7)	.001

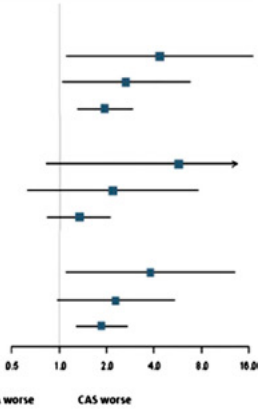
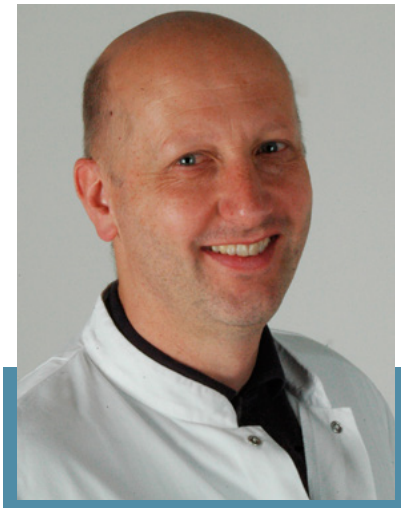


Fig. 2: The risk of stroke or death after treatment of symptomatic carotid stenoses by endarterectomy (CEA) or stenting (CAS), adopted from Rantner et al (2013).

Plastic, Reconstructive and Aesthetic Surgery



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Keywords

Fat, adipose derived stem cells, wound healing, immune cells, transplantation, congenital deformities, thoracic wall deformities, cytokines, leukocyte trafficking

Research Focus

- Physiology of fat tissue resident mesenchymal stem cells and adipocytes and their impact on wound healing
- Repair of congenital thoracic wall deformities and consequence on cardiopulmonary function and quality of life
- Transplantation Immunity: Discrimination of rejection and inflammatory processes in the skin

General Facts

VISION
The ISO-9001:2008 certified research unit of the Plastic, Reconstructive and Aesthetic Surgery was established in autumn 2011, enabling dedicated doctoral researchers to follow clinical goals based upon sound scientific principles. Our vision is to apply basic research techniques to address clinical challenges and translate these findings into new therapeutic approaches.

AIMS

1. **Improve the understanding of cellular processes in wounds, especially defining the role of fat tissue**
   Fat tissue has a great impact on physiological and psychological processes in the human body. We address the question of how cellular and secretory components of the fat tissue influence regeneration.
2. **Surgical correction of congenital thoracic wall deformities and the impact it has on physical and physiological health**
   We address how surgery of chest wall deformities impacts cardiopulmonal and psychological parameters and quality of life.
3. **Transplantation immunology: Discriminating early skin rejection from skin inflammation**
   The aim is to identify specific biomarkers for early detection of skin rejection in composite allotransplantation prior to histological findings.

STRUCTURE
Three research groups, equivalent to the 3 major units of the Department, i.e. the units for Breast/Limb/Nerve-Surgery, Congenital Deformities/Reconstructive Surgery and Wound management/healing are supported by the research laboratory unit headed by C. Ploner. The laboratory staff comprises 2 clinical PhD students, one technical assistant (BMA) and 2 clinical researchers.

Research

The Impact of Fat Tissue on Wound Healing and Tumorigenesis

Christian Ploner

Despite great advances in tissue-engineering of the skin, impaired wound healing still remains one of the most serious problems in plastic surgery. We are primarily interested in defining mechanisms of (chronic) wound healing, especially delineating the role of the fat tissue in this complex cellular interplay. Disdained as a dispensable tissue that is necessary for energy storage only, recent findings strongly suggested that fat tissue is a remarkable source of cytokines, metabolites and hormones. In addition, fat tissue harbors a high number of easily accessible, undifferentiated adipose-derived stem cells (ADSC) that are actually tested in clinical applications, including wound-healing approaches (Fig. 1).

However, the mere transplantation of these cells into wound beddings only marginally enhanced the healing process, and cells embedded in engineered matrices stayed entrapped and impacted wound healing by secretory action rather than by proliferation or differentiation.

Therefore, we initiated a project focusing on wound matrix controlled molecular processes affecting the regenerative potential of distinct cutaneous (keratinocytes, fibroblasts) and subcutaneous cell types (adipocytes, ADSC). One of the most important matrix components for dermal wound healing is fibronectin, a high molecular weight glycoprotein, which is recognized by specific cell surface proteins of the integrin family, namely integrin alpha 5 and alpha V. In a first line of experiments, we delineated the function of alpha 5 and V integrins in regenerative cell types, especially ADSC and basal keratinocytes. By applying lentiviral transduction technology we found that high expression of these integrins favors proliferation and migration over differentiation and that this integrin-dependent phenotype is mainly mediated by the PI3K/AKT pathway.

In a second study, we investigate how tumor cells from distinct origin (multiple myeloma, breast cancer, prostate cancer or ovarian

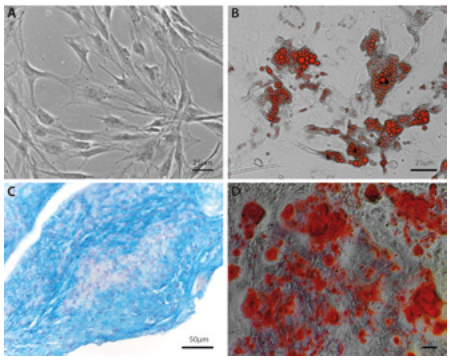

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Fig. 1: Multipotency of isolated primary human ADSC. In vitro expanded ADSC (A) were subjected to adipogenic (B), chondrogenic (C) or osteogenic (D) differentiation medium for 2 weeks (adipogenesis) or 3 weeks (chondrogenesis, osteogenesis), respectivly. Paraformaldehyde fixed cells were stained for lipid-containing droplets (OilRedO, B), sulfated proteoglycans (Alcian blue, C) or calcium depositions (Alizarin Red, D).

cancer) enslave proximal mesenchymal stem cells and adipocytes. We are especially interested in the mechanism by which tumor cell secreted cytokines affect adipocyte differentiation and delipidation at the molecular level. In first experiments, we found that, dependent on the tumor origin, adipocyte differentiation is enhanced or diminished by specific cytokines, suggesting a differential role of adipocytes in the development of the primary tumor.

Cytokine Patterns in Acute Skin Rejection and Inflammatory Skin Processes
Dolores Wolfram

Acute skin rejection in vascularized composite allotransplantation (VCA) is the major obstacle for wider adoption in clinical practice. Clinical success and outcome of VCA often depends on exact timing and the extent of the given immunomodulatory therapy. Traditionally, this decision is made upon histological appraisals focusing on inflammatory markers that hardly allow discrimination between skin rejection and an inflammatory skin process.

Therefore, we initiated a study to establish new biomarkers that enable this discrimination before the process is manifested in an inflammatory response.

To start with, we screened for the expression levels of 14 inflammatory mediators in skin and muscle biopsies from syngeneic grafts [n=10], allogeneic transplants without immunosuppression [n=10] and allografts treated with tacrolimus [n=10], applying the multiplex analysis technology (LuminexTM). We found that levels of IL-4, TNF-α and IL-12p70 correlated best with early skin rejection, whereas TNF-α and IL-12p70 were specific for muscle tissue rejection. Importantly, all identified markers preceded histological alterations. To differentiate between early rejection and an inflammatory skin process, we applied a contact hypersensitivity (CHS) and delayed type hypersensitivity (DTH) model in Lewis rats (Fig. 2). CHS and DTH result in skin irritation and swelling histologically comparable to grade I-II rejection in our rat allotransplant model. Based on a multivariate linear discriminant analysis, IL-12p70 and TNF-α were approved as specific biomarkers for early skin rejection.

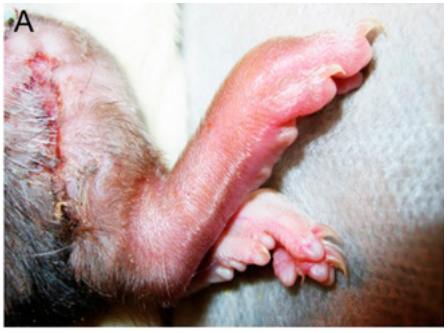

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Fig. 2: Representative picture of (A) a transplanted limb showing clinically Grade II rejection characterized by erythema and swelling. (B) DTH reaction on the planta pedis on the right paw presenting with localized erythema and swelling and the control footpad on the left side without any inflammatory reaction.

Cardiopulmonary Function after Chest Wall Deformity Surgery
Barbara Del Frari

Pectus excavatum (PE) and *carinatum* (PC) are the most common types of congenital anterior chest wall deformities. The deformities often present not only as an aesthetic disturbance, but also in association with obstructive pulmonary mechanics and abnormal cardiac physiology. Various methods of corrective thoracoplasty have been described. There is a significant challenge in thoracoplasty surgery, which emphasizes aesthetic restoration of large deformities, but should cause only low morbidity. As a result, there has been an increase in the number of patients seeking surgical correction. The aim of our prospective study is to evaluate the effect of the PE and PC deformity itself and whether there is a change of pulmonary function and quality of life in patients after surgical repair. In the study, all patients will undergo preoperative and postoperative evaluation with Computed Tomography CT scan, pulmonary function test and cycle ergometry in an upright, and furthermore, in a supine position, as well as a transthoracic echocardiogram. Additionally, all patients will undergo a pre- and postoperative standardized questionnaire (including quality of life, patient satisfaction and physical activity) and will be examined by a professional psychologist. We hypothesize that our results will provide evidence that pulmonary function is related to the depth of the depression or protrusion and probably causal for functional deficits, and might explain why repair of the defect can result in improved pulmonary function, exercise tolerance and quality of life.

Selected Publications

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Expert Opin Biol Ther. 2015 Jan;15(1):61–77. Epub 2014 Oct 11.

Clinical results and patient satisfaction after pectus excavatum repair using the MIRPE and MOVARPE technique in adults – 10 years experience. Del Frari B, Schwabegger AH.
PLAST RECONSTR SURG. 2013;132(6):1591–602.

Insights from computational modeling in inflammation and acute rejection in limb transplantation. Wolfram D, Starzl R, Hackl H, Barclay D, Hautz T, Zelger B, Brandacher G, Lee WP, Eberhart N, Vodovotz Y, Pratschke J, Pierer G, Schneeberger S.
PLoS One. 2014 Jun 13;9(6).

Development of a multipurpose GATEWAY-based lentiviral tetracycline-regulated conditional RNAi system (GLTR). Sigl R*, Ploner C*, Shivalingaiah G, Kofler R, Geley S.
PLoS One. 2014 May 19;9(5).

Selected Funding

- Clinical Research (KLIF), Austrian Science Fund (FWF), Barbara Del Frari
- Driving plasma cells MADi: the role of Myeloma-Adipocyte interaction in the progression and drug resistance of multiple myeloma, Standortagentur Tirol, C. Ploner & K. Jöhrer

Collaborations

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- Prof. Ivan Martin, Department of Biomedicine, University Hospital Basel, CH
- Prof. W.P. Andrew Lee, Johns Hopkins University, Baltimore, USA
- Prof. Gerhard Brandacher, Johns Hopkins University, Baltimore, USA
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Keywords

Clinical studies, biomechanics, fracture fixation, cell biology, osteoporosis, geriatric patients

Research Focus

Research in the Department of Trauma Surgery focuses on the evaluation, development and improvement of new and existing treatments and therapies for traumatic and degenerative musculoskeletal diseases, not exclusively, however, with focus on geriatric patients.

General Facts

In the clinical routine setting the department is organised into teams specialised in anatomical regions. The clinical patient based research, as well as the applied and basic research of all the clinical teams at the department, is supported by an infrastructure consisting of a clinical study and documentation unit, a biomechanics laboratory, a morphology and cell biology laboratory and the Core facility Micro CT. This setting supports clinical research, as wells as laboratory research on macroscopic, microscopic and cellular level.

Clinical research in Trauma Surgery represents a special challenge, because of its high throughput of in- and out-patients and its wide range of treatment modalities. The main research fields are medical device studies and investigator-initiated trials which explore new treatment methods. Our study coordinators ("study nurses") support clinical staff in the organization and administration of clinical trials, ensuring a complete collection and archiving of data and patient follow-ups according to the "Good Clinical Practice" guidelines and legal requirements. The clinical study centre unit was certified in 2011 by the Clinical Research Organization "AO Foundation". The main collaborators are the Clinical Trial Center of the Medical University Innsbruck and the AO foundation/Trauma.

In the biomechanics laboratory material testing machines are available for *in vitro* testing of soft and hard biological tissues, with several custom-made test setups for various anatomical regions as well as joint simulators for the spine, shoulder and hand. These allow *in vitro* functional evaluation of interventional surgical procedures for the stabilisation or reconstruction of joints as well as of soft and hard tissue. Research projects have been carried out in collaboration with the Dept. of Anatomy and Embryology, Dept. of Neurosurgery, Dept. of Craniofacial Surgery and Dept. of Orthopaedic Surgery.

The main focus of the morphological/cell biological laboratory lies on basic research into osteoporosis and its underlying mechanisms and the resulting stem cell differentiation defects, as well as on research on intervertebral discs. To conduct these studies a fully equipped tissue culture unit is at our disposal for adult stem cell differentiation experiments and investigations on intervertebral disc cells. In addition histological, ultrastructural and biochemical analysis can be carried out. Research projects have been carried out in collaboration with the Dept. of Anatomy, Histology and Embryology, Dept. of Therapeutic Radiology and Oncology, Dept. of Plastic-, Reconstructive- and Aesthetic Surgery, as well as with several groups of the CCB.

Research

Clinical Studies and Documentation Unit
Mariette Fasser, MSc

In recent years the focus of clinical studies in trauma surgery has no longer been limited to medical device investigations: due to growing experience and know-how, an expansion to interdisciplinary projects and further aims became possible. One example is the EU-funded DO-HEALTH study which is focused on Vitamin D supplementation, Omega 3 intake and home exercise as prophylactic measures aiding healthy aging (study goals: to reduce risk of falls, to improve cognitive impairment and cardiovascular improvement). The involvement of the department in this project was a new approach and opened doors for similar highly representative epidemiological projects. However, the main research focus continues to be on musculoskeletal topics, with investigations of trauma related research questions e.g. fixation of distal radius fractures, studies on proximal humerus fractures with focus on osteoporotic bone and loss of fracture reduction implant failure and steps to prevent fixation failure.

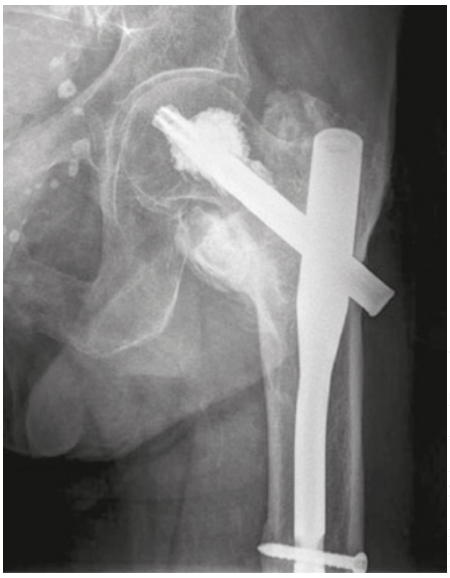

Fig. 1: Follow-up X-ray 1 year after an unstable proximal femur fracture was treated with an augmented PFNA nail, showing a well-healed fracture and no signs of osteonecrosis of the femoral head.

Biomechanics Laboratory
Werner Schmölz, Assoc. Prof., PhD, Dipl.-Ing (FH)

Implant anchorage in spinal stabilisation procedures in patients having reduced

bone quality still poses a challenge to the surgeons. Therefore, a new test setup was developed which allows the application of physiologic pedicle screw loading and is capable of reproducing the mechanism of pedicle screw loosening seen in clinical practice. Various augmentation techniques and materials as well as screw designs to enhance pedicle screw anchorage were investigated. It could be shown that augmentation significantly improves screw anchorage and while for PMMA as augmentation material the technique is only of secondary importance, for other augmentation materials e.g. silicon, the enhancement strongly depends on the augmentation technique applied. To improve instrumentation for cervical and lumbar spinal fusion procedures, experiments were conducted *in vitro* to investigate the primary and secondary stiffness of various supplementary instrumentations. Based on the results, recommendations on the type of instrumentations and their stiffness were given.

After surgical treatment of cruciate ligament injuries, graft elongation and graft fixation affect post-surgical joint stability. Therefore, currently established and recently developed new graft preparation techniques, as well as femoral and tibial graft-bone fixation techniques, were investigated in experiments *in vitro*. It could be shown that a graft preparation technique which had recently been developed for less invasive surgery resulted in an increased graft elongation after surgical treatment.

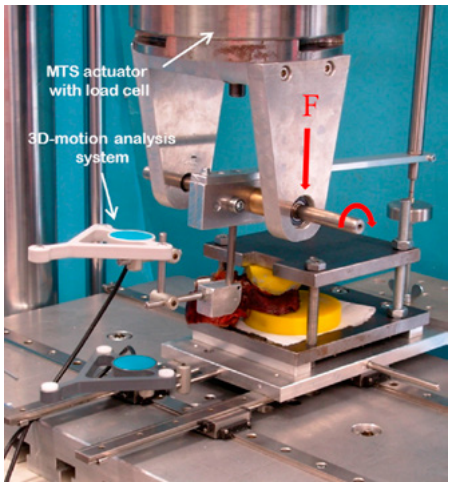

Fig. 2: In vitro test set-up used to apply physiological loading to pedicle screws and provoke screw loosening. Red arrows show the load application and the pivot axis to allow a tilting motion of the screw in the vertebral body.

Morphology and Cell Biology Laboratory
Hannes L. Ebner, PhD

To optimise future treatment of osteoporosis, the potential of aminobisphosphonates to enhance the development of bone-forming osteoblasts from progenitor cells was evaluated. The aminobisphosphonates investigated significantly enhanced osteoblast formation and thus provide further insights into their possible mode of action in the treatment of osteoporosis.

Adipose-derived stromal cells (ASCs) are increasingly being used for orthopaedic-based tissue engineering, due to their ability readily to undergo osteogenic differentiation. We used *in vitro* and *in vivo* approaches to evaluate the use of ASCs as a treatment strategy for age-related osteoporosis. When differentiated in conditioned culture media harvested from osteoporotic patient-derived human ASCs, osteoporotic patient-derived human bone marrow stromal cells showed a significant improvement in their osteogenic potential. These findings support the use of ASCs as an autologous cell-based approach for the treatment of osteoporosis.

The behaviour of bovine disc cells, and changes in disc matrix following *in vitro* compression, were tested to compare the findings to data on human intervertebral discs (IVD) after burst fracture of the cervical spine. Specimens were studied macroscopically, histologically, and ultrastructurally to define healthy cells, balloon cells, and disc cell death (DCD). There was a positive correlation between DCD and absorbed energy in all compartments of bovine discs. Both species showed similar patterns of DCD in the different compartments as well as similarities in cell morphologies and in matrix damage.

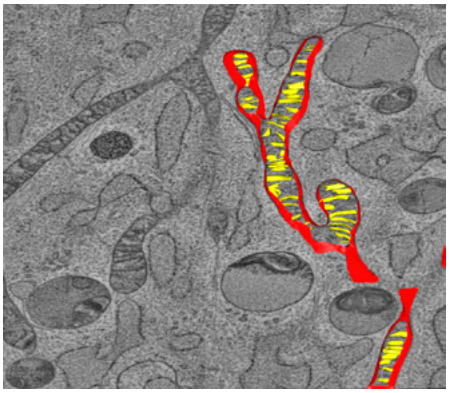

Fig. 3: 3D reconstruction of a section from a mesenchymal stem cell, based on an electron tomogram, showing a single, branched, threadlike mitochondrion with cristae, marked here in yellow, and mitochondrial membrane, in red.

Selected Publications

The influence of Local Bone Density on the Outcome of One hundred and Fifty Proximal Humeral Fractures Treated with a Locking Plate. Kralinger F, Blauth M, Goldhahn J, Käch K, Voigt C, Platz A, Hanson B.
J Bone Joint Surg Am. 2014 Jun 18;96(12):1026–1032.

Long-term result of augmented PFNA: a prospective multicener trial. Kammerlander C, Doshi H, Gebhard F, Scola A, Meier C, Linhart W, Garcia-Alonso M, Nistal J, Blauth M.
Arch Orthop Trauma Surg. 2014 Mar;134(3):343–9.

Osteoanabolic effect of alendronate and zoledronate on bone marrow stromal cells (BMSCs) isolated from aged female osteoporotic patients and its implications for their mode of action in the treatment of age-related bone loss.
Lindtner RA, Tiaden AN, Genelin K, Ebner HL, Manzl C, Klawitter M, Sitte I, von Rechenberg B, Blauth M, Richards PJ.
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Therapeutic potential of adipose-derived stromal cells in age-related osteoporosis. Mirsaidi A, Genelin K, Vetsch JR, Stanger S, Theiss F, Lindtner RA, von Rechenberg B, Blauth M, Müller R, Kuhn GA, Hofmann Boss S, Ebner HL, Richards PJ.
BIOMATERIALS. 2014; 35(26):7326–35.

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Biomechanical comparison of 2 anterior cruciate ligament graft preparation techniques for tibial fixation: adjustable-length loop cortical button or interference screw. Mayr R, Heinrichs CH, Eichinger M, Coppola C, Schmoelz W, Attal R.
Am J Sports Med. 2015 Jun;43(6):1380–5.

Primary stiffness of a modified transforaminal lumbar interbody fusion cage with integrated screw fixation: cadaveric biomechanical study. Keiler A, Schmoelz W, Erhart S, Gnanalingham K.
Spine (Phila Pa 1976). 2014 Aug 1;39(17):E994-E1000.

Effect of augmentation techniques on the failure of pedicle screws under cranio-caudal cyclic loading. Bostelmann R, Keiler A, Steiger HJ, Scholz A, Cornelius JF, Schmoelz W.
Eur Spine J. 2015 Mar 27.

Biomechanical comparison of vertebral augmentation with silicone and PMMA cement and two filling grades. Schulte TL, Keiler A, Riechelmann F, Lange T, Schmoelz W.
Eur Spine J. 2013 Dec;22(12):2695–701.

A full list of the publications and the currently running projects is listed on the departmental website:
www.unfallchirurgie-innsbruck.at

Selected Funding

DO-HEALTH, EU- 7th framework, Http://www.do-health.eu

Collaborations

Clinical Investigation unit:
- AO Foundation/Trauma

Morphology and Cell Biology Laboratory:
- Prof. Dr. med. B. von Rechenberg, University of Zürich, Zürich, Swisse
- Prof. Dr. med. P. Pietschmann, MedUni Wien, Wien, Austria
- Priv. Doz. Dr. P. J. Richards, University of Zürich, Zürich, Swisse
- Priv. Doz. Dr. G. Krumschnabel, Oroboros Labs, Innsbruck, Austria

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- Prof. Ralph Müller, ETH, Zürich, Swisse
- Priv-Doz. Dr. med Heiko Koller, Bad Wildungen, Germany
- Priv. Doz Dr. med Stefan Freude, University of Tübingen, Germany
- Dr. med. Richard Bostelmann, University of Düsseldorf, DE
- Dr. med Claudia Druschel, Charite University medicine, Berlin, Germany
- Dr. Kanna Gnanalingham, Dept of Neurosurgery, Manchester, UK

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Keywords

Prostate cancer and prostatic diseases, urological tumors, cancer markers and screening, androgen receptor, cytokine & growth factors signaling, immunology & immunotherapy, urogenital tract, andrology

Research Focus

- Prostate cancer treatment and therapy resistance mechanisms
- Androgen receptor signaling and its role in prostate cancer development, therapy and therapy resistance
- Tumor immunology and immunotherapy with a focus on dendritic cells and γδ-T-lymphocytes
- Diagnostics and tumor markers for urological tumors, in particular prostate cancer

General Facts

The Innsbruck Department of Urology was founded in 1964 under the direction of Hans Marberger. Georg Bartsch was director from 1988 to 2010 and since 2011, the Urological Department is directed by Wolfgang Horninger. The Department covers the entire diagnostic and therapeutic range of urology, running five operating theaters, urological and neuro-urological outpatient clinics, two adult urological wards, and a pediatric ward. The Division of Experimental Urology is integrated in the Department of Urology. A main focus for the Department is the treatment of urological malignancies.

In 1993, the European Prostate Center Innsbruck was founded in order to ensure optimal patient care and clinical research on prostate cancer and prostatic diseases. In addition to the diagnosis and treatment of prostate diseases, a prostate cancer-screening project called Tyrol Project was implemented in 1993 to offer early detection and curative treatment of prostate cancer for affected men. Reconstructive Urology covers surgical repair of the urogenital tract after trauma or for treatment of incontinence, whereas neuro-urology treats patients with functional disorders of the bladder and the sphincter. Pediatric Urology offers diagnoses and treatments for all congenital, as well as acquired genitourinary problems, from birth to adulthood.

Research

Prostate Cancer Screening
Wolfgang Horninger

More than 20 years after the introduction of prostate specific antigen (PSA) testing in clinical practice, early detection of prostate cancer is still a matter of debate. Some prostate cancer-screening studies, mainly conducted in Europe, showed a decrease in prostate cancer mortality and a stage migration towards lower, potentially curable prostate cancer stages at the time of diagnosis.

However, the same studies showed a considerable number of overdiagnoses and overtreatment. Our own data ("Prostate Cancer demonstration Project", "Tyrol Study") showed that 20 years after initiation of an area-wide early detection program, a 64% decrease in prostate cancer mortality was achieved. Overdiagnosis was seen in 16–20% of all screened men. Therefore, the aim of our Prostate Cancer Unit is to identify new, better markers for prostate cancer. Moreover, we try to optimize prostate cancer detection (mpMRI) and prostate cancer treatment to avoid overdiagnosis and reduce the side effects of (over)-treatment.

The Androgen Receptor – Key Regulator in Prostate Cancer
Helmut Klocker

The androgen receptor (AR), a hormone induced transcription factor, is intimately linked to prostate cancer and is the primary therapeutic target in this malignancy. For two decades, researchers of the Department of Urology have been contributing to worldwide efforts to elucidate the molecular mechanism of AR function and its role in progression and therapy resistance.

Several mechanisms have been identified and were the basis for the development of new AR targeting drugs that led to prolonged survival of patients.

Current research is focused on the AR transcriptome. This includes protein-coding genes, such as AGR2, a cellular chaperone, which is a potential tumor marker, or microRNA genes, such as the host genes of miR22 and miR29a, two epigenetic regulators involved in invasion and apoptosis, respectively. Investigation of posttranslational regulation of AR protein and activity uncovered a feed-back-loop regulation, which is potentially targetable by the well-known diabetes drug, metformin (Fig. 1).

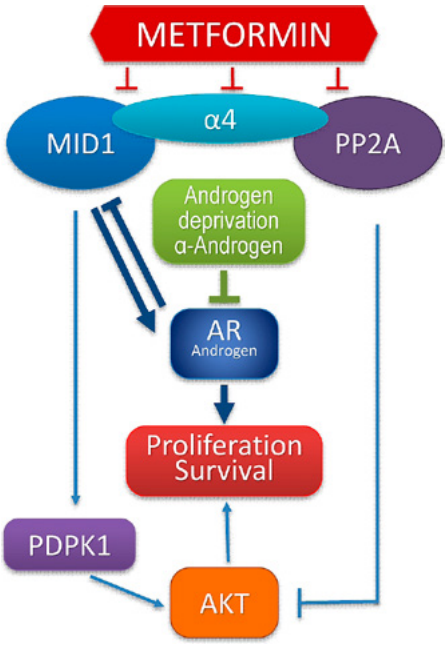

Fig. 1: Posttranslational feedback-regulation of androgen receptor. AR and its transcriptional activity is enhanced by the ribonuclear protein complex, MID1/α4-PP2A via stimulation of mRNA translation. On the other hand, AR inhibits MID1 expression. During therapeutic androgen deprivation or anti-androgen treatment, this fine-tuning mechanism of AR activity is interrupted, which may contribute to therapy resistance. Metformin, an anti-diabetic drug disrupts the MID1 protein complex and downregulates AR protein level.

Cytokines and Growth Factors in Prostate Cancer

Zoran Culig

Researchers are primarily interested in the regulation of cellular events by cytokines in castration therapy-resistant prostate cancer. There is a particular focus on interleukin-6, whose levels are up-regulated in prostate malignancy, and on endogenous regulators of cytokine signaling. In this context, it is especially interesting that these molecules are implicated in the acquisition of resistance to chemotherapy with docetaxel (Fig. 2). In order to improve therapy in advanced prostate cancer, inhibition of growth factors and other oncogenes up-regulated during prostate cancer progression by androgen ablation therapy are investigated. Combination therapies will be developed in the future in order to establish personalized therapies. This research work, performed in several projects, received numerous international recognitions for its contribution to the current understanding of prostate cancer development and progression.

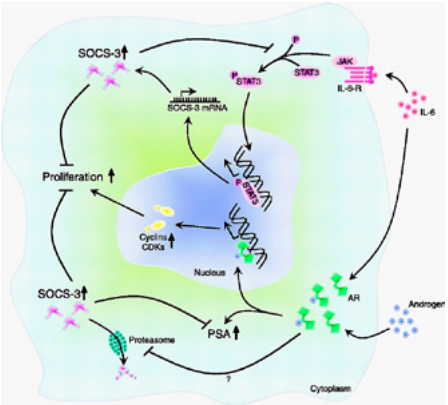

Fig. 2: SOCS-3 function in prostate cancer. SOCS-3 is a common negative regulator for androgen and IL-6 pathways in prostate cancer. IL-6 may cause a pro-differentiation effect as evidenced by PSA increase. Sustained activation of the JAK/STAT pathway is prevented by up-regulation of SOCS-3 by IL-6. SOCS-3 is also a negative feedback regulator for androgen signaling in prostate cancer cells.

Models for Prostate Cancer Research

Iris E. Eder-Neuwirt

In-vitro prostate cancer research is mainly conducted with immortalized cell lines, which lose relevant growth characteristics when grown on a plastic surface. In addition, the human prostate is composed not only of epithelial cells, but also contains several types of stromal cells. In tumor tissue, the interplay between the epithelium and the stroma is thought to create an optimal microenvironment for tumor growth and progression driven by "activated" stromal cells. Hence, the use of 3D co-culture systems for *in vitro* cancer research is a highly important issue when studying the molecular changes occurring in the different cell types as well as for testing novel therapies and drugs. Recently 3D prostate cancer organoid culture protocols were established. The studies have shown that the molecular expression pattern of cell type specific markers is markedly altered in 3D versus 2D cultures. In addition, androgen responsiveness, as well as drug responses, are significantly changed in 3D epithelial-stromal co-culture organoids, suggesting a strong influence of fibroblasts on tumor cell behavior (Fig. 3). Future goals will focus on the interplay between epithelial cells and fibroblasts using this 3D cell culture system with the aim of improving responsiveness to current therapies.

Immunology and Immunotherapy of Urological Tumors

Martin Thurnher

The immunology/immunotherapy group has a research interest on how the immune system reacts against growing tumors. Specifically, they are interested in the activation of γδ-T-lymphocytes by intermediates of the mevalonate pathway (Fig. 4). Since deregulation of mevalonate metabolism can lead to malignant transformation, γδ-T-cells also play an important role in the immunosurveillance of tumors, such as bladder cancer. Improved understanding of these interactions will foster the development of innovative immunotherapies, as well as the establishment of prognostic markers and monitoring technologies.

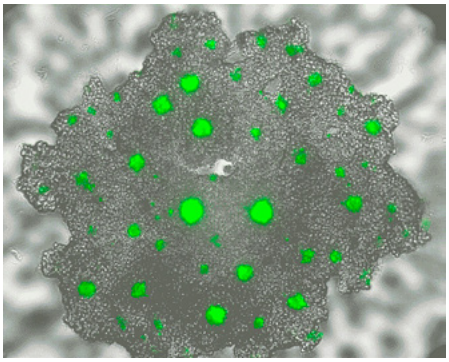

Fig. 3: LNCaP prostate cancer epithelial cells co-cultured with GFP-labeled cancer associated fibroblasts (CAF) at a ratio of 1:1 in 3D Perfecta 96 well plates. Cells form irregular stellate organoids within 4 days of 3D culture. CAFs appear as small green islands within the organoid.

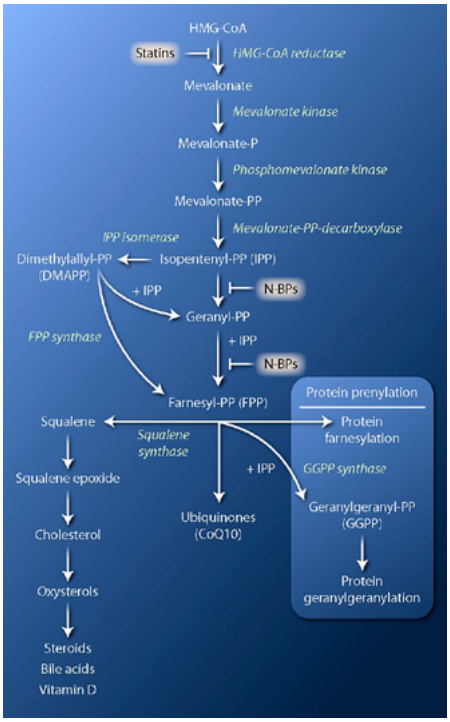

Fig. 4: Mevalonate metabolism. HMG-CoA reductase, the target of statins, catalyzes mevalonate formation, which is further converted into IPP and its isomer DMAPP. Sequential condensations form FPP and GGPP. Activated FPP and GGPP are the building blocks for posttranslational protein prenylation. By inhibiting FPP synthase, nitrogen-containing bisphosphonates induce depletion of downstream FPP and GGPP, and thus, inhibition of prenylation, as well as the accumulation of IPP that is specifically recognized by certain γδ-T-lymphocytes.

Selected Publications

http://urologielabor-innsbruck.tirol-kliniken.at/page.cfm?vpath=publikationen-gesamtuebersicht/publikationen--wissenschaft

Selected Funding

- Austrian Research Fund, FWF
- K1 Center Oncotyrol
- MUI Start Grant Fund
- Tyrolean Research Fund
- Tirolean Cancer Society (Krebshilfe Tirol)
- Research Fund of the Austrian National Bank
- Medical Research Fund (MFF)
- Astellas Pharma Investigator Driven Grant

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- Mark A. Rubin, Weill Cornell Medical College, New York, US
- Michal R. Schweiger & Hans Lehrach, MPI for Molecular Genetics, Berlin, D
- William R.G. Watson, Conway Institute of the University College Dublin, IRE
- Francesca Demichelis, University of Trento, I
- Christian Fuchsberger & Johannes Rainer, EURAC Bolzano,I
- Narisu Naris, NIH Bethesda, US
- Glen Kristiansen, University of Bonn, Bonn, D
- Normam, J. Maitland, University of York, UK
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Keywords

Orthopaedics, microbiology, medical microbiology, bacteriology, molecular biology, immunology, minimal-invasive surgery, medical engineering, biomedical engineering, prosthetics

Research Focus

Clinical Research
We perform applied studies mainly in the fields of spine, arthroplasty, knee, and paediatric orthopaedics, with a special interest in infection, implant migration and postoperative car driving ability. We also host the office of the European Arthroplasty Register.

Experimental Orthopaedics
The area of biomedical engineering focuses on allograft stability and bone harvesting. The area of Implant-related infections develops studies on infections related to biofilm attachment.

General Facts

Clinical Research
Additionally to a new VICON system in clinical use we perform gait and motion analysis in our Biomechanics Lab (Dr. Haid) and outdoor with a Lukotronic system.

Implant migration measurement based on EBRA was developed and is developing in cooperation with the Unit of Geometry and CAD at Innsbruck University (Prof. Husty). Software and scanning equipment are available.

Brake reaction time for car driving is measured in an experimental setting with high accuracy. Postoperative measurements have been performed for various operations.

Experimental Orthopaedics
The unit of Experimental Orthopaedics is a research unit within the Department of Orthopaedic Surgery, and is divided in two major research areas.

The area of biomedical engineering (Dr. Putzer) focuses on biomechanical studies aiming to increase allograft stability in difficult revision cases and to improve techniques and instruments for bone removal. In the area of implant-related infections (Dr. Coraça-Huber) different biofilm models are carried out using the main strains associated with implant-related infections. Antibiotic and antiseptic susceptibility tests can be carried out. Scanning electron microscopy (SEM) is available. Molecular identification of biofilms is under development. Immunological research aims to detect immune activation parameters as signs of infection and monocyte differentiation and activation in co-evolution with microbial infection.

Research

Clinical Research
Bone Graft Substitutes in Posterior Lumbar Interbody Fusion
Thaler
ß-tricalcium phosphate is widely used in cages in order to achieve bone fusion in posterior lumbar interbody fusion. In 45 discs CT assessment revealed inadequate fusion (non-union) in 17 levels (39%). This technique of PLIF using ß-TCP cannot be recommended.

Brake Response Times after Various Surgeries
Different Authors
In 43 patients, 6 weeks after unicompartmental knee arthroplasty, brake response time reached preoperative values (Liebensteiner). In 12 patients, brake response times after anterior cervical fusion were immediately ameliorated after operation, but did not reach normal values after 4–6 weeks (Thaler). Studies on different knee and ankle braces as well as on herniated lumbar discs with paresis are currently running.

Implant Registers
Labek
Data of implant registers of 5 countries showed a need for methodological improvement. Revision rate was approximately 10% after 5 years, with a high rate of inlay fractures which indicates potential for improvement of implants. In an analysis of worldwide arthroplasty registers, data have been extracted with respect to reason for revision surgery and pooled causes. Aseptic loosening is responsible for 55% of hip arthroplasty revisions, and for 30% in the knee. Septic loosening was the cause for revision in 7.5% in the hip and 15% in the knee.

AO Spine Injury Classification System
Reinhold
In this project of the AO Spine Classification Group, five experienced spine trauma surgeons from various parts of the world classified in a structured, iterative process consecutive case with TL injuries. The reasons for disagreements were examined systematically during review meetings.

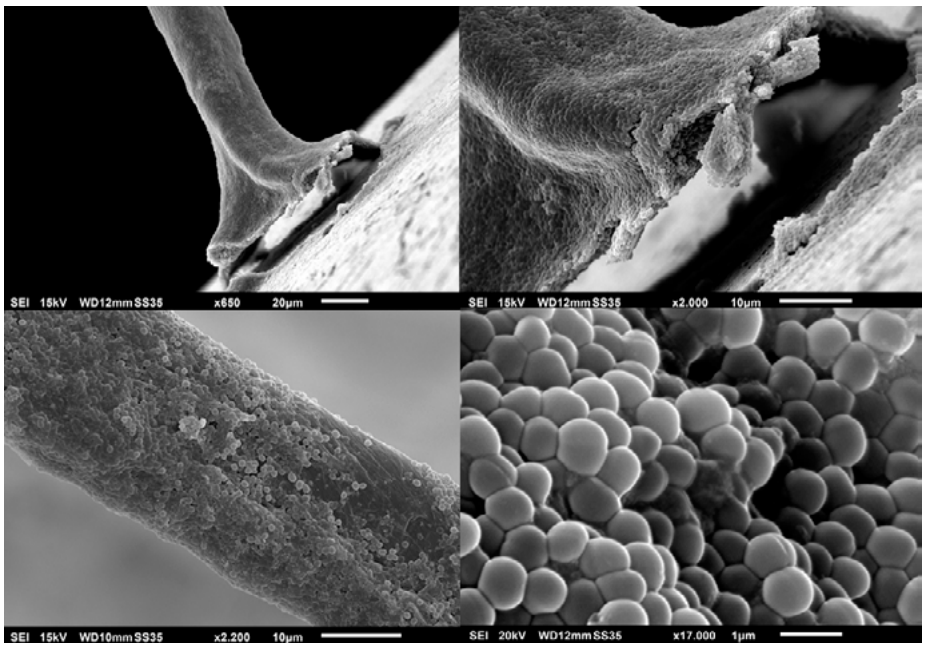

Fig. 1: S. epidermidis biofilm

In four successive sessions, the system was revised until consensus and sufficient reproducibility were achieved.

Gait Analysis after Ankle Arthrodesis Versus Arthroplasty
Biedermann
A gait analysis and clinical assessment have been performed in 101 ankle arthroplasties and 40 ankle arthrodesis cases. Significant asymmetry in gait and reduced range of motion compared to normal remained after both procedures, although subjective outcome has been improved after both procedures. As hindfoot fusion improved postoperative function and pain more than arthroplasty, the implantation of current arthroplasty designs in large patient series may be questioned.

Experimental Orthopaedics

Biofilm Formation and Antimicrobial Susceptibility Tests
Coraça-Huber
In this study we investigated whether biofilms grow *in vitro* on metal discs and on microtiter plates.

The evaluation of the biofilms formed on different surfaces was assessed by comparing the antibiotic susceptibility of S. aureus and by examining the structure of S. aureus biofilms grown by scanning electron microscopy (SEM). Also, several biomaterials can be tested for biofilm growth and efficacy tests for biomaterials with antimicrobial properties.

Molecular Profile of Biofilms
Coraça-Huber
Bacterial biofilm follows a life cycle. Bacterial cells attach to a surface with proteins, adhesins and through other nonspecific interactions with the substratum. Attached cells can develop into small clusters with biofilm-like properties called microcolonies and these can grow and accumulate into a mature biofilm. The accumulation phase requires exopolysaccharide and/or protein-protein interactions. In mature biofilms, the accumulation or dispersal of cells is controlled by inter cell communication mediated by quorum sensing activation. Cells dispersed from a mature biofilm regain the physiological characteristics of planktonic cells and may disseminate causing acute infection. With this study we can obtain the molecular profile of the strains causing device-related infection. This knowledge can help us develop a preventive method against biofilm formation on implants and/or a treatment to remove already established biofilms.

Immunology of Biofilm Infection
Ammann
Here we study the interaction of the complement system with bacteria in nosocomial joint infections. Results achieved during this study will not only broaden the basic knowledge about complement in nosocomial joint infections but also have clinical implications. This study not only increases our knowledge about interactions of bacteria causing nosocomial infection with the innate immune system but can ultimately lead to the development of a novel, indirect detection strategy helping reduce the number of false negative samples drawn from patients after joint reconstruction surgery.

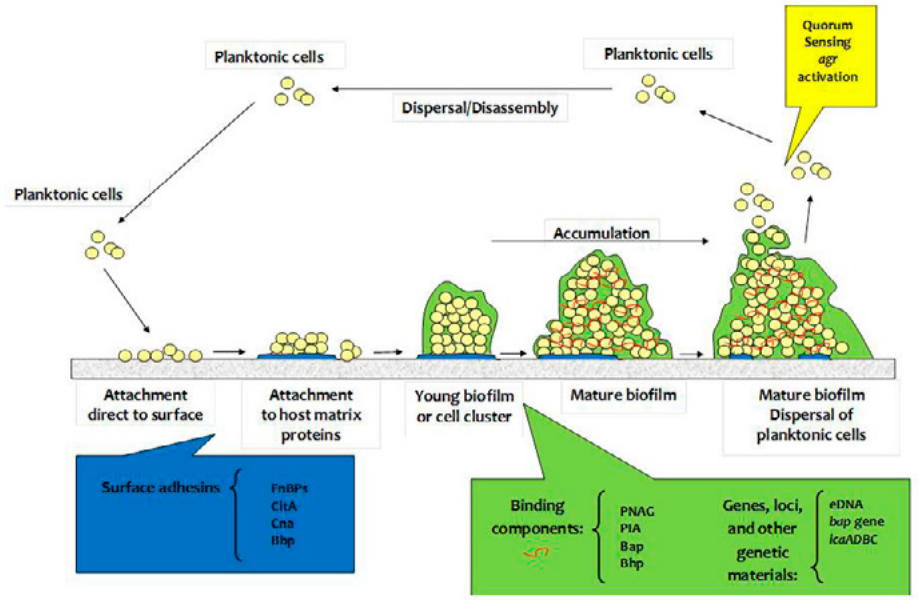

Fig. 2: Staphylococcal biofilm life cycle (FnBPs – fibronectin binding proteins; ClfA – fibrinogen-binding protein-clumping factor A; Cna – collagen binding protein; Bbp – bone sialoprotein-binding protein; PNAG – poly-N-acetylglucosamine; PIA – polysaccharide intercellular adhesion; Bap – biofilm associated protein; Bhp – Bap homologue protein; eDNA – extracellular DNA; icaADBC – genes involved in the synthesis of PIA; bap gene – involved in the synthesis of Bap).

Bone Tissue as Antibiotic Carrier
Coraça-Huber, Putzer

Bone grafts can either be used as large structural bone grafts from post-mortem donors or as bone chips from morselized femoral head donated by living patients undergoing total hip arthroplasty. Such bone chips are used to fill defects that require biomechanical stability, which can be achieved by compressing the chips into the defect site. Fresh frozen bone chips contain the original osteoconductive and osteoinductive proteins, but can add the risk of local contaminations. Antibiotics delivered from an implanted biomaterial can be potentially used to prevent infections. Morselized bone allografts can be used as carriers by impregnating them with antibiotic solutions or by mixing them with antibiotic powders. Also, biomechanical compression tests were carried out for different preparation procedures to study the mechanical effect of grain size distribution, water and fat content and the possibility of enhancing osteoconductive and osteoinductive properties of allograft by adding bioglass or platelet rich plasma.

Intelligent Antibiotic Carriers

Bone cements can be used as antibiotic carriers. Adding antibiotics in different concentrations is influencing the mechanical properties, as well as the antibiotic release of the bone cement. Antibiotic loaded cements as well as antibiotic loaded implants are a way to fight periprostetic joint infections. This research is conducted in collaboration with Inocon GmbH and the Consiglio Nazionale di Ricerca di Parma.

Computer Assisted Bone Removal Procedures

In a collaboration project, an intraoperative planning tool for bone removal procedures is being tested in surgical simulation scenarios. In a simulation study the maximum reachable depth of straight instruments inserted into the femoral canal was determined. Constraints for a simulated bone removal procedure in a femoral canal could be defined. In a cadaver study the usage of an optical digitizer was evaluated do define the soft tissue envelope of the surgical situs during hip arthroplasty. In almost every surgical procedure retraction of soft tissue is necessary. To control retraction forces and minimize soft tissue damages related to it, the possibility of using a semiactive robotic retractor holder was evaluated in a concept study.

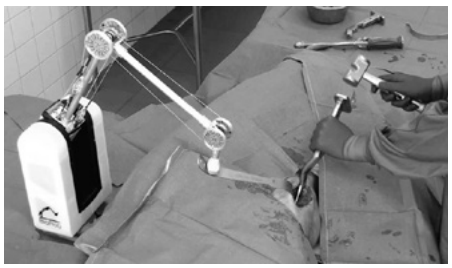

Fig. 3: Surgical Innovation

Selected Publications

Bactericidal Activity of N-Chlorotaurine against Biofilm-Forming Bacteria Grown on Metal Disks. Coraça-Huber DC, Ammann CG, Fille M, Hausdorfer J, Nogler M, Nagl M.
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EUROPEAN SPINE JOURNAL. 2013; 22; p. 2184–2201.

The Use of Beta-Tricalcium Phosphate and Bone Marrow Aspirate as a Bone Graft Substitute in Posterior Lumbar Interbody Fusion. Thaler M, Lechner R, Gstöttner M, Kobel C, Bach C.
EUROPEAN SPINE JOURNAL. 2013; 22: p. 1173–1182.

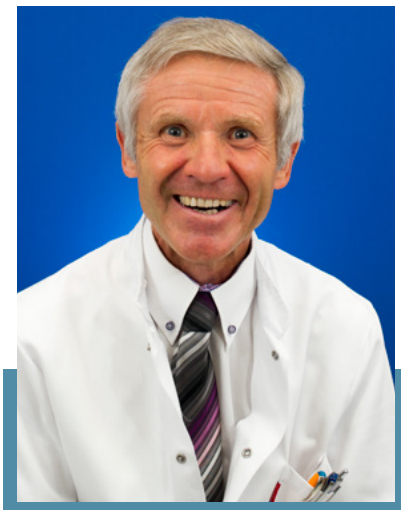
Collaborations

- Heraeus Medical GmbH, Wehrheim, Germany
- BonAlive Biomaterials Ltd, Turku, Finland
- Stryker Leibinger GmbH & Co. KG, Freiburg, Germany
- Hochschule Offenburg, Offenburg, Germany
- Incocon GmbH, Attnang-Puchheim, Austria
- Innsbruck University, Unit of Geometry and CAD, (Prof. Husty).

Devices & Services

- Zeiss Fluorescence Microscope Axio Lab.A1
- Scanning Electron Microscope JSM-6010 InTouchScope
- BactoSonic Ultrasonic Bath Bandelin
- Formlabs Stereolithographic 3D Printer
- VICON Nexus 2.1.1 gait lab with 2 Amti OR6-7-1000 ground reaction force measurement plates
- Lukotronic motion analysis for outdoor use
- Brake reaction time measurement setting

Anaesthesiology and Critical Care Medicine
General and Surgical Critical Care Medicine



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Keywords

Anaesthesiology, critical care medicine, emergency medicine, pain medicine, palliative care, breathing gas, coagulation

Research Focus

Anaesthesiology, critical care medicine, emergency medicine, pain medicine, palliative care, cardiopulmonary resuscitation, airway management, vasodilatory shock, posttraumatic shock, coagulation, hypothermia, regional anaesthesia, transplantation, neuro- and obstetrical anaesthesia, muscle relaxants, mountain rescue, microcirculation, prediction models, breathing gas analysis.

General Facts

The Department of Anaesthesiology and Critical Care Medicine employs 150 full-time equivalent physicians (about 60 residents), with additional nursing, secretarial, technical, and research staff totalling about 450 employees for the entire department. Besides performing about 40,000 anaesthesia cases per year in one of our 60 operating/diagnostic rooms, our department is responsible for a general surgery, post-operative, transplantation, and trauma intensive care unit, six postanaesthesia care units, anaesthesiology outpatient clinic, medical and nursing student education, emergency medical service ground and rotorwing unit, pain service, basic science research laboratory, and animal operating room. This variety is very large even for a university hospital, and allows a wide focus in clinical care, teaching, and research.
Our department is one of the most popular training institutions in Austria combining ambitious young residents and extremely experienced attendings. For example, we feature regular EMS physician, airway management, transesophageal echo, and regional anaesthesia courses for in-house and out of town participants, and organize annual international mountain rescue, and emergency medicine conferences in Innsbruck. Individual schedules ensure work-life balance (i.e. 25% of attendings and 10% of residents are on various part time plans); transparent rotation assignments and leave of absence plan distribute fairness across all parties. Forty percent of our attendings, and 49% of our residents are female. We have tenured 10 female colleagues to the Associate Professor level and 3 of them and one female clinical colleague achieved chair positions. One of our three chiefs of staff is female, and the female president of the Austrian Society of Anesthesiology and Critical Care Medicine is based in our department. Prof. Linder has been the interim director of “General and Surgical Critical Care Medicine” since 2013.

Research

Our physicians provide extremely wide clinical services reaching from very basic clinical procedures (serving the Innsbruck area as a county hospital) to complex tertiary care of severely injured or sick patients, serving as a national referral medical center and also for Southern Tyrol in Italy. When taking together this clinical backbone and our scientific activities, we have substantial potential to develop bench-to-bedside treatments in any area of our specialty. Continuous positive airway pressure (CPAP) ventilation, arginine vasopressin during cardiopulmonary resuscitation and vasodilatory shock as well as fibrinogen during life-threatening haemorrhage are examples for current global implementation of novel treatment strategies that were developed in our department.

Fig. 1: Gerinnungsmanagment in der Intensivmedizin. Fries D und Streif W. Springerverlag. ISBN-13978-3-642-05003-9.

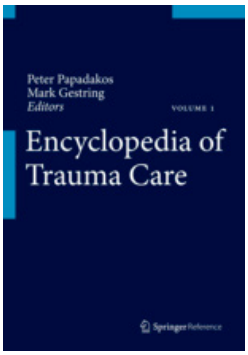


Fig. 2: Enceclopedia of Trauma: Chapter: Adjuncts to transfusion. Fries D. Springerverlag. ISBN 978-3-642-29611-6.

Peter Mair *et al.* are studying the role of snow avalanche-associated hypothermia and injuries. **Corinna Velik Salchner** and colleagues are studying coagulation and regional anesthesia aspects in critically ill cardiovascular patients. **Stephan Eschertzhuber** and his team study critical care medicine aspects in transplantation patients. **Volker Wenzel** and **Karl-Heinz Stadlbauer** have recently completed the "VITRIS.at" trial studying the role of vasopressin as on-top medication during life threatening posttraumatic shock. **Petra Innerhofer**, the current president of our professional society, is looking at coagulation in posttraumatic haemorrhage and is conducting a randomized controlled clinical trial assessing coagulation factors vs. fresh frozen plasma. **Thomas Luger** *et al.* are leading the geriatric trauma center, the fastest growing section in traumatology, and study how to optimize anesthesia for geriatric patients. **Axel Kleinsasser** *et al.* assess pulmonary function postoperatively. **Hans-Ulrich Strohmenger** is our critical incident analyst and works on making clinical treatment safer. **Arnulf Benzer** and team is studying depth of anaesthesia in neurosurgical patients. **Günter Putz** *et al.* assesses the role of regional anaesthesia in obstetric patients. **Michael Baubin** *et al.* studies quality issues in emergency medicine, which recently resulted in our emergency medicine system unit being the best in the German resuscitation register analysis. **Ingo Lorenz** and colleagues study critical care medicine. **Dietmar Fries** and a large team analyse the role of fibrinogen after posttraumatic shock in a randomised controlled trial and after large surgical procedures. **Barbara Friesenecker** *et al.* are studying end-of-life issues in the intensive care unit. **Birgit Mair** *et al.* analyse outcomes of helicopter emergency medicine system patients. **Franz Wiedermann** is studying the antiphospholipid syndrome. **Marc Kaufmann** is responsible for the helicopter emergency medical system "Christophorus 1" in Innsbruck with a special interest in mountain medicine. **Günter Luckner**, **Werner Pajk** and **Markus Mittermayr** have a special interest in paediatric anaesthesia and study the role of coagulation in cardiac surgery and complex cranial procedures. **Karin Khünl-Brady** *et al.* study the role of muscle relaxants. **Peter Paal** and team assess accidental hypothermia, especially in combination with snow avalanches. **Stefan Jochberger** studies the role of critical care medicine in developing countries. **Wolfgang Lederer** is studying ethical aspects in emergency medicine. **Judith Martini** assesses the role of microcirculation and infusion solution aspects in shock. **Thomas Mitterlechner** *et al.* study technical adjuncts to facilitate endotracheal intubation. **Ruth Kröss** studies paediatric anaesthesia. **Janett Kreutziger** and team are looking at prediction models after trauma. For the sake of simplicity and readability, we have kept this list brief in order to give an overview, as the complete list of ongoing projects would render reading exhausting.

Several of our colleagues are contributing experts in updating clinical guidelines such as in cardiopulmonary resuscitation, and coagulation management after severe hemorrhage.

Selected Publications

The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma. Innerhofer P, Westermann I, Tauber H, Breitkopf R, Fries D, Kastenberger T, El Attal R, Strasak A, Mittermayr M. INJURY. 2013;44:209–16.

A review of the volatiles from the healthy human body. de Lacy Costello B, Amann A, Al-Kateb H, Flynn C, Filipiak W, Khalid T, Osborne D, Ratcliffe NM. JOURNAL OF BREATH RESEARCH. 2014;8:014001.

Pulmonary function after emergence on 100% oxygen in patients with chronic obstructive pulmonary disease: a randomized, controlled trial. Kleinsasser AT, Pircher I, Truebsbach S, Knotzer H, Loeckinger A, Treml B. ANESTHESIOLOGY. 2014;120:1146–51.

Accidental hypothermia. Brown DJ, Brugger H, Boyd J, Paal P. NEW ENGLAND JOURNAL OF MEDICINE. 2012;367:1930–8.

European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. NEW ENGLAND JOURNAL OF MEDICINE. 2004;350:105–13.

Fibrinogen concentrate in dilutional coagulopathy: a dose study in pigs. Martini Judith, Maisch Sonja, Pilshofer Lisa *et al.* TRANSFUSION. 2014; 54(1); 149–157.

Management of postpartum hemorrhage (PPH). Algorithm of the interdisciplinary D-A-CH consensus group PPH (Germany – Austria – Switzerland). Schlembach D, Moertl MG, Girard T *et al.* ANAESTHESIST. 2014; 63(3); 234–242.

Effects of Fibrinogen Concentrate After Shock/Resuscitation: A Comparison Between *In Vivo* Microvascular Clot Formation and Thromboelastometry. Martini Judith, Cabrales Pedro, Fries Dietmar *et al.* ECRITICAL CARE MEDICINE. 2013; 41(11); E301-E308.

The early use of fibrinogen, prothrombin complex concentrate, and recombinant-activated factor VIIa in massive bleeding. Fries D. TRANSFUSION. 2013; 53(1); 91s-95s.

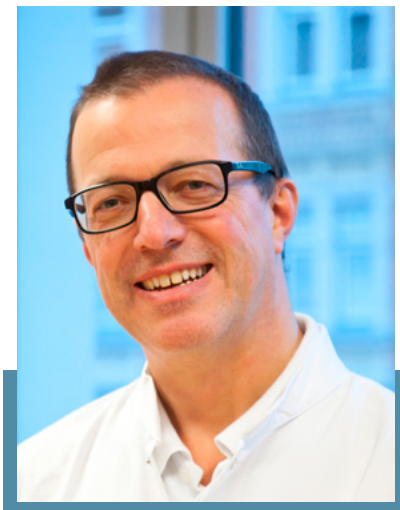
Selected Funding

- Christophorus-Flugrettungsverein vom ÖAMTC und die Schweizerische Rettungsflugwacht, VITRIS-Project, Volker Wenzel
- Suche nach antidotes für neue orale Antikoagulantien und Plättcheninhibitoren (NOAC Linie), OENB, Dietmar Fries

Devices and Services

60 operating/diagnostic rooms, general surgery, post-operative, transplantation, and trauma intensive care unit, six postanesthesia care units, anesthesiology outpatient clinic, medical and nursing student education, emergency medical service ground and rotorwing unit, pain service, basic science research laboratory, and animal operating room.

Internal Medicine I



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Keywords

Gastroenterology, hepatology, endocrinology, metabolism, inflammation, diabetes mellitus, microbiota, non-alcoholic fatty liver disease, nutrition, inflammatory bowel diseases

Research Focus

The research focus of our department is translational research in the fields of inflammation and metabolism and is represented by several research groups. The major objective of our research activities is to improve clinical management of patients with chronic inflammatory disorders, such as Crohn's disease, ulcerative colitis, type 2 diabetes or obesity. The major research topics are:

- the cause and effects of intestinal inflammation particularly in connection with diseases like Crohn's disease and ulcerative colitis
- studies of the composition of the human microbiota and its effects on human health and different diseases
- role and mechanisms of insulin resistance in type 2 diabetes and non-alcoholic fatty liver disease with a focus on various diets
- bariatric surgery and metabolic/immunological effects on the host
- lipoprotein metabolism and atherosclerosis

General Facts

The Department of Internal Medicine I has its focus in the specific medical areas of gastroenterology, endocrinology and metabolism. Our division has about 40

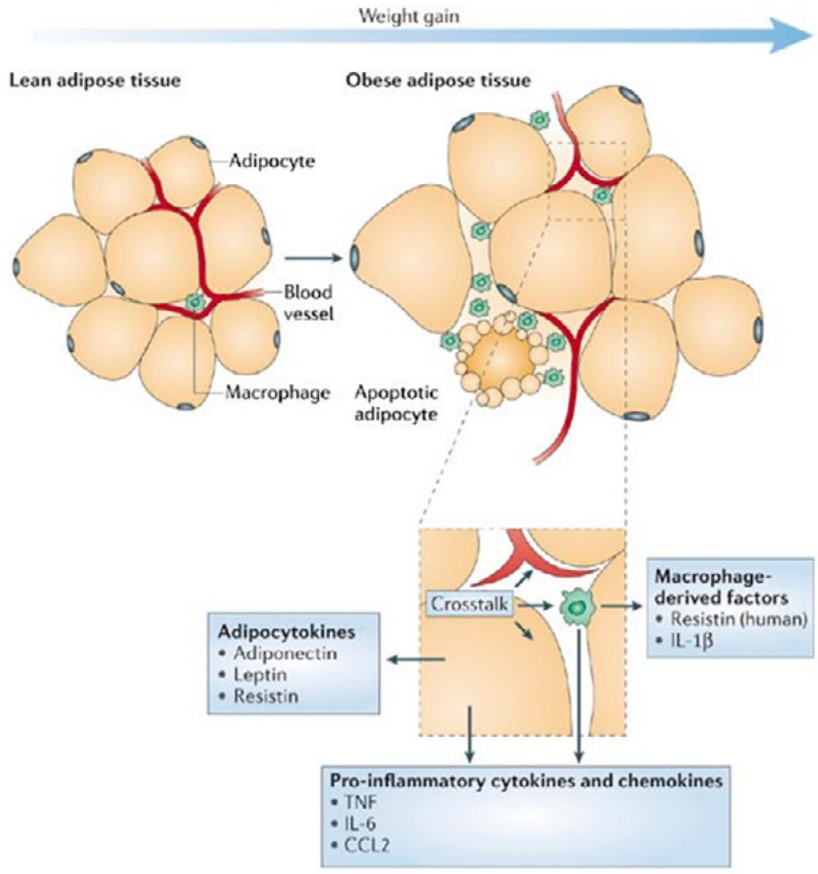

Fig. 1: Adipose tissue: cellular components and molecules synthesised.
Expansion of the adipose tissue during weight gain leads to the recruitment of macrophages through various signals, which might include chemokines synthesized by adipocytes, such as CC-chemokine ligand 2 (CCL2). These macrophages are found mainly around apoptotic adipocytes. Various mediators synthesized by adipocytes and resident macrophages might contribute to local and systemic inflammation. The overall adipocytokine-cytokine cocktail might favour a pro-inflammatory milieu. IL interleukin, TNF tumor-necrosis factor (from Tilg H., Moschen A.R., Nat Rev Immunol 2006, 6:772–83).

employees and many members are involved both in clinical work and research. Our laboratories are perfectly equipped and our researchers are able to perform state-of-the art research in the field of cellular and molecular work. The common aim of our research activities is to increase knowledge in respective disease areas and to improve patient care. We have established many different national and international collaborations throughout the world and, especially in the field of gastroenterology, our department is internationally well established and well known.

Our research is funded by the Austrian Research Promotion Agency (FFG), Austrian Science Fund (FWF), European Union (FP7), Christian Doppler Research Association (CDG) and we have published our research in highly respected international Journals such as Nature, Nature Medicine, Nature Reviews of Immunology, Cell, New England Journal of Medicine, Proceedings National Academy of Sciences, Gastroenterology, Gut, Hepatology and many others.

Research

Gastroenterology

Intestinal inflammation has been the focus of our research activities in the last two decades. One focus has been traditionally clinical research and our clinical research group has been involved in many important clinical studies in the last years which led to major improvements in the clinical management of patients with inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis. As prototypic examples, we have participated in the seminal SONIC study published in the New England Journal of Medicine demonstrating the superior efficacy of anti-TNF agents in combination with immunosuppressants in the treatment of Crohn's disease. We also contributed substantially to the success of the clinical study programme with vedolizumab demonstrating superior activity of this agent especially in the treatment of ulcerative colitis. These studies have also been published in the New England Journal of Medicine.

Another major focus of our research group has been preclinical models of IBD assessing various pathway mechanisms of intestinal inflammation. Here, we could identify in the past several years new mechanisms contributing to intestinal inflammation, which were published in high ranked Journals such as Cell or Journal of

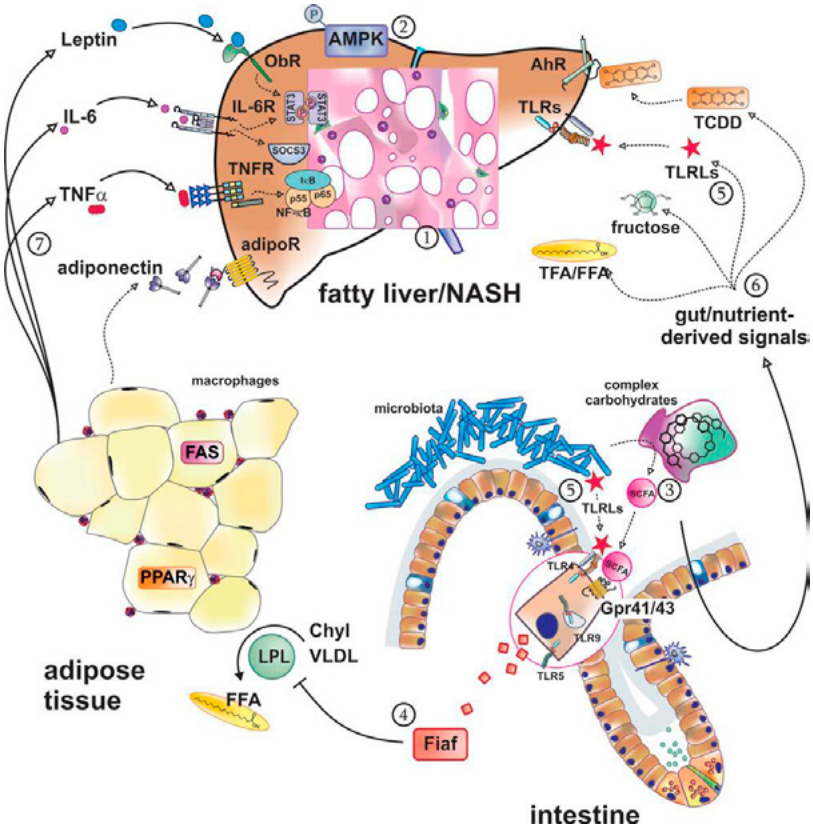

Fig. 2: The multiple parallel hits model. Lipotoxicity: (1) A liver loaded with lipids consisting primarily of trigylcerides might reflect a benign process because trigylcerides might exert mostly protective effects. Furthermore, hyperleptinemia leads to oxidation of hepatic lipids, thereby also protecting this organ from lipotoxicity. When the capacity of peripheral and central organs of detoxifying "aggressive lipids" fails, lipotoxic attack of the liver might begin. Inflammation may precede steatosis in NASH. Gut-derived signals: Many signals beyond endotoxin might affect hepatic steatosis and inflammation. Several pathways have been identified how the gut microbiota might influence host energy metabolism: (2) Absence of the microbiota in germ-free mice correlates with increased activity of phosphorylated AMPK in the liver and the muscle (not shown). (3) Some of the breakdown products of polysaccharides are metabolized to SCFAs. SCFAs such as propionate and acetate are ligands for the G protein-coupled receptors Gpr41 and Gpr43. Shortage of SCFAs might allow the evolution of systemic inflammatory events. Such mechanisms elegantly combine diet, microbiota, and the epithelial cell as "nutrient sensor". (4) The microbiota decreases epithelial expression of fasting-induced adipocyte factor (Fiaf), which functions as a circulating lipoprotein lipase (LPL) inhibitor and therefore is an important regulator of peripheral fat storage. (5) Several TLRs, such as TLR5 or TLR9, are not only able to affect microbiota but also to regulate metabolism, systemic inflammation, and insulin resistance, thus highlighting the role of the innate immune system in metabolic inflammation as observed in NASH. (6) Various nutrients such as trans fatty acids (TFAs), fructose or aryl hydrocarbon receptor (AhR) ligands such as 2,3,7,8-tetrachlorodibenzodioxin (TCDD) may directly lead to steatosis / liver inflammation. Adipose tissue-derived signals: Signals derived from the adipose tissue beyond toxic lipids might play a central role in NAFLD / NASH. (7) Here, adipocytokines such as adiponectin and leptin, certain proinflammatory cytokines such as TNFα or IL-6, and others (the death receptor Fas, PPARγ) are of key relevance. The cytokine / adipocytokine milieu might be critical because ob / ob-adiponectin tg mice, although becoming severely obese, are not insulin-resistant. This suggests that in the hierarchy of processes soluble mediators play the central role. Adipose-derived mediators might indeed affect target organs such as the liver, because JNK1 adipose-deficient mice are protected from diet-induced obesity, and experiments have demonstrated that this effect is mediated mainly by IL-6 (a cytokine), which is of key importance in human obesity. (from Tilg H., Moschen A. R., Hepatology 2010; 52:1836–46)

Experimental Medicine. Another major research topic is the role of diet on immunity and disease development.

Hepatology

Another focus of our research group is non-alcoholic fatty liver disease (NAFLD). Inflammation has always been a major interest of our research group and we have published more than 20 years ago a highly cited paper demonstrating the important role of inflammatory cytokines in chronic liver diseases. Research in the last ten years has concentrated on the role of innate immunity and microbiota in NAFLD and several key papers could be published in this field. Our contributions are also reflected by the fact that members of our research group are commonly invited to the top international meetings in this field. Importantly, we have also contributed intellectually substantially as we have established disease models and hypotheses in this field of research. Our hypothesis paper suggesting that NASH reflects a disease caused by multiple parallel hits is highly cited (Tilg H. Hepatology 2010) and internationally well respected. Several current studies are focussing on the role of innate immunity and microbiota in NAFLD. For these studies we have established an international network with highly respected international leaders. In respect to our leadership in this field, we have recently also been involved in the development of European guidelines in NAFLD.

Endocrinology and Metabolism

Diet-induced obesity has become a huge socio-economic burden worldwide. Obesity is commonly associated with several metabolic alterations, especially insulin resistance, type 2 diabetes, dyslipidemia and, as a consequence, with strongly increased cardiovascular morbidity and mortality. Among others, high-fat and high-carbohydrate intake have been held responsible for increased incidences of obesity and type 2 diabetes.

While metabolic phenotypes of diet-induced forms of obesity are quite similar, partly different pathophysiological mechanisms seem responsible for glucose intolerance and dyslipidemia. The overall aim of our

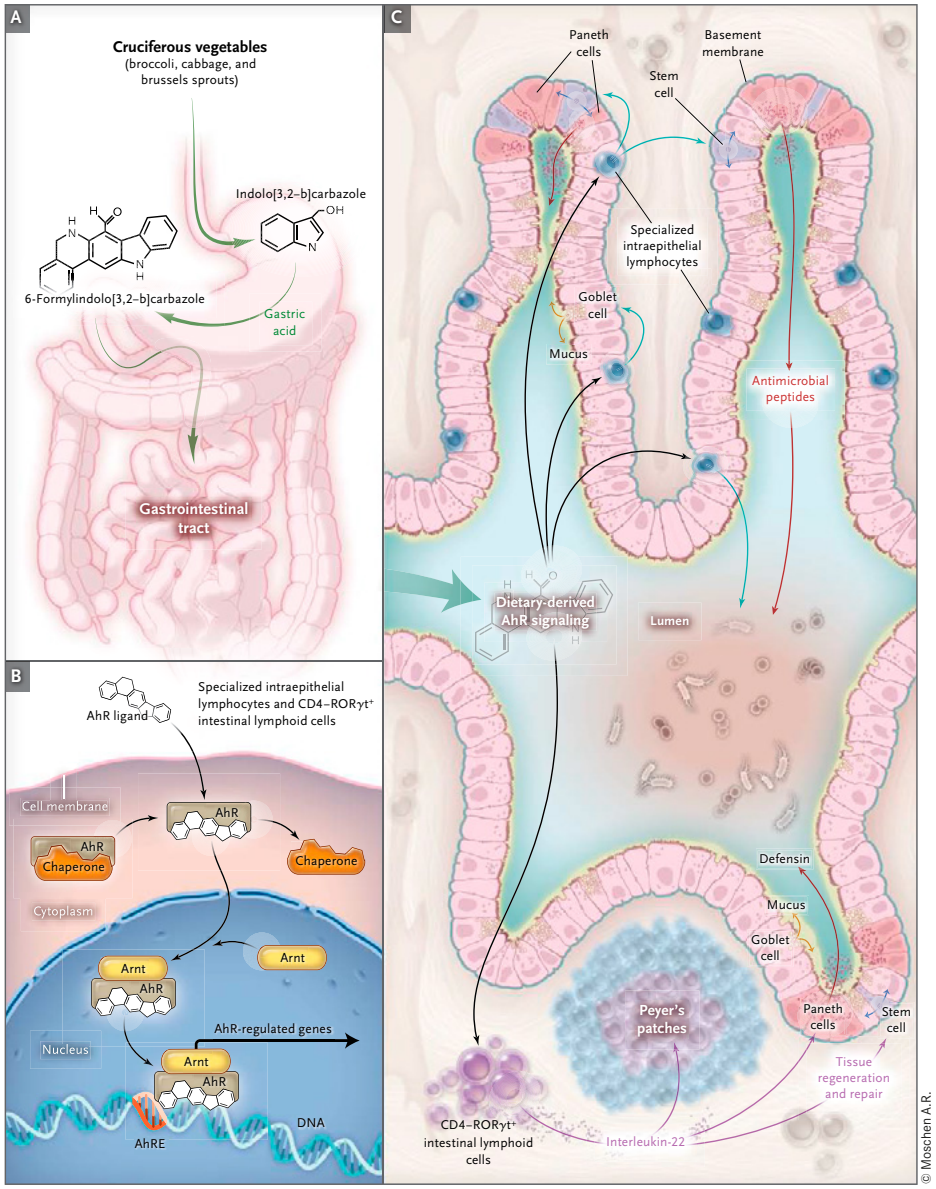

Fig. 3: Dissecting Diet and Intestinal Immunity. Kiss et al.1 and Li et al.2 recently reported that intestinal immune functions are dependent on dietary aryl hydrocarbon repector (AhR) ligands. Indole-3-carbinol is an AhR ligand found in cruciferous vegetables, such as broccoli and brussels sprouts. After oral consumption, indole-3-carbinol is converted in the presence of gastric acid to high-affinity ligands such as indolo[3,2-b] carbazole or 6-formylindolo[3,2-b]carbazole (Panel A).
AhR ligands activate chaperone-bound AhRs that dimerize with the AhR nuclear translocator (Arnt) and regulate gene expression (Panel B).
The studies showed that two cell types are critically dependent on dietary-derived AhR signals: specialized intraepithelial lymphocytes (e.g. intraepithelial T-cell receptor γδ cells) and CD4-RORγt+ intestinal lymphoid cells with lymphoid tissue-inducing function (e.g. Peyer's patches) (Panel C).
Mice lacking AhR signals (obtaining genetically or through dietary deprivation) lack specialized intraepithelial lymphocytes and intestinal lymphoid cells, which results in reduced epithelial turnover, reduced expression of antimicrobial peptides, an altered microbiota, and increased susceptibility to intestinal inflammation (induced by dextran sulfate sodium or in response to Citrobacter rodentium infectin) (Panel C). The pathogenesis of enhanced inflammation in the mutant mice is incompletely understood and probably involves defective interleukin-22 production.
(Interleukin-22 is a cytokine that controls intestinal homeostasis and protects against intestinal pathogens) (from Tilg H., NEJM 2012; 12:181–3)

work is to clearly define harmful effects of different diets on relevant tissues or organs in glucose and lipid metabolism. In detail, we currently investigate systemic and cellular effects of various carbohydrate- or fat-enriched diets in a mouse model of diet-induced obesity. At the cellular level, our studies are focused on diet-specific effects on adipose tissue, the liver, intestine and skeletal muscle. In adipose tissue we are especially interested in lipid droplet formation and adipogenesis. In particular, these studies aim to allow characterization of metabolically healthy and unhealthy adipocytes. Additionally, our studies will include investigations of the role of DPP-IV and apolipoprotein A5, which are both well known candidate genes in metabolic disease, in diet induced obesity and insulin resistance.

Another focus of our work is to more clearly define the crosstalk between metabolically important tissues and organs: To do so we are currently studying the effects of various diets on (adipo)cytokines, hormones and fatty acids which are all thought to play a major role in the interaction between metabolically important tissues. Results from these studies will hopefully allow new insights into diet-specific contributions of various tissues in pathophysiology of insulin resistance and its harmful consequence on health.

Metabolism, Diabetes and Atherosclerosis

Our major research intentions are focused on but not limited to bariatric surgery, type 1 and type 2 diabetes mellitus, atherosclerosis and its short and long term influence on metabolic homeostasis, cardiovascular health, and telomere length.

Bariatric Surgery

Over the past decade, bariatric surgery was one of our pronounced research topics. We examined the short-, mid-, and long-term effects of pronounced and sustained weight loss induced by bariatric surgery on metabolic homeostasis, cardiovascular health and telomere attrition. Topics examined in numerous studies on bariatric surgery patients comprise phospholipid-transfer-activity, HDL-C, markers of chronic inflammation, adipokines, visceral adipose tissue, adipocyte fatty acid-binding protein, retinol-binding protein 4, markers of atherosclerosis, chemerin, matrix metalloproteinase 7, interleukin 1 and 6, tumour necrosis factor alpha, plasminogen activator inhibitor 1, gallstone formation, proprotein subtilisin/kexin type 9, non-alcoholic fatty liver disease and telomere length.

Type 2 Diabetes and the Metabolic Syndrome

Several studies were performed in order to identify risk factors for the development of type 2 diabetes mellitus and the metabolic syndrome.

Studies included the protective effects of uncoupling protein 2, the increased risk for diabetes mellitus due to psychotropic and anti-epileptic drugs, parameters associated with increased insulin resistance, comparisons of different definitions of the metabolic syndrome as well as statistical analysis of different anthropometric surrogate-markers and their accuracy to correlate to cardiovascular risk factors associated with obesity.

Diabetes Registry Tyrol (DRT)

The DRT was established in 2005 in order to register all patients with type 1 and type 2 diabetes mellitus as well as women diagnosed with gestational diabetes mellitus who attend the out-patient clinics in Tyrol. Up to date, the DRT population comprises approximately 7,500 patients and therefore covers about 15 % of all prevalent diabetes in Tyrol. A recent study investigated the association between diagnosis of type 2 diabetes mellitus and certain types of cancer in Tyrol.

Atherosclerosis

Our research is focused on the implication of lipid and lipoprotein metabolism on the development of cardiovascular diseases. We are interested in the role of reverse cholesterol transport in this scenario. Our research work encompasses basic research, animal-based studies as well as clinical studies and is targeting the development of new strategies for prevention and therapy of atherosclerotic diseases in humans.

<u>Research Interests</u>

- Lipoprotein metabolism and atherosclerosis
- Reverse cholesterol transport with focus on High Density Lipoprotein (HDL), Cholesteryl Ester Transfer Protein (CETP) and Scavenger Receptor Class B Type I (SR-BI)
- Transgenic rabbit models for atherosclerosis
- Gene transfer (receptor mediated endocytosis, viral vectors)

Selected Publications

Adipose tissue and liver expression of SIRT 1, 3 and 6 increase after extensive weight loss in morbid obesity.
Moschen AR, Wieser V, Gerner RR, Bichler A, Enrich B, Moser P, Ebenbichler CF, Kaser S, Tilg H.
JOURNAL OF HEPATOLOGY. 2013; 59: p. 1315–22.

Blockade of receptor activator of nuclear factor-κB (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. Kiechl S, Wittmann J, Giaccari A, Knoflach M, Willeit P, Bozec A, Moschen AR, Muscogiuri G, Sorice GP, Kireva T, Summerer M, Wirtz S, Luther J, Mielenz D, Billmeier U, Egger G, Mayr A, Oberhollenzer F, Kronenberg F, Orthofer M, Penninger JM, Meigs JB, Bonora E, Tilg H, Willeit J, Schett G.
NATURE MEDICINE. 2013: 19: p. 358–63.

ER stress transcription factor Xbp1 suppresses intestinal tumorigenesis and directs intestinal stem cells. Niederreiter L, Fritz TM, Adolph TE, Krismer AM, Offner FA, Tschurtschenthaler M, Flak MB, Hosomi S, Tomczak MF, Kaneider NC, Sarcevic E, Kempster SL, Raine T, Esser D, Rosentiel P, Kohno K, Iwawaki T, Tilg H, Blumberg RS, Kaser A.
THE JOURNAL OF EXPERIMENTAL MEDICINE. 2013: 210: p. 2041–56

IL-37 protects against obesity-induced inflammation and insulin resistance. Ballak DB, van Diepen JA, Moschen AR, Jansen HJ, Hijmans A, Groenhof GJ, Leenders F, Buflet P, Boekschoten MV, Müller M, Kersten S, Li S, Kim S, Eini H, Lewig EC, Joosten LA, Tilg H, Netea MG, Tack CJ, Dinarello CA, Stienstra R.
NATURE COMMUNICATIONS. 2014: 5: p. 4711.

Microbiota and diabetes: an evolving relationship. Tilg H, Moschen AR.
GUT 2014. 63: p. 1513–21.

Selected Funding

Establishment and development of new models of the metabolic syndrome as screening platform for phytodrugs, Austrian Research Promotion Agenca (FFG), BRIDGE, € 109,000.00, 2013–2015; Univ.-Prof. Dr. Herbert Tilg

Long-term effects of weight loss on atherosclerosis, Austrian Science Fund (FWF), € 177,000.00, 2014–2016; ao. Univ.-Prof. Dr. Christoph Ebenbichler

Body weight and cellular aging: effects of weight loss on the telomere length, Austrian Science Fund (FWF), € 154,000.00, 2014–2016; Priv.-Doz. Dr. Markus Laimer

VASCage – Research Center of Excellence in Vascular Ageing, Austrian Research Promotion Agency (FFG), COMET, € 360,000.00, 2014–2018; Univ.-Prof. Dr. Herbert Tilg

HDL function and atherosclerosis: Studies in apolipoprotein E Knockout Rabbits, Austrian Science Fund (FWF), € 231,000.00, 2015–2018; ao. Univ.-Prof. Mag. Dr. Andreas Ritsch

Christian Doppler Research Laboratory for metabolic crosstalk, Christian Doppler Research Association (CDG), € 770,000.00, 2015–2022; Assoz.-Prof. Priv.-Doz. Dr. Susanne Kaser

Collaborations

- Charles A. Dinarello, Denver, Colorado, USA
- Georg Schett, Erlangen, Germany
- Stefan Schreiber, Kiel, GermanyW
- Arthur Kaser, Cambridge, UK
- Fredrik Bäckhed, Gothenburg, Sweden
- Patrice Cani, Brussels, Belgium
- Willem de Vos, Wageningen, The Netherlands
- Roberto Vettor, Verona, Italy

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Keywords

Management of liver failure, chronic liver disease, cirrhosis and hepatocellular carcinoma, treatment of chronic viral hepatitis, liver transplantation
Treatment of portal hypertension and complications, endoscopic therapy of benign and malignant biliary and pancreatic disease, endoscopic diagnosis and treatment of benign and malignant mucosal disorders of the gastro-intestinal tract

Research Focus

- Regulation of iron homeostasis with a special emphasis on HFE and non-HFE hemochromatosis. Functional characterisation of mutations in proteins involved in iron metabolism.
- Treatment optimization in end stage liver disease and complications after liver transplantation including recurrent and *de novo* malignancies, recurrent viral hepatitis and genetic risk factors for graft disease
- Clinical trials with new therapeutic agents for liver and gut diseases.

General Facts

The department of internal medicine II links basic and clinical science in hepatology and gastroenterology. It is structured into an inpatient ward, an outpatient center and the hepatology laboratory. This structure enables us to carry out clinical research as well as basic science. As a tertiary referential center for patients with gut and liver diseases and, in cooperation with the department

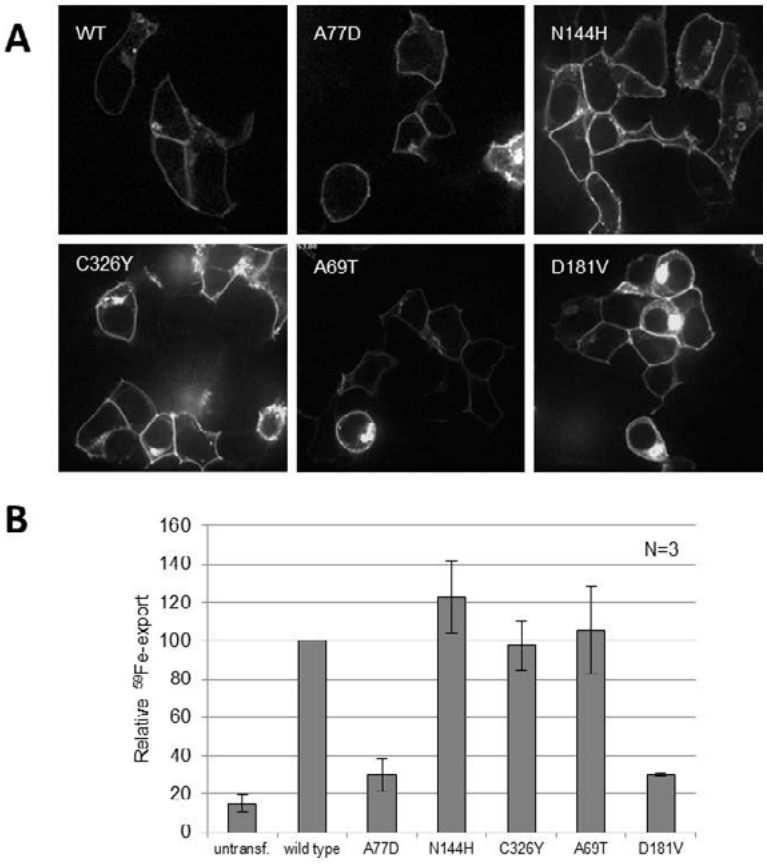

Fig. 1: Confocal microscopy (A) and iron export experiments (B) are part of functional characterization of ferroportin mutations. Confocal microscopy reveals prominent membrane fluorescence of wild-type and A77D, N144H, C326Y, A69T and D181V mutant GFP-ferroportin. Only ferroportin correctly localized to the plasma membrane is able to export iron from the cell. Wild-type, N144H, C326Y and A69T mutant ferroportin cause a more than 5-fold increase in iron export when compared to untransfected cells. No such increase can be observed in A77D and D181V mutant ferroportin overexpressing cells. These finding strongly support the concept that the apparent reduction in iron export function of D181V and A77D mutant ferroportin is caused by a defective pump mechanism and not by intracellular retention.

of transplant surgery, as one of the three liver transplant centers in Austria, we have access to a large number of interesting patients with a wide spectrum of diseases. Furthermore our laboratory provides viral hepatitis diagnostics and genetic testing for HFE haemochromatosis and other genetic causes of iron disorders for primary and secondary care centers in western Austria.

The hepatology laboratory is a well-equipped laboratory carrying out clinical routine and basic research work. Full equipment for molecular biology work including genotyping, PCR, cloning and vector production is available. Furthermore, the laboratory has a sterile tissue culture hood and incubator for cell culture experiments, centrifuges, chromatography, ELISA reader and blotting equipment for biochemical experiments and a mass spectrometer. The close collaboration between our laboratory and the clinical wards is the key to translate findings made in basic research into clinical studies and to further investigate genetics and disease pathways in patients recruited from our inpatient or outpatient ward.

Research

Regulation of Iron Metabolism, HFE and Non-HFE Hemochromatosis

The hepatology laboratory (Head Prof. Dr. Heinz Zoller) is primarily interested in the regulation of iron homeostasis with a special emphasis on HFE and non-HFE hemochromatosis. Hemochromatosis is the most common genetic and metabolic liver disease in adults and an important differential diagnosis in patients with chronic liver disease. Although a majority of patients with hemochromatosis are homozygous for the C282Y polymorphism of the HFE gene, non-HFE associated hemochromatosis variants like ferroportin disease or aceruloplasminemia are increasingly recognized to contribute to the overall burden of iron overload disorders.

Recent studies of our workgroup have investigated the disease mechanisms of novel mutations in the only known mammalian iron exporter ferroportin. We have shown that some mutations cause a loss of function while others cause a dose-dependent hepcidin resistance. Hepcidin is known as the “iron hormone” and is the main regulator of iron homeostasis. The results from our studies further indicate that intact iron export might be necessary for hepcidin-induced downregulation of ferroportin and therefore have implications beyond the sole classification of novel mutations.

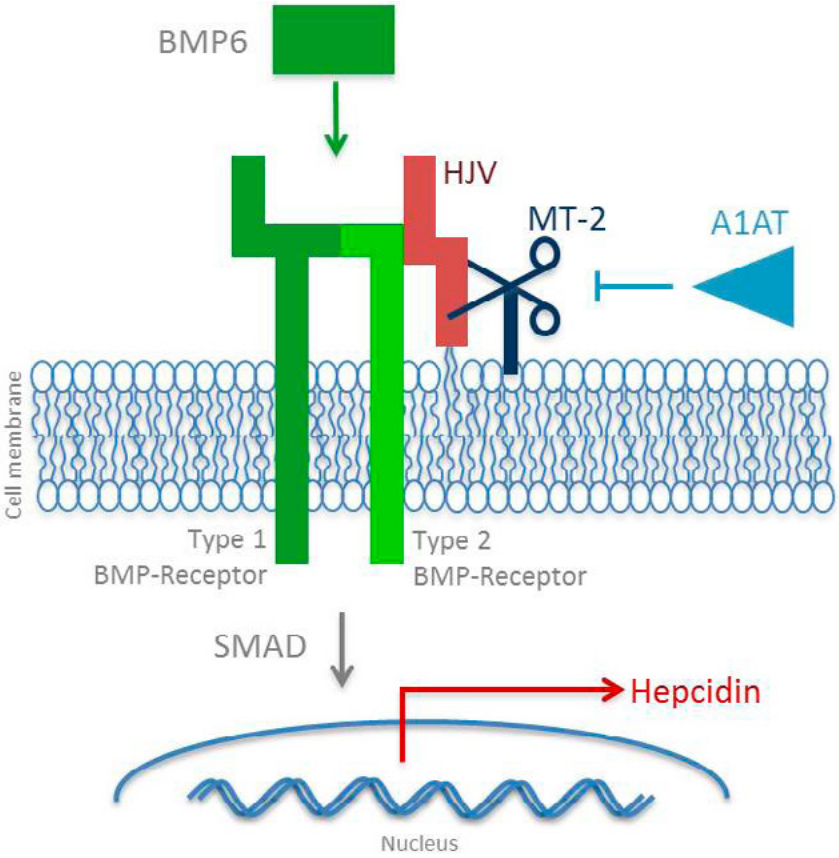

Fig. 2: Proposed molecular mechanism of alpha-1-antitrypsin’s effect on hepcidin expression via matriptase-2 inhibition: Hemojuvelin (HJV) is a membrane-bound coreceptor for the heterodimeric BMP Type I receptor and BMP Type II receptor complex and is essential for BMP-6-induced activation of SMAD proteins which increase hepcidin expression. The serine protease matriptase-2 (MT-2) cleaves HJV and subsequently inhibits hepcidin expression. Alpha-1-antitrypsin (A1AT) medicated inhibition of MT-2 thus stimulates hepcidin expression via reduced hemojuvelin cleavage.

Hepcidin regulation is a further research topic in our lab where we have shown that hepcidin is induced by the acute-phase protein alpha-1-antitrypsin, which is not primarily associated with iron metabolism. Full exome sequencing in a family that presented with severe alpha-1-antitrypsin deficiency and liver iron overload at our outpatient center revealed the presence of heterozygous hepcidin mutations in affected individuals. Further *in vitro* studies showed that alpha-1 antitrypsin regulates hepcidin expression via hemojuvelin and matriptase-2.
Aceruloplasminemia is another genetic disease causing liver iron overload but also iron deposition in the central nervous system, which cannot be treated so far and causes a lethal neurological disease. A focus of our working group is the functional characterisation of novel mutations in the ceruloplasmin gene and the development of new therapeutic strategies for this devastating disease.

For this aim, we have established a colony of CP-knockout mice and are conducting experiments for viral gene transfer of the intact CP-gene to establish a gene therapy for this otherwise untreatable disease. Apart from this basic science work we have initiated a European registry to collect structured information on the clinical presentation, biochemistry, radiology, family history, genetics and histology of patients with non-HFE hemochromatosis, ferroportin disease and aceruloplasminemia. This will help us determine the incidence, prognosis, treatment strategies and complications

of these rare syndromes and to identify patients eligible for future clinical studies.

Clinical Research Liver Disease and Liver Transplantation

Chronic liver diseases can result in end stage liver disease or hepatocellular carcinoma necessitating liver transplantation as the only curative treatment. Although chronic hepatitis C, a formerly frequent cause of chronic liver disease, will decrease as a consequence of effective direct antiviral agents, chronic or even end stage liver disease caused by alcoholic or non-alcoholic fatty liver disease, hemochromatosis and metabolic diseases will remain a major problem in hepatology. The second research focus of our department is therefore optimisation of patient care in this population and the improvement of long-term survival and quality of life in patients who undergo liver transplantation. The access to a large number of patients with chronic liver disease and liver transplant recipients via our inpatient and outpatient center enables us to carry out clinical research in the pre- and post-transplant phase.

Magnetic resonance imaging (MRI) is an important tool in the evaluation of patients with chronic liver diseases. In several research projects conducted in collaboration with Dr. Henninger from the department of radiology we have shown that MRI is a valuable tool for non-invasive quantification of liver iron and the degree of steatosis. This will help us reduce the need of liver biopsies and gives us the possibility to follow-up patients non-invasively, for example during clinical trials in non-alcoholic fatty liver disease. Recently, we were able to show that liver transplantation is an excellent treatment modality in patients with acute-on-chronic liver failure, but only a minority of affected patients will undergo liver transplantation as the mortality on the waiting list is high. This has further implications for organ allocation, which, at the moment, does not allow high urgency status for patients with chronic liver disease.

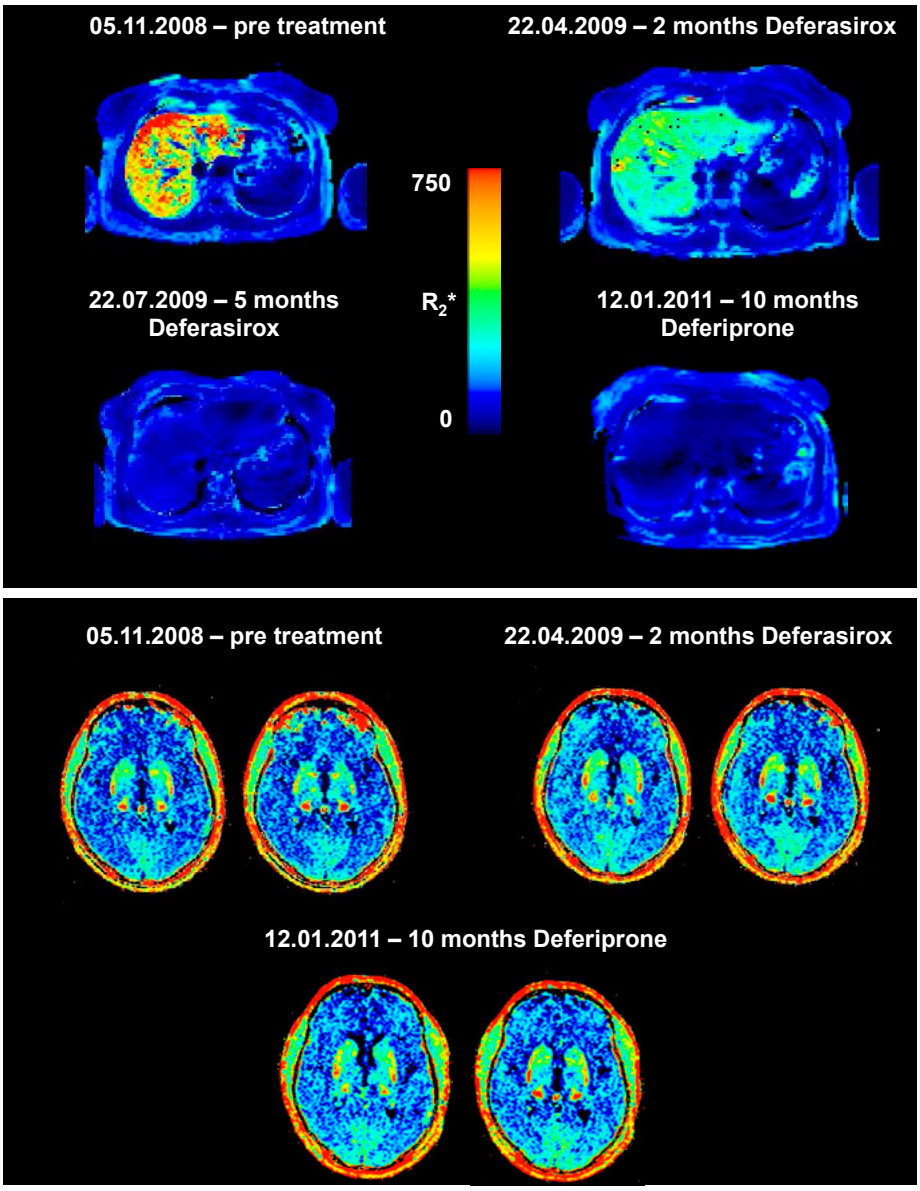

Fig. 3: Non-invasive liver and brain iron quantification in a patient with aceruloplasminemia. Therapy with oral iron chelators caused a rapid normalization of liver iron concentration but did not affect brain iron deposition or neurological symptoms.

If patients successfully undergo liver transplantation, careful follow-up is a requirement to achieve good long-term survival rates. Recurrence of the underlying disease is a common problem, especially in patients transplanted for fatty liver disease or hepatocellular carcinoma. We have identified rs738409-G in the PNPLA3 gene as a risk factor for hepatic triglyceride accumulation and graft steatosis after transplantation. Furthermore we were able to show that patients with hepatocellular carcinoma outside classic transplant criteria can undergo transplantation without increased risk of recurrence depending on their response to neoadjuvant therapies. These observations can lead to a more tailor-made post-transplant surveillance adjusted to the individual risk factors of transplant recipients.

The future goal of our research unit is to further improve pre- and post-transplant care in patients with liver disease and to translate findings from basic research into clinical research and finally into clinical routine.

Clinical Trials in Inflammatory Bowel Disease and Chronic Liver Diseases

As a tertiary referral center for gut and liver diseases the department of internal medicine II has a large number of patients potentially available for clinical trials. This enables us to collaborate with other academic centers or pharmaceutic companies in multicenter trials and ensures our patients access to novel therapies not yet available outside clinical studies.

We conduct clinical trials in inflammatory bowel disease, viral hepatitis, biliary diseases, hepatocellular carcinoma or non-

alcoholic liver disease. To ascertain the high quality requirements of good clinical practice our department employs two study coordinators, Mag. Toaba and Mag. Zotter.

Selected Publications

Impact of D181V and A69T on the function of ferroportin as an iron export pump and hepcidin receptor. Praschberger Roman, Schranz Melanie, Griffiths William JH, Baumgartner Nadja, Hermann Martin, Lomas David J, Pietrangelo Antonello, Cox Timothy M, Vogel Wolfgang, Zoller Heinz.
BIOCHIMICA ET BIOPHYSICA ACTA. 2014; 1842(9): 1406–1412.

Patatin-like phospholipase domain-containing protein 3 rs738409-G in recipients of liver transplants is a risk factor for graft steatosis. Finkenstedt Armin, Auer Claudia, Glodny Bernhard, Posch Ursula, Steitzer Hansjoerg, Lanzer Gerhard, Pratschke Johann, Biebl Mathias, Steurer Michael, Graziadei Ivo W, Vogel Wolfgang, Zoller Heinz. CLINICAL GASTROENTEROLOGY AND HEPATOLOGY. 2013; 11(12): S.1667–1672.

Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list.
Finkenstedt Armin, Nachbaur Karin, Zoller Heinz, Joannidis Michael, Pratschke Johann, Graziadei Ivo W, Vogel Wolfgang. LIVER TRANSPLANTATION. 2013; 19(8): S. 879–886.

MNGIE Syndrome: Liver Cirrhosis Should Be Ruled Out Prior to Bone Marrow Transplantation.
Finkenstedt Armin, Schranz Melanie, Bösch Sylvia, Karall Daniela, Scholl-Bürgi Sabine, Ensinger Christian, Drach Mathias, Mayr Johannes A, Janecke Andreas R, Vogel Wolfgang, Nachbaur David, Zoller Heinz. JIMD REPORTS. 2013; 10: S.41–44.

The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma.
W Sieghart, M Pinter, F Hucke, I Graziadei, M Schöniger-Hekele, C Müller, W Vogel, M Trauner, M Peck-Radosavljevic M. Hepatology. 2013; 57(6):2261–73.

A single determination of C-reactive protein at the time of diagnosis predicts long term outcome of patients with hepatocellular carcinoma. W Sieghart, F Hucke, M Pinter, I Graziadei , W Vogel, C Müller, H Heinzl, M Trauner, M Peck-Radosavljevic.
Hepatology 2013. 57(6):2224–34.

The ART-strategy: sequential assessment of the ART score predicts outcome of patients with hepatocellular carcinoma re-treated with TACE.
F Hucke, W Sieghart, M Pinter, I Graziadei, W Vogel, C Müller, H Heinzl, F Waneck, M Trauner, M Peck-Radosavljevic.
J Hepatol. 2014; 60(1):118–26.

How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma.
F Hucke, M Pinter, I Graziadei, S Bota, W Vogel, C Müller, H Heinzl, F Waneck, M Trauner, M Peck-Radosavljevic, W Sieghart W.
J Hepatol. 2014 Dec; 61(6):1287–96.

Collaborations

- M. Peck-Radosavljevic, Vienna Medical University
- MARC CREUS, Department of Chemistry, University of Basel, Basel, Switzerland
- RANIA BAKRY, Department of Analytical Chemistry & Radiochemistry, Leopold Franzens University of Innsbruck, Innsbruck, Austria
- WILLIAM J. H. GRIFFITHS and TIMOTHY M. COX, Department of Medicine, Cambridge University Hospitals, NHS Foundation Trust, Cambridge, England
- ANTONELLO PIETRANGELO, Center for Hemochromatosis, University Hospital of Modena, Modena, Italy
- MAYKA SANCHEZ-FERNANDEZ, Department of Genetics and Epigenetics, Institute of Predictive and Personalized Medicine of Cancer (IMPPC), Barcelona, Spain

Devices

- Maldi-TOF mass spectrometer
- 2D high pressure liquid chromatography
- Fast protein liquid chromatography
- French Press
- Lyophylisation
- CCD-Camera/Imager
- Genetic sequencing for different genes of iron regulation
- Full exome sequencing (in collaboration)
- Proteomics/Functional characterisation
- HFE genotyping, HBV and HCV genotyping and quantification

Internal Medicine III

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Keywords

cardiac regeneration, neovascularization, stem cells, SDF-1, CXCR4, DPPIV, translational research, MRI, MSCT, clinical studies

Research Focus

The focus of our cardiovascular research group is based on 3 complementing columns to develop novel therapies for cardiac and vascular regeneration as well as the implementation of new imaging methods and translational research to the clinic:
Column 1: Cardiac Regeneration and Aging: The aim is to develop novel therapies to build new heart tissue and vessels,
Column 2: The major goal is to utilize novel imaging technologies like MSCT or MRT to monitor and improve clinical therapies,
Column 3: Monitoring of international phase 2–3 Clinical studies.

General Facts

Heart Diseases are the main reason for mortality and morbidity in the Western world. Is-chemic cardiomyopathy following myocardial infarction (MI) is the most prevalent. Although new medical therapies can reduce the progression of diseased hearts to chronic heart failure, once lost, replacement of functional myocardium is very limited. Therefore, therapies to augment and preserve myocardial tissue are warranted.

1. Cardiovascular Regeneration and Aging,
2. Cardiac Imaging and Translational Research, and
3. Clinical Studies.

The focus of our experimental approach in column 1 is the development of novel strategies for cardiac regeneration and neovascularization. Our specific aim is to understand the cell recruitment of progenitor cells to the ischemic heart and vessels, as well as the process of regeneration through transition from the neonatal stage to adulthood with the intention to develop new regenerative therapies. Furthermore, we are interested in the process of atherosclerosis and angiogenesis. Another important aspect of our experimental work is to elucidate the process of aging. Since patients suffering from premature aging (progeria) develop severe cardiovascular morbidities like stroke, myocardial infarction, and severe atherosclerosis, we are currently using this model to investigate new targets which can inhibit these aging processes. In our second column, we aim to develop novel imaging protocols for TAVI patients or to look for novel biomarkers with MRI based protocols.

We are also focusing on translational research that combines basic research with clinical data. Additionally, our research unit takes part in multinational projects and clinical trials that are depicted in column 3.

Research

Column 1: Cardiovascular Regeneration and Aging

I. Therapeutic Targeting of CXCR4+ Cell Populations in the Ischemic Heart
Ass.-Prof. M. M. Zaruba, S. K. Ghadge (PhD), M. Messner (PhD student)
In previous work, we showed that stem cell mobilization with Granulocyte colony-stimulating factor (G-CSF) and Parathyroid hormone (PTH) was associated with improved cardiac function after MI. However, a major drawback is the inactivation of the important homing factor, stromal derived factor 1 (SDF-1) by activated proteases, like DPP-IV after myocardial infarction. Therefore, we developed a novel dual medical therapy based on mobilization of progenitor cells with G-CSF and inhibition of SDF-1 degradation by blocking the protease DPP-IV/CD26. This strategy preserved SDF-1 after MI, enhanced the migration of CXCR4+ blood derived progenitors, improved cardiac function, and decreased mortality in mice (Fig. 1). The same treatment combined with cell cycle activation in cardiomyocytes was even capable of enhancing myocardial regeneration after MI. Based on these promising findings, we initiated the first clinical trial analysing the effect of G-CSF and a DPP-IV inhibitor treatment on cardiac function after acute MI (SITAGRAMI-TRIAL; EudraCT number: 2007-003941-34).

However, SDF-1-CXCR4-mediated cell recruitment and repair mechanisms are still barely understood. Therefore, we are currently working to expand our knowledge about SDF-1/CXCR4 based cardiac repair utilizing novel CXCR4-EGFP reporter mice and tissue specific SDF-1 knock-out mice to enhance the recruitment of progenitor cells to the heart. Our preliminary data suggest that inhibition of prolyl hydroxylase may be a promising target for HIF-1a mediated SDF-1 activation to increase stem cell homing and myocardial repair.

Future Goals:

- Lineage tracing of regenerative cell populations in the neonatal and adult heart to develop new therapies for severe heart failure.
- Elucidating the role of aging-related enzymes in the development and progression of heart failure.

II. Aging Related Splicing Variants in Patients with Cardiomyopathy
Ass.-Prof. M. M. Zaruba, S. K. Ghadge (PhD), M. Messner (PhD student)
Defined mutations in the human lamin A gene or in enzymes processing the important nuclear membrane protein LMNA (e.g. Zmpste24) are causally involved in premature aging syndromes like progeria. Patients suffering from progeria develop severe cardiovascular morbidities like stroke, myocardial infarction, and severe atherosclerosis leading to early death. We are currently using this model to investigate new targets that can inhibit this aging process. In the current projects we investigate whether premature aging enzymes, like LMNA, play a role in the development of heart failure.

III. Neonatal MI Mouse Model to Study Cardiac Regeneration
Dr. B. Haubner (PhD),
T. Schütz (PhD student)
Cardiac regeneration is one of the prime

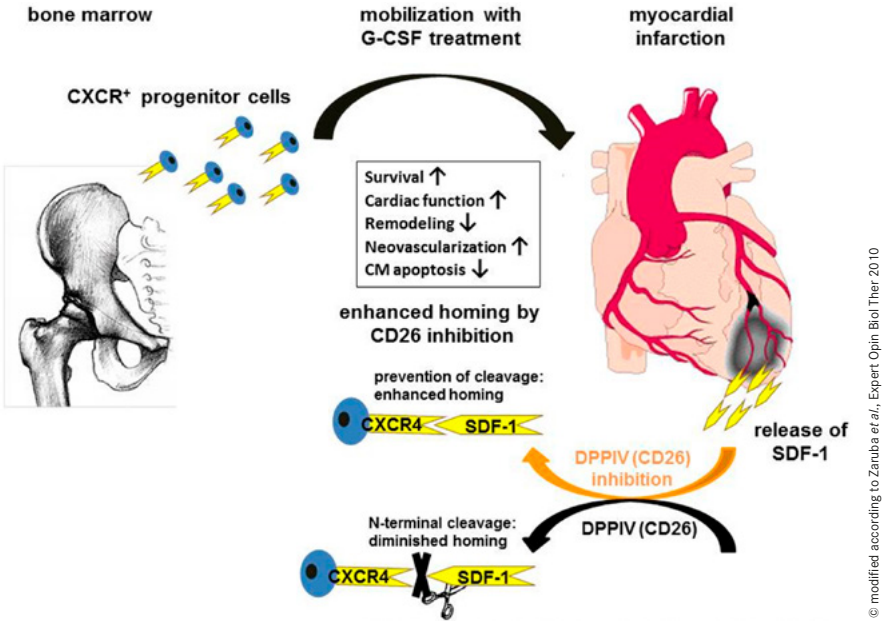

Fig. 1: Targeting of CXCR4+ cells with DPP-IV/CD26 inhibition plus G-CSF treatment. After acute myocardial ischemia, G-CSF administration mobilizes CXCR4+ progenitor cells from BM. Thereupon, CD34+CXCR4+ cells circulate in enhanced numbers to the injured heart. In the myocardium, CXCR4+ cells interact with functionally intact SDF-1. Pharmacological inhibition of DPPIV/CD26 prevents the degradation of intact SDF-1. Thus, stabilization of SDF-1 improves homing of mobilized stem cells. This strategy yielded enhanced neovascularization, reduced cardiomyocyte apoptosis and finally improved cardiac function and survival by attenuating the development of ischemic cardiomyopathy.

visions in cardiovascular therapeutics. Accumulating experimental evidence hint at a modest annual cardiomyocyte turnover in the adult mammalian heart that is obviously not sufficient to replace millions of lost cardiomyocytes upon myocardial injury. Newts and zebrafish are well-known *in vivo* animal models for cardiac regeneration but the evolutionary distance to humans limits their translational potential. In 2011, experiments by Porrello *et al.* reported a short window after birth of complete cardiac regeneration following apical resection in the neonatal mouse. Stimulated by their work we independently established a neonatal mouse model of left anterior descending artery (LAD) ligation and proved excellent recovery of murine neonatal hearts after clinically relevant myocardial infarction (MI). We demonstrated that the heart of neonatal mice regenerates after massive MI within one week after LAD ligation. Importantly, this regenerative potential is lost within seven days after birth. Therefore, we are fascinated by the question: What are the transcriptional changes within the first seven days that transform a mammalian heart from a regenerative to a scarring state? In order to answer this question, we set out to analyse the time course changes of the mouse cardiac coding and noncoding transcriptome during the first week of life using RNA-Seq (Fig. 2). Interesting candidate genes will be identified using bioinformatics and consecutively targeted *in vitro* and *in vivo* to test the potential influence on cardiac regeneration.

Future Goals: Identification of novel regulators of cardiac regeneration using the above described mouse neonatal myocardial infarction model in combination with our transcriptome database. The long-term aim of our group is to stimulate cardiac regeneration in adult mammalian hearts by studying *in vivo* neonatal cardiac regeneration as an experimental model.

IV. Novel Strategies for Improved Angiogenesis

ao. Univ.-Prof. Rudolph Kirchmair and Dr. Markus Theurl

Our research focuses on endothelial cell biology and angiogenesis. Over the last years our laboratory identified the neuropeptides catestatin and secretoneurin as novel angiogenic factors. These peptides derive from the precursor molecules secretogranin II or chromogranin A and are found mostly in the neuroendocrine system but are also expressed in the ischemic skeletal muscle and myocardium. Similar to prominent angiogenic factors like vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (FGF), secretoneurin and catestatin induce proliferation and chemotaxis of endothelial cells and protect them from apoptosis. A therapeutic application was tested *in vivo* in several animal models by our group. In the so-called hind limb ischemia model, the application of a secretoneurin-expressing plasmid or catestatin as peptide was associated with a dramatic reduction of ischemia-related tissue defects and a significant improvement in limb reperfusion.

In the experimental myocardial infarction model, treatment with secretoneurin significantly improved cardiac parameters like left ventricular ejection fraction and reduced infarct size. These effects were induced by interaction with several tyrosine kinase receptors like VEGF-receptor 2 or members of the FGF-receptor family. Recently, we could demonstrate effectiveness and safety of secretoneurin gene therapy also in animal models with impaired vascular response like the Apo E -/- mouse.

Future Goals:

- Development of tissue-specific gene therapeutic vectors,
- clarify the molecular mechanism of secretoneurin and catestatin induced actions on vascular cells in more detail.

V. Macrovascular Protection and Regeneration

Dr. Christoph Brenner and Friedericke Remm (Vet. med. PhD student)

Disturbances of the vascular endothelial integrity can occur during the process of atherosclerosis and its interventional therapy in diseased arteries. De-endothelialized areas of the vascular wall can lead to local thrombus formation and thus can impair blood flow with resulting ischemic events. Although endogenous endothelium has remarkable capabilities for self-renewal, the time span between injury and endothelial recovery is precarious. Therefore, we have recently established a therapeutic regimen to accelerate endothelial regeneration. After arterial denudation, attached platelets, activated endothelial and smooth muscle cells secrete the cytokine SDF1 that can bind to the CXCR4 receptor of circulating progenitor cells (ciPCs). Subsequently, these cells are recruited to the injured vascular wall. After migration into the diseased tissue, ciPCs can accelerate endothelial regeneration mainly by secretion of paracrine factors. By pharmacological inhibition of SDF1 cleavage, e.g. by using the DPP4-inhibitor Sitagliptin, we were able

to boost ciPC-recruitment and vascular re-endothelialization (Fig. 3). Future projects of our group will now investigate the impact of pharmacological DPP4 inhibition on the development of atherosclerosis.

VI. Experimental Ischemia/ Reperfusion *in Vivo* Mouse Model
Doz. Bernhard Metzler
The group investigates cardioprotective mechanisms to reduce ischemia/reperfusion injury after myocardial infarction. In particular, we are interested in signal transduction cascades PI3K and migfilin.

Column 2: Cardiac Imaging and Translational Research

I. New Cardiac Imaging Appraoches with Multislice Computed Tomography (MSCT)
ao Prof. G. Feuchtner,
ao Prof. G. Friedrich, F. Plank
The aim of the group is to develop new protocols for cardiac imaging utilizing multislice computed tomography (MSCT).
In particular, the following research topics are on the agenda:
- evaluation of TAVI patients with MSCT, particularly with respect to calcification and their impact on the TAVI procedure.
- evaluation of the diagnostic value of MSCT in patients suffering from chest pain in cooperation with EU sponsored multi-center studies (DISCHARGE).
- value of MSCT to relate coronary morphology and size to the prediction of hemodynamic relevance.
- MSCT based measurement of fractional flow reserve (FFR) to evaluate the hemodynamic significance of coronary artery stenosis and the impact on further therapeutic approaches.
- evaluation of coronary segments after Bioresorbable Vascular Scaffold (BVS) implantation: Possibilities of non invasive assessment of BVS.
- development and composition of an Austrian TAVI registry with data related to the pre-peri-post interventional results together with the department of cardiac surgery.
- development of general guidelines for MSCTA based appraisal of coronary arteries and protocols.

II. Development of New Heart-MRI Protocols and Biomarkers
Doz. Bernhard Metzler,
Ass.-Prof. G. Klug, S. Reinstadler,
H. Feistritzer
The focus of the group is to investigate the correlation of infarct size with the patient delay after acute myocardial infarction after primary-PCI using late-enhancement-MRI. The group also utilizes this technique to investigate novel biomarkers like copeptin with respect to the correlations of infarct size, as well as acute inflammatory processes after an acute myocarditis. The group could show a good correlation with an impaired microvascular perfusion. Actual projects include the evaluation of pulse-wave-velocity measurements of the aorta in patients after acute MI.

III. Lab-2-Go:
Prof. J. Mair, S. Plangger, B. Will, K. Wegscheidler
The Lab2Go project, co-funded by the European Commission, is a study to determine the value of a point-of-care testing system for measuring cardiac Troponin-I (cTnI) at the patients' bedside as an aid in the diagnosis of patients with the indications of a Myocardial Infarction (MI). A blood sample can be taken and tested by the doctor, nurse or paramedic to provide a cTnI measurement during clinical assessment, rather than having to wait for laboratory results. The aim is to have a solution available at the end of the project which meets the targeted system specifications, is accepted by the intended users and is ready for clinical validation. The Point-of-Care system that will be demonstrated is referred to as the Minicare system – an innovative biophotonics based technology that employs a surface sensitive optical detection technique to determine a biomarker concentration in blood. The system is designed to enable various biomarkers to be measured in whole blood within 10 minutes at lab-quality precision. The Lab2Go project is a European Union funded multicenter Research and Development project conducted at six hospitals in the European Union bringing together a pan-European consortium of leading companies, universities, hospitals and healthcare suppliers.

IV. Sleep apnea syndrome and cardiac resynchronization therapy in patients with conventional pacemakers. The study is funded by the OeNB Anniversary Fund.
W. Dichtl

V. TAKINSULA: pilot study to evaluate ventral venous/hormonal changes in TakuTsubo cardiomyopathy. W. Dichtl

VI. P-Select in Study.
P. Marschang, R. Kirchmair
The purpose of the study is to evaluate the correlation of atherosclerotic plaque volume and intima-media-thickness with soluble p-selectin as a potential new biomarker for atherosclerosis. The study is funded by the OeNB Anniversary Fund.

VII. The Role of FGF23 and Klotho in Chronic Heart Failure
G. Pölzl, S. K. Ghadge, M. Messner, M. M. Zaruba
The project comprises clinical studies in a large heart failure cohort on the predictive role of FGF23 and sKlotho, as well as molecular, immunohistological, and immunofluorescence in endomyocardial biopsies from myopathic hearts.

VIII. LevoRep Study
G. Pölzl
The LevoRep study is a multicenter randomised trial to test the efficacy and

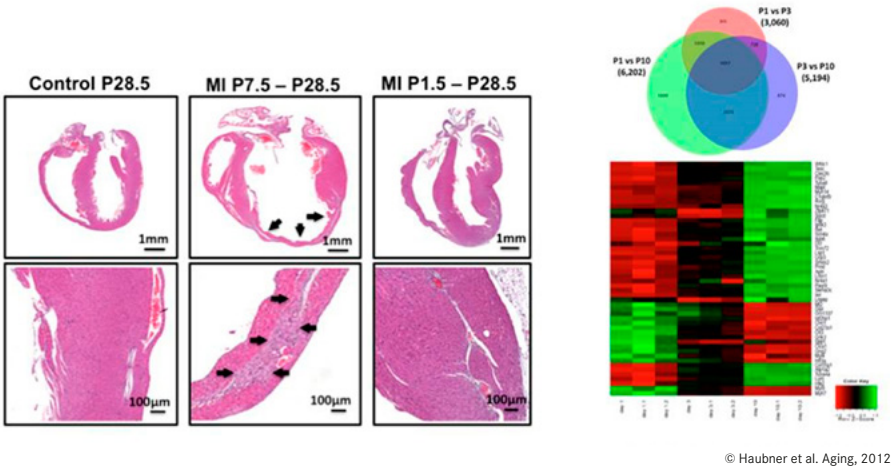

Fig. 2: Complete cardiac regeneration 28 days following myocardial infarction in a neonatal mouse heart (P1.5). Regenerative potential is lost within the first week after birth (P7.5). Transcriptional analyses between neonatal and 7 day old mouse hearts are used to unravel the enigma of bona fide in vivo cardiac regeneration.

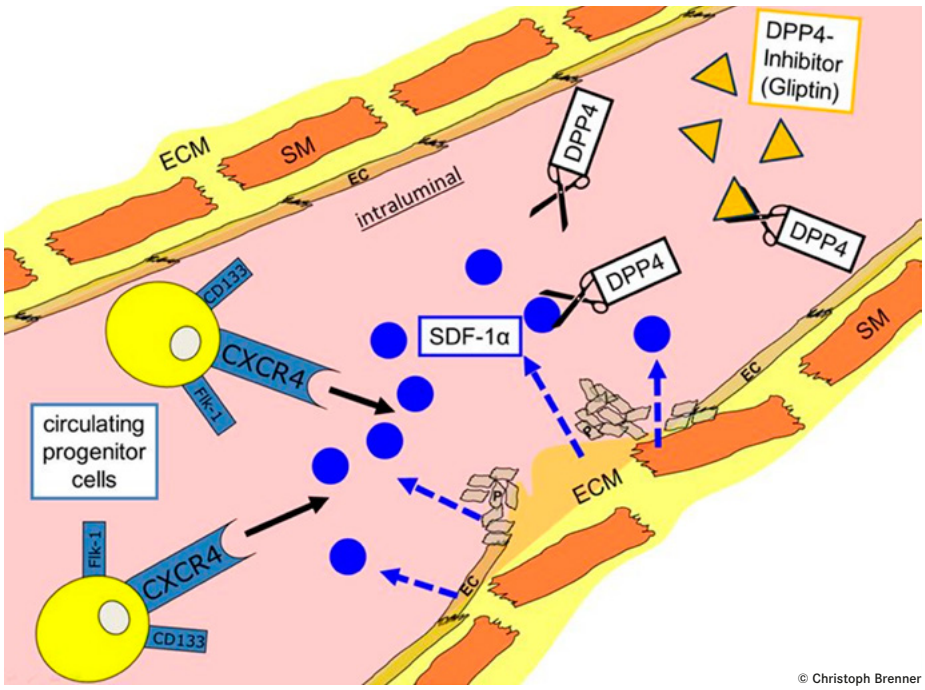

Fig. 3: Schematic effect of Gliptin therapy. Circulating CXCR4+ progenitor cells can home to sites of endothelial injury via the SDF1/CXCR4 pathway. SDF1 that is secreted by attached platelets and activated smooth muscle and surrounding endothelial cells can bind to the CXCR4-receptor and thus facilitate recruitment of progenitor cells into the injured vascular wall. The dipeptidyl peptidase 4 (DPP-4) inactivates SDF1 by cleavage of two N-terminal amino acids. Pharmacological inhibition of DPP-4 (Gliptin therapy) leads to an enhanced recruitment of progenitor cells. These progenitors can mediate an accelerated endothelial regeneration mainly by paracrine effects. (ECM = extracellular matrix, SM = smooth muscle cell, EC = endothelial cell, P = platelet).

safety of pulsed infusions of levosimendan in outpatients with advanced heart failure. It is an international study organized and conducted at the Medical University Innsbruck. The study was started in 2009 and finalized in 2013. A biomarker substudy, in cooperation with the Medical University Würzburg, Germany (S. Störk, S. Frantz), is still ongoing.

Column 3: Clinical Studies

Our clinical study team supports the clinic with conducting national and international multi-centre trials to answer important issues in current cardiology. The following clinical trials are currently under investigation:

- Global Leaders (phase 3)
  Sponsor: AstraZeneca
  Aim: To determine if there is a better medication strategy to prevent blood from clotting and at the same time minimizing the number of complications.
  PI: G. Friedrich
- FER-CARS-05 Study (phase 4)
  Sponsor: Daiichi Sankyo Inc.
  Aim: to determine, relative to placebo, the effect of iron repletion therapy using intravenous (IV) ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency.
  PI: G. Pölzl
- RELAX-AHF-EU (phase 3)
  Sponsor: Novartis Pharma GmbH
  Aim: This is a multinational, multicenter, randomized, open-label study to confirm and expand the efficacy, safety and tolerability evidence of 48 hours intravenous infusion of serelaxin (30 micrograms/kg/day) when added to Standard of Care (SoC) in patients admitted to hospital for Acute Heart Failure (AHF).
  PI: G. Pölzl
- EINSTEIN-CHOICE (phase 3)
  Sponsor: Bayer
  Aim: This is a multicenter, randomized, double-blind, event-driven, superiority study for efficacy. Patients with confirmed symptomatic DVT (Deep Vein Thrombosis) or PE (Pulmonary embolism) who completed 6 or 12 months of treatment of anticoagulation are eligible for this trial.
  PI: P. Marschang
- CATCH-AMI (Phase 2)
  Sponsor: Polyphor Ltd.
  Aim: The purpose of this study is to investigate the effects of POL6326 (CXCR4 antagonist) as a stem cell mobilizing agent, on cardiac function and infarct size and on safety and tolerability, in patients with reperfused ST-Elevation Myocardial Infarction (STEMI). PI: MM Zaruba.

Registries:

- GABI_R registry
  German-Austrian registry to evaluate of short and long-term safety and success of the ABSORBTM Everolimus-coated bioresorbable scaffolds in patients with coronary artery disease. G. Friesdrich
- Austrian TAVI registry (long-term follow-up) Source Registry. G. Friedrich
- Austrian Heart Failure Registry. G. Pölzl
- Acute Coronary Syndrome – STEMI pilot registry. J. Dörler
- EORP Atrial Fibrillation Ablation Long-term Registry. M. Stühlinger

Selected Publications

Pluripotent-stem-cell-derived epicardial cells: a step toward artificial cardiac tissue. Brenner C, Franz WM.
Cell Stem Cell. 2014 Nov 6;15(5):533-4. doi: 10.1016.

First treatment of a child suffering from severe ischemic cardiomyopathy with G-CSF and sitagliptin. Zaruba MM, Hiergeist L, Mechea A, Kozlik-Feldmann R, Theisen D, Netz H, Franz WM.
Int J Cardiol. 2013 Dec 10;170(2):e41-2. Epub 2013 Oct 26.

Left ventricular global function index: Relation with infarct characteristics and left ventricular ejection fraction after ST-segment elevation myocardial infarction. Reinstadler S, Klug G, Feistritzer HJ, Mayr A, Kofler M, Aschauer A, Schocke M, Müller S, Franz WM, Metzler B. Int J Cardiology. 2014; 175: 579-81. Epub ahead of print 2014 Jun 10.

Short-term inhibition of DPP-4 enhances endothelial regeneration after acute arterial injury via enhanced recruitment of circulating progenitor cells. Brenner C, Kränkel N, Kühlenthal S, Israel L, Remm F, Fischer C, Herbach N, Speer T, Grabmaier U, Laskowski A, Gross L, Theiss H, Wanke R, Landmesser U, Franz WM.
Int J Cardiol. 2014 Nov 15;177(1):266-75.

Long-term predictive value of copeptin after STEMI: a cardiac magnetic resonance study. Reinstadler SJ, Klug G, Feistritzer HJ, Mair J, Schocke M, Franz FM, Metzler B. Int J Cardiology. 2014, 172:359-360. Epub ahead of print 2014 Jan 16.

Selected Funding

- MesP1 dependent signalling pathways during the formation of common cardiovascular progenitors *in vivo* and *in vitro*. Deutsche Forschungsgemeinschaft (DFG). W. M. Franz
- Elucidating the fate of CXCR4+ cell populations in the ischemic heart. Deutsche Forschungsgemeinschaft (DFG). M. Zaruba
- Catestatin zur Behandlung der kardialen Ischämie. Fonds zur Förderung der wissenschaftlichen Forschung (FWF). M. Theurl
- Lab2Go project. EU-FP7 programm. J. Mair
- Anlaysis of the protective effects of pharmacological DPP-4-inhibition on endothelial regeneration and atherosclerosis. Else Kröner-Fresenius-Stiftung. Christoph Brenner
- Schlafapnoe und kardiale Resynchronisation bei Patienten mit bisher konventioneller Schrittmachertherapie. OeNB Anniversary Fund. W. Dichtl
- P-Selectin Studie. OeNB Anniversary Fund. P. Marschang

Collaborations

- Michael Bader, Max-Delbrück-Center for Molecular Medicine (MDC), Robert-Rössle-Str. 10, 13125 Berlin, Germany
- Loren Field, PhD, Riley Heart Research Center, Indiana University School of Medicine, Indianapolis, USA
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- Rüdiger Wanke, Institute of Veterinary Pathology, Ludwig-Maximilians-University, Munich, Germany
- Univ.-Prof. Dr. O. Müller, University of Heidelberg, Germany
- Sushil Mahata, PhD, University of California, San Diego, USA
- Dieter Zimmermann, Univ. Zurich, Switzerland
- Michail Sitkovsky, Dana-Farber Cancer Institute, Boston, USA

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Keywords

Chronic kidney disease, pathophysiology, systems biology, stratified/personalized medicine, epidemiology, autoimmune disease, haemodialysis, cardiovascular mortality, renal transplantation

Research Focus

In order to better characterize patho-physiologically complex phenotypes such as chronic kidney disease, we apply modern epidemiology and "omics"-techniques in conjunction with state-of-the-art systems biology approaches to derive predictive biomarkers to implement innovative, stratified/personalized treatments. This translational research focus is supported by experimental and clinical studies in selected populations and by strong national and international collaborations.

General Facts

The Department is the tertiary referral centre for patients with renal disease (native kidney, renal replacement therapy, kidney transplantation) and hypertension for the Western region of Austria and Southern Tirol. Specialised outpatient, as well as inpatient facilities and a state-of-the-art unit for extra-corporal therapy (haemo- as well as peritoneal dialysis, plasmapheresis, liver support therapy, immunoadsorption) allow service to a large clinical population and this background drives our translational research efforts. The laboratories of the Department hold a clinical routine as well as a molecular biology (including microarray facility) and cell culture unit. Our clinical trial core unit manages investigator driven projects as well as the participation in large multicentre clinical trials and a large bio-banking effort. The common denominator of the Department's research activity is the area of personalized medicine in the various aspects of Nephrology and we collaborate with multiple academic and industry partners in national and/or EU funded projects (EMERGENTEC biodevelopment Vienna, AbbVie, TEVA, University of Vienna, University of Groningen, STENO Diabetes Center, University of Glasgow, Semmelweis University, University of Silesia, University Erlangen, Charite Berlin, Stanford University, etc.). During our recent activities, we focused primarily on the application of systems-biology techniques within the FP-7 funded project SysKid (www.syskid.eu), to which our Department was one of the main contributors.

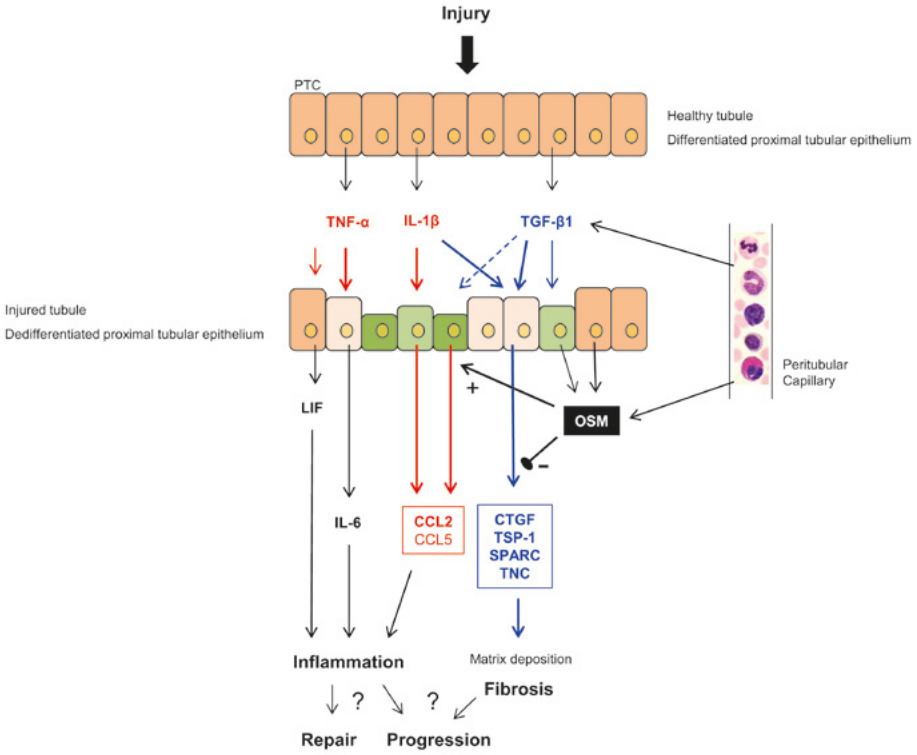

Fig. 1: Alterations of proximal tubular cell (PTC) phenotype and gene expression in response to tubular injury.

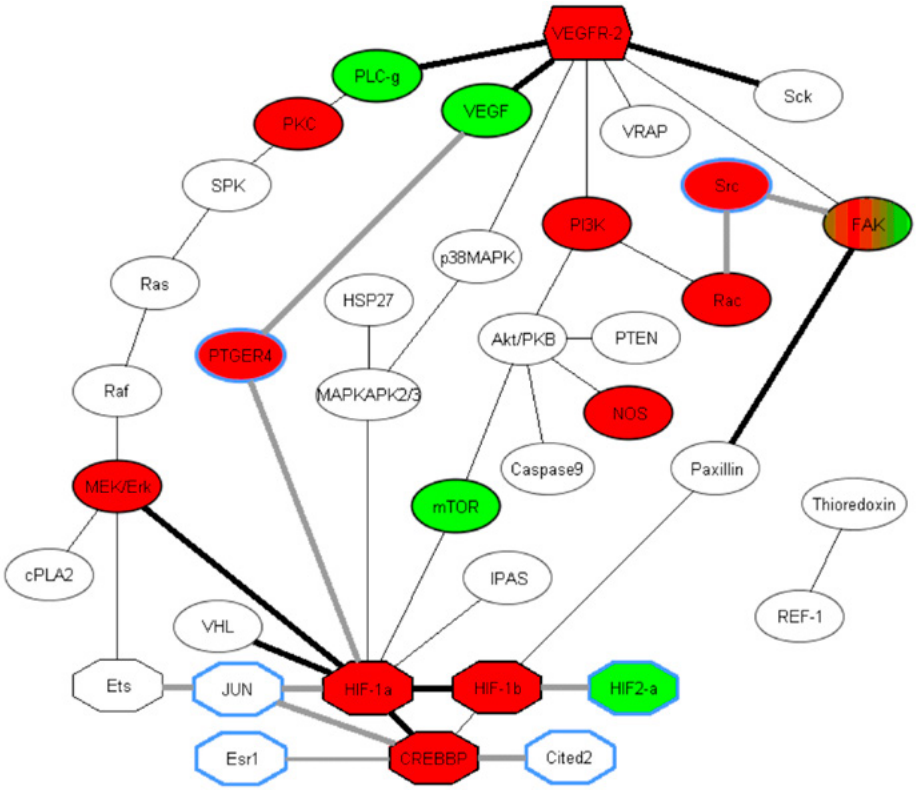

Fig. 2: Integrative systems biology analysis of renal gene expression data shows differential regulation of hypoxia and angiogenesis pathways in stable and progressive kidney diseases.

Research

Basic Research Activities

Cellular and Molecular Nephrology
Univ.-Prof. Dr. Herbert Schramek

Renal fibrosis is the final, common pathway leading to nephron loss. The pathophysiological mechanisms include tubular cell injury, infiltration of inflammatory cells, accumulation of (myo)-fibroblasts, and rarefaction of the peritubular microvasculature. Of all the cell types involved, proximal tubular epithelial cells (PTCs) play a central role. The laboratory is predominantly interested in this specific cell type during tubulointerstitial injury and fibrogenesis. Utilizing pro-inflammatory and pro-fibrotic ligands, such as IL-1β, TNF-α, and TGF-β1, we not only investigate novel molecular mechanisms, which are associated with cellular injury leading to an activated, dedifferentiated PTC phenotype, but also those which induce cell protection or repair. Distinct human PTC lines have been used to investigate expression and regulation of several pro-inflammatory and pro-fibrotic genes including CCL2 and CTGF, respectively (Fig. 1). Interestingly we discovered that oncostatin M (OSM) is able to stimulate acute inflammation via its synergistic effects with other pro-inflammatory cytokines early after injury, but may attenuate chronic inflammation and fibrogenesis at later time points. Additional gene silencing approaches identified some of the intracellular signalling pathways involved, for example STAT3 as an OSM-induced signalling molecule involved in both inhibition of CTGF expression and super-induction of CCL2 mRNA expression in human PTCs. Future goals include the functional analysis of novel genes of interest involved in the regulation of PTC phenotype during PTC injury, inflammation and progressive renal fibrosis.

Translational Research Activities

Transcriptional Profiling and Systems Biology Application in Chronic Renal Disease – Univ.-Prof. Dr. Gert Mayer

Several years ago, we established (in collaboration with the University of Stanford, California) microarray technology to study whole organ and, via application of laser capture micro-dissection, renal compartment specific differential mRNA and miRNA expression in human and animal tissue. When compared to normal controls tubular cells from patients with proteinuric nephropathies revealed significant transcriptional de-regulation of pro-fibrotic but also tubulo-protective (e.g. BMP-7) mechanisms. When compared to patients with stable renal disease, patients with progressive renal failure showed attenuated tubular VEGF-A expression despite a strong hypoxia signal (see Fig. 2). These gene expression profiles also helped to define new, clinically relevant biomarkers.

Univ. Doz. Dr. Michael Rudnicki, a member of our group, has recently started to focus on simultaneous analysis of renal miRNA and mRNA profiles. His work revealed regulatory networks, in which specific miRNAs activate entire signal transduction pathways such as inflammation or apoptosis.

Recently, transcriptomics data were complemented by proteomic, metabolomic and genomic profiles in the large, multinational EU FP-7 funded project SysKid (Systems Biology towards Novel Chronic Kidney Disease; www.syskid.eu). In collaboration with EMERGENTEC biodevelopment and the Medical Universities of Vienna and Groningen we developed a proprietary systems biology-derived molecular model

of renal disease in type II diabetes and identified molecular processes associated with progressive renal function loss. Biomarkers associated with these pathways were discovered and validated in large patient cohorts. Currently, we are working to match the disease specific molecular profiles with drug mode of action molecular profiles to gain access to targeted therapy (Fig. 3).
Another area of interest is the effect of ageing on transcriptional profiles in the kidney, an area of special relevance to the field of renal transplantation. Ass. Prof. DDr. Hannes Neuwirt, another team member, is working on biomarkers that predict long-term graft function and is also interested in the role of the complement system in kidney transplant models.

In this context, we have recently published a 3-biomarker-panel that was able to predict renal function on top of serum creatinine. We are currently establishing a biobank of serum, urine and renal tissue of zero-hour biopsies (taken at the time of transplantation) in renal transplant recipients and a corresponding prospective registry in order to establish and validate biomarkers of renal function in this cohort. In the same framework, Dr. Neuwirt is also working on the role of the complement system in chronic allograft nephropathy in kidney transplant models *in vitro.*

Additionally, he is exploring alternative dialysis modalities, such as electro-osmosis in collaboration with Prof. Thomas Bechtold (Research Institute of Textile Chemistry and Textile Physics, University of Innsbruck). Finally, he also collaborates with the Department of Experimental Urology in the field of cytokine signaling and prostate cancer.

In order to validate our *"in silico"* derived hypotheses on predictive biomarkers, we are also leading several large-scale, national and multinational prospective cohort studies (e.g. The Austrian Dialysis and Transplant Registry; PROVALID, a study of over 4,000 patients with type 2 diabetes in 5 European countries; TOPVAS, a project including over 240 patients after renal transplantation in Austria). The data collected there form the basis for outcomes and health economics research on a European level.

Clinical Research Activities

Targeted Therapy in Renal Disease
Doz. Dr. Rudnicki (PD, anti CD20, Mb. Fabry), Dr. Markus Pirklbauer (cardiovascular mortality on hemodialysis); Dr. Andreas Kronbichler (autoimmune diseases)
Peritonitis is the most serious complication in patients on peritoneal dialysis (PD). In an analysis of PD patients treated locally and in a multicenter national study we identified factors associated with risk of peritonitis. Interestingly, oral active vitamin D therapy was associated with decreased incidence and improved survival.

In collaboration with the Department of Nephrology, Ospedali Riuniti di Bergamo, Italy, we examined the effect of an anti CD20 antibody in frequently relapsing nephrotic diseases in children and in adults. Based on data obtained in a prospective study and a review, we were able to show that this approach is a valuable therapeutic option. In collaboration with the Department for Pediatrics, we treat and recruit patients with rare diseases, in particular Fabry's disease, into a European multicenter study on enzyme replacement therapy.

Regarding the excessive cardiovascular mortality in patients with end-stage renal disease, we are interested in the possible detrimental effect of positive calcium mass balance during haemodialysis. We propose that a disturbance in the rapidly accessible bone calcium pool in chronic renal disease diminishes the capacity to buffer a calcium load, thereby contributing to vascular calcification. Based on an individual OENB grant ("Impact of the exchangeable calcium pool on cardiovascular risk in chronic hemodialysis patients", Dr. Markus Pirklbauer) a novel assessment approach

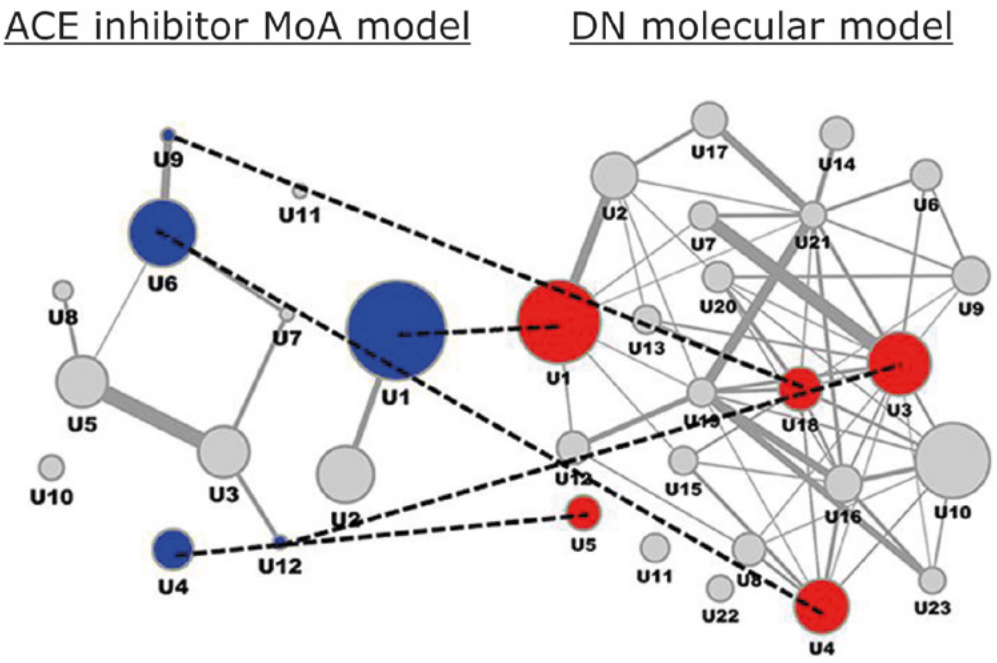

Fig. 3: Interference of a drug mechanism of action molecular model (left) with the diabetic nephropathy phenotype molecular model (right). Interfering processes on the drug (blue) and phenotype side (red) are indicated.

for calcium mass balance and calcium buffer capacity has been established in hemodialysis patients. To elucidate pathophysiological mechanisms underlying the high cardiovascular mortality in hemodialysis patients, we evaluate the association of our calcium kinetic data with clinical outcome and attempt to identify novel biomarkers by using ELISA-based serum analysis. Based on these new insights in calcium regulatory mechanisms, it is our aim to individualize hemodialysis treatment by using novel approaches for calcium mass balance assessment in order to improve cardiovascular prognosis. This innovative clinical project is performed in collaboration with national (Central Institute for Clinical Chemistry and Laboratory Medicine, Innsbruck, Head: Prof. Griesmacher) and international (PD Dr. med. Andreas Pasch, University Hospital for Nephrology and Hypertension, Inselspital Bern, Switzerland) partners. The kidney is often affected by autoimmune disorders.

Our research aim is to delineate pathogenetic steps that lead to the onset of autoimmunity, predicting treatment failure and relapse, in particular in nephrotic syndrome (membranous nephropathy, minimal change disease and focal segmental glomerulosclerosis), anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis and systemic lupus erythematosus. We have worked on several projects including rituximab's efficacy in minimal change disease and focal segmental glomerulosclerosis and more recently in ANCA-associated vasculitis. In the latter entity, we recently published a review summarizing factors that predispose patients towards infections. In the future, we want to decipher risk factors leading to infections in rituximab treated patients and in larger 'general' cohorts.

Moreover, we will study renal involvement in the context of ANCA-associated vasculitis within the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS). With the help of modern laboratory approaches ('omics'), we aim to improve patient care substantially by identifying a panel of peptides/proteins indicative of disease relapse in proteinase 3-positive vasculitis using SWATH-mass spectrometry and working on the nasal microbiome (metagenomics) in patients with granulomatosis with polyangiitis (GPA, Wegener's).

This clearly highlights our future goal to combine clinical findings with an experimental setting to a) increase the understanding of these diseases, b) bring forward this understanding to clinical utility and c) translate this knowledge into design of clinical trials with the aim to individualize/personalize treatment measures. These effort are driven forwards via a collaboration with Dr. David Jayne (Cambridge University Hospitals, UK).

Selected Publications

From molecular signatures to predictive biomarkers: modeling disease pathophysiology and drug mechanism of action. Heinzel A, Perco P, Mayer G, Oberbauer R, Lukas A, Mayer B.
Front Cell Dev Biol. 2014; 2:37.

A 3-biomarker-panel predicts renal outcome in patients with proteinuric renal diseases. Neuwirt H, Perco P, Kainz A, Mühlberger I, Leierer J, Braniff SJ, Mayer B, Mayer G, Rudnicki M.
BMC Med Genomics. 2014; 7:75.

Tacrolimus increases Nox4 expression in human renal fibroblasts and induces fibrosis-related genes by aberrant TGF-beta receptor signalling. Kern G, Mair SM, Noppert SJ, Jennings P, Schramek H, Rudnicki M, Mueller GA, Mayer G, Koppelstaetter C.
PLoS ONE. 2014; 9: e96377.

SOCS-3 is downregulated in progressive CKD patients and regulates proliferation in human renal proximal tubule cells in a STAT1/3 independent manner. Neuwirt H, Eder IE, Puhr M, Rudnicki M. Lab Invest. 2013; 93:123–34.

Renal involvement in autoimmune connective tissue diseases. Kronbichler A, Mayer G. BMC Med. 2013; 11:95.

Selected Funding

- SKID – Systems biology towards novel chronic kidney disease diagnosis and treatment; EU - FP7 (€ 1,882,583) Gert Mayer
- PROVALID – Multi-centre study regarding the cumulative incidence of renal outcomes in patients with type II diabetes in different European countries; AbbVie research fund (US$ 4,200,000) Gert Mayer
- TOPVAS – The Transplant Outcome Prediction Validation Study; TEVA research grant fund (€ 732,000) Gert Mayer
- Hämoelektroosmose; Austria Wirtschaftsservice Ges.m.b.H. (€ 150,000) Hannes Neuwirt
- Der labile Kalziumpool und seine Bedeutung für das kardiovaskuläre Risiko in Hämodialysepatienten; OENB (€ 150,000) Markus Pirklbauer

Collaborations

- Bernd Mayer, EMERGENTEC biodevelopment GmbH; Vienna, Austria
- Rainer Oberbauer, Division of Nephrology and Dialysis; Medical University Vienna
- Harald Mischak, Mosaiques Diagnostics GmbH; Hannover, Germany
- Peter Rossing, STENO Diabetes Center; Gentofte, Denmark
- Johannes Mann, Universität Erlangen; Erlangen, Germany
- Dick de Zeeuw, Hiddo Lambers Heerspink, Academisch Ziekenhuis; Groningen, The Netherlands
- Andrzej Wiecek, Slaski Uniwersytet Medyczny Katowicach; Katowice, Poland
- Laszlo Rosivall, Semmelweis University; Budapest, Hungary
- Patrick Mark, University of Glasgow; Glasgow, UK
- Kitty Jager, Academisch Medisch Centrum bij de Universiteit van Amsterdam; Amsterdam, The Netherlands
- Mariano Rodriguez, Universidad de Cordoba; Cordoba, Spain
- Timothy Meyer, Stanford University School of Medicine; California, USA
- David Jayne, Vasculitis and Lupus Clinic, Cambridge University Hospitals; United Kingdom
- Annette Bruchfeld, Division of Renal Medicine, Karolinska Institutet; Stockholm, Sweden
- Luis Quintana, Servicio de Nefrología y Trasplante Renal, Universidad de Barcelona; Barcelona, Spain
- Daiki Nakagomi, Department of Allergy and Clinical Immunology, Chiba University; Chiba, Japan
- Thomas Neumann, Department of Internal Medicine III, Jena University Hospital; Jena, Germany
- Jae Il Shin, Department of Pediatric Nephrology, Yonsei University College of Medicine, Severance Children's Hospital; Seoul, Korea
- Piero Ruggenenti, Department of Nephrology, Ospedali Riuniti di Bergamo/Italy
- Andreas Pasch, University Hospital for Nephrology and Hypertension, Inselspital Bern; Bern, Schweiz

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Keywords

Personalized cancer medicine, geriatric oncology, ageing, tumor immunology, angiogenesis, myeloma, EpCAM

Research Focus

The University Clinic for Internal Medicine 5– Hematology & Oncology – (UCIM5) represents a core member of the Comprehensive Cancer Center Innsbruck (CCCI) and shares its goals and research with all the partner institutions of the CCCI. Primary goals of CCCI are to improve the clinical care and outcome of cancer patients by developing and conducting state-of-the art clinical trials and translational research. UCIM5 conducts translational and clinical research and participates in national and international clinical trial programs. The Clinic is particularly well-placed to readily translate basic research advances into clinical progress. Approximately 50% of the clinical trial program is confined to phase III trials. Clinical research also includes retrospective and prospective observational studies. For this purpose, national web-based registries for chronic myeloid leukemia and multiple myeloma have been established and are being coordinated by our Clinic. Moreover, UCIM5 participates and serves as a country coordinator for the European MDS Registry of the European Leukemia Net (ELN). UCIM5 has been a founding institution of the K1 Center ONCOTYROL (Competence Center for Personalized Cancer Medicine) and has been receiving major funding by the Austrian Agency for Advancement of Research (FFG) for promoting strategies to improve personalized cancer care and foster precision oncology.

General Facts

Within the Medical University Department of Internal Medicine UCIM5 comprises a 50 bed-hospital including 20-bed stem cell transplation unit, an outpatient clinic and day hospital, an oncology trial center (OTC), laboratory services, translational research facilities and a FACS sorting core facility.

In general, UCIM5 provides state-of-the-art clinical care primarily for patients with hematological malignancies and solid tumors. Solid tumors include primarily cancers of the lung, GI tract and sarcomas. Clinical care includes diagnostic services such as cytomorphology, immunophenotyping and molecular genetics. Approximately 15% of the patients are currently entered into clinical trials. Annually approximately 50 clinical trial protocols are carried out by the OTC; our clinical trial portfolio includes the following:

- clinical studies for the establishment and improvement of diagnostic techniques (e.g. minimal residual disease assessment by multicolor flow cytometry, molecular tumor profiling by next generation sequencing),
- phase I-VI clinical trials for the development of investigational new anticancer drugs or drug combinations and the optimization of existing anticancer treatments
- the evaluation and validation of prognostic scores (e.g. for geriatric cancer patients), including the integration of geriatric assessment for elderly cancer patients to adjust treatment algorithms, improve clinical outcome, ameliorate toxicities and improve cost-effectiveness.

UCIM5 is an academic teaching hospital and forms an integral part of the University

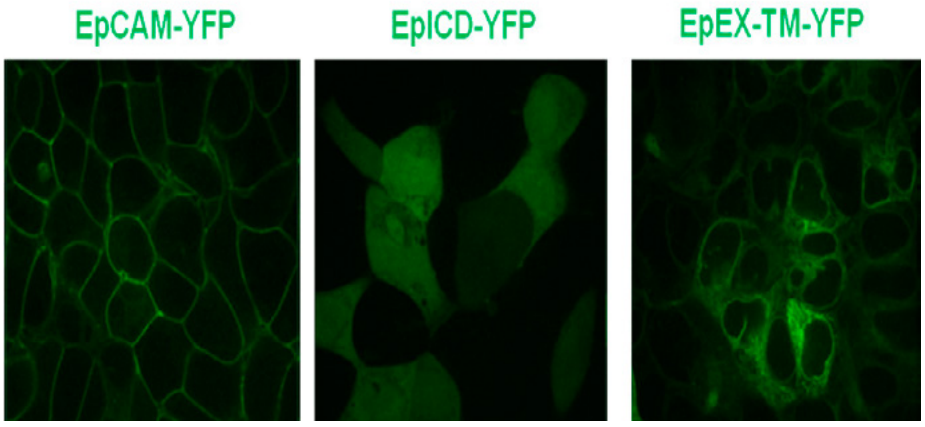

Fig. 1: Real time confocal imaging of EpCAM processing and signalling in human cells. Cleavage of EpCAM results in the generation of an extracellular shedded domain (EpEX) and an intracellular part (EpICD) translocating to the nucleus and inducing Wnt signalling.

Hospital Innsbruck and the Medical University Innsbruck. UCIM5 participates in teaching & training activities for medical graduate students and postdoctoral fellows, and offers a clinical PhD program for Clinical Cancer Research.

Clinical research, disease management and continouos medical education are structured into 8 separate clinical programs headed by physician scientists:

Clinical Programs & Program Heads
- Acute leukemias & stem cell transplantation: David Nachbaur, M.D
- Indolent lymphomas: Michael Steurer, M.D.
- Agressive lymphoma: Wolfgang Willenbacher, M.D.
- Myeloma & other plasma cell dyscrasias: Eberhard Gunsilius, M.D
- Myelodysplastic syndromes, geriatric hematooncology, anemia in the elderly: Reinhard Stauder, M.D., M.Sc.
- Myeloproliferative syndromes: Stefan Schmidt, M.D.
- Gastrointestinal tumors: Wolfgang Eisterer, M.D.
- Head/neck & thoracic cancers: Georg Pall, M.D
- Breast & genitourinary cancers: Christoph Leitner, M.D.
- Koagulopathies: Clemens Feistritzer, M.D.
- Palliative Medicine & Supportive Care: Walpurga Weyrer, M.D.

Research

Clinical Research:

Oncology Trial Center (OTC)

Clinical Research is organized by the OTC. The OTC staff includes administrative personnel study nurses and clinical investigators. For the planning and performance of academic trials the OTC collaborates with the Clinical Trial Competence Center at the Medical University Innsbruck. The clinical trial portfolio within the time-period 2013/2014 is summarized below.

Tumor Entities / No. of Ongoing Clinical Trials (Phase I-II / III-IV)

CLL	09 (03/06)
Lymphoma (non CLL)	13 (03/10)
Myeloma	04 (01/03)
Acute leukemias	12 (05/07)
Myeloproliferative neoplasis	09 (06/03)
MDS	05 (01/04)
GI-Cancers	23 (10/13)
Lung Cancers	10 (02/08)
Sarcomas	03 (02/01)

Translational Cancer Research

UCIM5 houses 4 translational research groups. Forward and reverse tanslational research benefits from the clinical trial program, hospital- and population-based registries, in-house biobanks, diagnostic facilities and modern laboratory technologies.

Experimental & Clinical Oncogenomics; Leaders: Gerold Untergasser, Ph.D.
Michael Steurer, M.D.
Gilbert Spizzo, M.D.

The experimental oncogenomics group works on the detection of tumor-derived circulating DNA (ctDNA) in peripheral blood, liquor and malignant effusions. The functional importance of genetic abnormalities is evaluated in tissue culture systems and murine tumor models. As an example, overexpression of the transmembrane adhesion molecule EpCAM on epithelial cancer cells was found to indicate poor prognosis for various solid tumor types and to predict responsiveness of EpCAM+ carcinomas for the anti-EpCAM antibody treatment. Carcinoma cells in general and in particular cancer stem cells process EpCAM glycoprotein by cell surface-associated proteases into a soluble extracellular fraction (EpEX) and a short intracellular signaling peptide (EpICD). Shuttling of EpICD into the cell nucleus stimulates Wnt signalling, c-myc expression and tumor cell proliferation. Assays for EpCAM expression in tumor specimens and the analysis of soluble EpEX in blood and malignant effusions have been developed by this group.

The Clinical Oncogenomics group is integrated into the Molecular Cancer Diagnostics Center and focusses on the genomic profiling of solid and liquid malignancies. Recently, a public-private-partnership with Caris Life Sciences (Phoenix, Arizona) has been set up for a

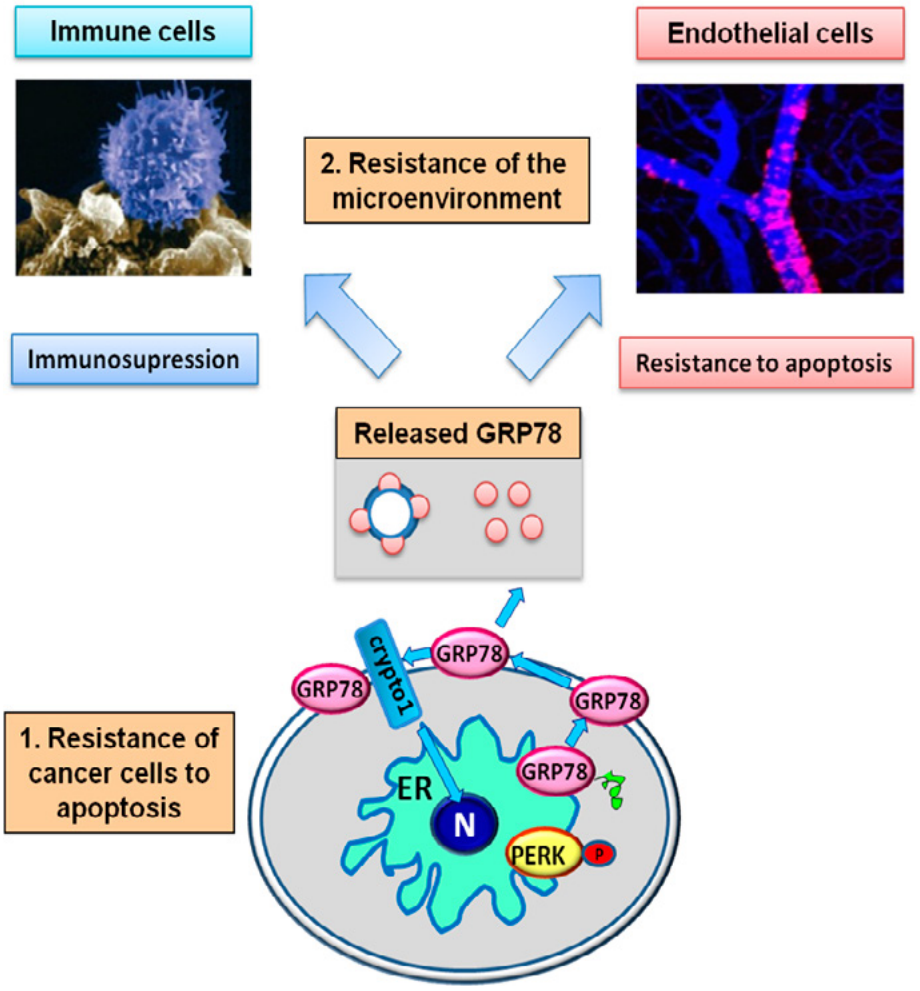

Fig. 2: The chaperone protein GRP78 can be overexpressed in various malignancies and released into the tumor microenvironment, thereby mediating resistance to anticancer drugs and angiogenic inhibitors.

molecular profiling program to identify druggable molecular tumor targets and to offer cancer patients customized therapies based on their individual tumor profiles. As a next step, an in-house Next Generation Sequencing (NGS) facility will be established to complement routine cancer diagnostics by histopathology, immune phenotyping, cytogenetics and PCR-based molecular genetics.

Tumor Immunology
Leaders: Sieghart Sopper, Ph.D.
Brigitte Kircher, Ph.D.
Major research topics of this group are the enhancement of T cell mediated antitumor immunity by modifying T-cell signalling and the search for clinically applicable immune biomarkers to predict responsiveness for immuno-oncological interventions. In this respect inhibition of Cbl-b signalling by siRNA in T cells was found to markedly improve T-cell mediated antitumor immunity in murine tumor models. Together with Dr. Penninger's group (IMP, Vienna) and Dr. Baier's group (Molecular Immunology, Medical University Innsbruck) this strategy is currently translated being into an immunotherapeutic clinical program. Immune biomarker research includes monitoring of circulating and tumor-associated immune cells in various maligancies. By multidimensional flow cytometry, expression of CD62L was found to be decreased on T cells of CML patients and to predict response to TKI treatment.
Another area of immune biomarker research is the analysis of immune checkpoint antigen expression and the assessement of tumor-infiltrating immune cells in hematological malignancies (e.g. myeloma) and solid tumors.

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a curative approach for hematologic malignancies based on the induction of graft-versus-tumor (GvT) reactivity. However, its effectiveness can be limited by the often severe toxicity of graft-versus-host disease (GvHD). GvT activity and GvHD share many similar pathways in cellular immunity. Both effects are mediated primarily by donor T-cell recognition of minor histocompatibility antigens (mHag). On the other hand, natural killer (NK) cells expressing a variety of activating and inhibitory killer-cell immunoglobulin-line receptors (KIR) have been reported to mediate a GvT effect without GvHD. Thus, the clinical success of allogeneic SCT relies on a small window which may be predicted by the mismatch of one or several mHags and/or on the KIR ligand status of the host as well as the donors' activating KIRs. This research group expanded HA-1-specific CD8+ T cells from the patient's peripheral blood following donor lymphocyte infusion concomitantly with the disappearance of leukemic cells and identified among HLA-identical patient/donor pairs the mHag HA-1 as a valid target for the GvL effect. Further research is warranted to get a more thorough understanding of the molecular targets and mechanisms of the anti-mHag-specific T-cell response and the importance of NK cell activity after HSCT.

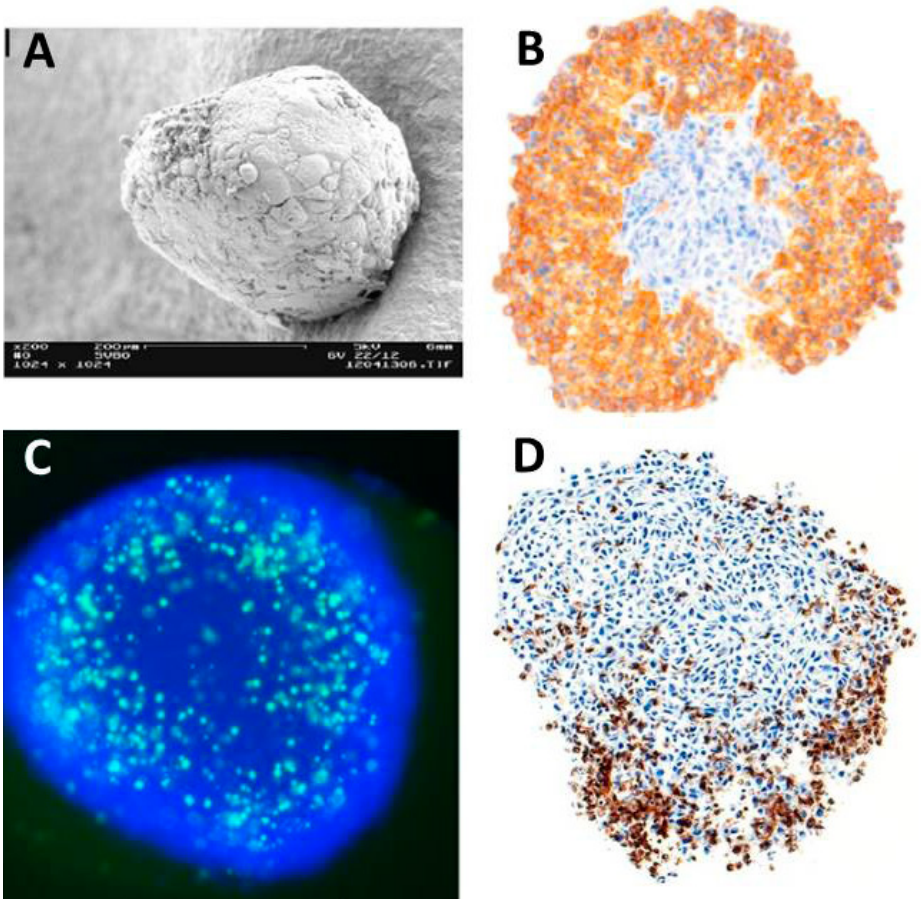

Fig. 3: 3D-composite tumor & stromal cell culture for in vitro drug screening.

Tumor Cell Biology
Leader: Heinz Zwíerzina, M.D.
This research group searches for druggable molecular targets of cancer stem cells e.g. in ovarian cancer, and has established an *in vitro* 3D-tumor cell culture system including stromal fibroblasts and immune cells for anticancer drug screening. By differential gene expression analysis, the guanosine exchange factor VAV3 has been identified as potential stem cell specific target in epithelial ovarian cancer. Expression of a truncated variant of VAV3 was found to be associated with refractoriness to platinum-based therapies in a cohort of ovarian cancer patients. A patent has been filed on the use of VAV3 splice variants as a predictive biomarker for platinum-based chemotherapy in ovarian cancer.

For cancer drug screening the group has established a 3D-cell culture system ("hanging drops" method) to generate multicellular tumor spheroids. This cell culture method allows incorporation of immunocompetent cells and study in depth of tumor-immune cell intercations. Recently, this cell culture technique has been adapted for primary tumor cells isolated form fresh tumor biopsies or maligant effusions.

Tumor Angiogenesis
Leader: Eberhard Gunsilius, M.D.
The tumor angiogenesis group investigates predictive biomarkers for antiangiogenic therapies and screens natural and synthetic compounds for their anti-angiogenic activity in-vivo using the chorion allantois membrane assay. Chemoresistant carcinoma cells were found to translocate

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Fig. 4: Individualized treatment algorithms are essential in elderly patients

the endoplasmatic reticulum chaperone protein GRP78 from the cytoplasm onto their cell membrane and to release this chaperone protein under stress conditions into the tumor microenvironment. Soluble GRP78 can activate pro-survival signaling in tumor cells (intrinsic tumor resistance) and protect endothelial cells of the tumor vasculature against anti-angiogenic drugs (extrinsic tumor resistance).

This, GRP78 expression and release in the tumor tissue can predict resistance against various anticancer drugs and angiogenesis inhibitors. Currently studies are ongoing to elucidate the underlying molecular mechanisms of GRP78-induced drug resistance and to measure soluble GRP-78 in tissue and peripheral blood by a sensitive ELISA.

Biology of Ageing and Personalised Treatment in Elderly Cancer Patients
Leader: Reinhard Stauder M.D., M.Sc.

At present, elderly people (>70 yrs) constitute about 50% of cancer patients. Despite this huge number, evidence-based recommendations and guidelines are rare. The outcome of a given patient is influenced by the biology of the tumor ("seed") as well as by that of the patient ("soil"). To integrate aspects of individual patient, geriatric assessment (GA) has been established and implemented at UCIM5 for elderly cancer patients. Thus, different dimensions in a given patient including comorbidities, performance status, functional activities, mood (depression, quality of life), social support and nutritional status are assessed.

The impact of restrictions due to these different dimensions on clinical outcome and therapy toxicity are being analyzed and assessment based treatment algorithms developed in cooperation with SIOG, EHA and ASH. Molecular aberrations are characterized in myeloid neoplasms by NGS in cooperation with EU-MDS (J Jansen, Nijmegen, NL; EU-Horizon 2020 Project: Translational Implementation of Genetic Evidence in the management of MDS (TRIAGE–MDS) and the IWG–MDS (International Working Group – MDS). The interplay of molecular aberrations, assessment status and anemia are analyzed and compared with reference populations to elucidate mechanisms of ageing both in frail and in elderly cancer patients. These analyses form the basis for individualized treatment algorithms and establish the relevance of assessment scores including quality of life and functional capacities as patient-reported outcomes (PROs).

Selected Publications

Reduction of complement factor H binding to CLL cells improves the induction of rituximab-mediated complement-dependent cytotoxicity. Hörl S, Bánki Z, Huber G, Ejaz A, Windisch D, Muellauer B, Willenbacher E, Steurer M, Stoiber H.
Leukemia. 2013; 27(11): 2200–8.

EpCAM overexpression prolongs proliferative capacity of primary human breast epithelial cells and supports hyperplastic growth. Martowicz A, Rainer J, Lelong J, Spizzo G, Gastl G, Untergasser G. Mol Cancer. 2013; 12:56. doi: 10.1186/1476-4598-12-56.

Rituximab plus subcutaneous cladribine in patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue: a phase II study by the Arbeitsgemeinschaft Medikamentose Tumortherapie. Troch M, Kiesewetter B, Willenbacher W, Willenbacher E, Zebisch A, Linkesch W, Fridik M, Müllauer L, Greil R, Raderer M. Haematologica. 2013; 98: 264–68.

The role of the e3 ligase cbl-B in murine dendritic cells. Wallner S1, Lutz-Nicoladoni C, Tripp CH, Gastl G, Baier G, Penninger JM, Stoitzner P, Wolf D. PLoS One. 2013; 8(6): e65178.

PPT and VES-13 in elderly cancer patients: evaluation in multidimensional geriatric assessment and prediction of survival. Augschöll J, Kemmler J, Hamaker M, Stauder R. J Geriatr Oncol. 2014; 5: 415–421

Development of an innovative 3D cell culture system to study tumour–stroma interactions in non-small cell lung cancer cells. Amann A, Zwierzina M, Gamerith G, Bitsche M, Huber JM, Vogel GF, Blumer M, Koeck S, Pechriggl EJ, Kelm JM, Hilbe W, Zwierzina H. PLoS One. 2014; 9(3):e92511.

Prevalence and possible causes of anemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Clinical Interventions in Aging. 2014; 9:1187–1196.

The side population of ovarian cancer cells defines a heterogeneous compartment exhibiting stem cell characteristics. Boesch M, Zeimet AG, Reimer D, Schmidt S, Gastl G, Parson W, Spoeck F, Hatina J, Wolf D, Sopper S.
Oncotarget. 2014; 30;5(16):7027–39.

Expression of EpCAM(MF) and EpCAM(MT) variants in human carcinomas. Fong D, Seeber A, Terracciano L, Kasal A, Mazzoleni G, Lehne F, Gastl G, Spizzo G. J Clin Pathol. 2014;67(5): 408–14.

The relevance of a geriatric assessment for elderly patients with a haematological malignancy – a systematic review. Hamaker ME, Prins MC, Stauder R. Leuk. Res. 2014; 38(3):275–83.

The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy. Hamaker ME, Mitrovic M, Stauder R. Ann. Hematol. 2014; 93(6): 1031–40.

The E3 ligase Cbl-b and TAM receptors regulate cancer metastasis via natural killer cells. Paolino M, Choidas A, Wallner S, Pranjic B, Uribesalgo I, Loeser S, Jamieson AM, Langdon WY, Ikeda F, Fededa JP, Cronin SJ, Nitsch R, Schultz-Fademrecht C, Eickhoff J, Menninger S, Unger A, Torka R, Gruber T, Hinterleitner R, Baier G, Wolf D, Ullrich A, Klebl BM, Penninger JM.
Nature. 2014;507(7493):508–12.

Neoadjuvant chemo-immunotherapy modifies CD4(+)CD25(+) regulatory T cells (Treg) in non-small cell lung cancer (NSCLC) patients. Pircher A, Gamerith G, Amann A, Reinold S, Popper H, Gächter A, Pall G, Wöll E, Jamnig H, Gastl G, Wolf AM, Hilbe W, Wolf D. Lung Cancer. 2014; 85(1):81–7.

New antiangiogenic strategies beyond inhibition of vascular endothelial growth factor with special focus on axon guidance molecules. Pircher A, Wellbrock J, Fiedler W, Heidegger I, Gunsilius E, Hilbe W. Oncology. 2014;86(1):46–52.

Selected Funding

Monitoring GRP78 mediated resistance to treatment with novel drugs by specific ELISA: ONCOTYROL/FFG, Eberhard Gunsilius, M.D.; 480,000.00 €

Microtissue engineering – innovative 3D coculture model for *ex vivo* drug efficacy testing & biomarker identification in NSCLC; ONCOTYROL/FFG, Heinz Zwierzina, M.D.; 425,111.00 €

Austrian CML Registry – Predictive markers for the response, outcome and cost effectiveness: ONCOTYROL/FFG, Steafn Schmidt, M.D.; 530,667.00 €

OPTATIO (Optimizing Targets & Therapeutics in high risk and refractory Multiple Myeloma): EU-FP7 Program, Wolfgang Willenbacher, M.D. (coord.); 510,700.00 €

Translational implementation of genetic evidence in the management of MDS (TRIAGE-MDS): EU-Horizon 2020; Reinhard Stauder, M.D., M.Sc.;190,000.00 €

Collaborations

- Competence Center ONCOTYROL, Innsbruck, Austria
- Arbeitsgemeinschaft Tumortherapie, Salzburg, Austria
- Austrian Breast and Colon Cancer Study Group (ABCSG), Vienna, Austria
- MDS Net, Duesseldorf, Germany
- Central European Society for Anticancer Research (CESAR), Vienna, Austria
- Schweizerische Arbeitsgemeinschaft für klinische Krebsforschung (SAKK), Bern, Switzerland
- Arbeitsgemeinschaft Internistische Onkologie (AIO), Berlin, Germany
- Vesalius Research Center, Leuven, Belgium
- European MDS Registry of the European Leukemia Net (ELN), T. de Witte, Nijmegen, The Netherlands
- Jansen, Joop , PhD; Radboud University Medical Center, Nijmegen, The Netherlands
- EHA (Europ Hematology Association) SWG Elderly Task Force in Hematology, D. Bron, Institut Jules Bordet, Brussels, Belgium
- CALGB, Chicago, USA
- Caris Life Sciences, Phoenix, USA
- IWG-MDS (International Working Group – MDS), Peter Greenberg MD, Stanford, USA
- International Society of Geriatric Oncology (SIOG), L. Balducci, Lee Moffit Comprehensive Cancer Centre, Tampa, FL, USA
- ASH (Am Soc Hematology) – Hematology and Aging Special Interest Group, H. Klepin MD, Comprehensive Cancer Center of Wake Forest University, NC, USA

Core Facilities

- FACS Sorting Core Facility (Cell sorting, multidimensional flow cytometry)

Devices & Services

- Instrumentations: FACSAria Cell Sorter, AutoMACS Cell Separator, FACSCalibur Cell Analyzer, MagPix Biomarker Analyzer
- Molecular Cancer Diagnostics Network (histomorphology, flow cytometry, cytogenetics, PCR, NGS)

Internal Medicine VI

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Keywords

Internal medicine, infectious diseases, immunology, rheumatology, pneumology, host-pathogen interaction, metal and lipid metabolism, immune mediated diseases, immune deficiency, tropical medicine

Research Focus

Based on the broad clinical expertise in our department the research at our institution covers many different aspects of basic research and clinically relevant topics in the areas of infectious diseases, immunology, rheumatology and pneumology, both at the level of laboratory based science and clinical research. The work includes clinical studies with a major aim being to translate the results of our scientific investigations at the bench to the bedside for the benefit of our patients.

General Facts

Apart from all aspects of general internal medicine our institution has a focus and core expertise in infectious disease, clinical immunology, rheumatology and pneumology and has established itself as a reference centre for Western Austria in some of these medical fields. As there is significant clinical and scientific overlap between these medical disciplines the combined expertise at our department creates a positive synergy and gain of knowledge for the optimized treatment of patients and in performing clinical and laboratory based research. Our department consists of three in patient wards, three outpatients' clinics with a focus on infectious disease/immunology and tropical medicine, rheumatology and pneumology respectively. Apart from routine investigations of internal medicine, we also perform laboratory diagnostics of infectious diseases, tropical infections, auto-immune disorders and immunodeficiency disorders as well as functional pulmonary analyses along with bronchoscopy. A study center co-ordinates the clinical studies at our institution.

Several research groups investigate relevant topics in our fields of interest as detailed below making use of up to date laboratory technologies of biochemistry, molecular biology, cell biology, immunology, microbiology and genetics both *in vitro* and *in vivo*. Our laboratories are well equipped with modern infrastructure including high throughput PCR, a FACS analyser and an *in vivo* fluorescence imager. A major goal of our institution is to provide high quality education in clinics and science, to provide an excellent environment for international competitive research in the laboratory and at the bedside, and to inspire medical doctors to combine research with their clinical occupation and to critically evaluate the clinical practice and the currently available information.

Research

Laboratory for Infectious Diseases and Immunology

The laboratory is interested in host-pathogen interactions, the role of innate resistance

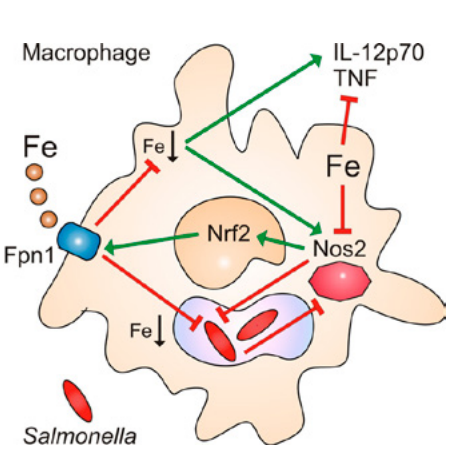
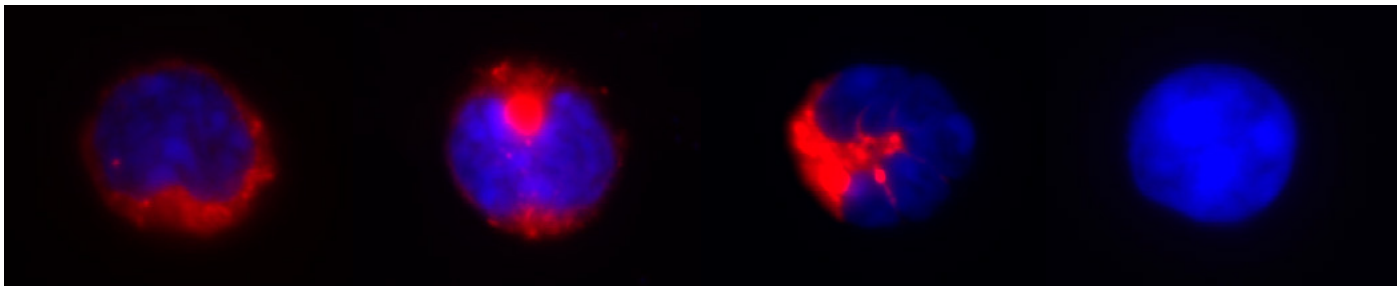


Fig. 1: Nitric oxide (NO) produced by NO-synthase (Nos2) inhibits central metabolic pathways in Salmonella directly and also activates ferroportin (Fpn1)-mediated iron export via Nrf2. The subsequent reduction of intracellular iron levels restricts the availability of iron to intracellular microbes and enhances TNF-α and IL-12 production.



Macrophage after RBC uptake | Monocyte after RBC uptake | Granulocyte after RBC uptake | No RBC uptake in B-Cells

Fig. 2: Phagocytosis of red blood cells (RBC) by different immune cells

genes in neutrophils and macrophages in host control of infection and orchestration of innate and adaptive immune responses, and how metabolic alterations (metals, lipids, hormones, peptides) of the host or microbial environment affects the course of infections or auto-immune diseases. We aim to identify new targets for the treatment of infections either by compromising host/microbial metabolism or through favourably affecting host immune responses.

A second major focus of this laboratory is iron homeostasis in health and disease. We have studied pathways leading to iron loading (genetic and disease related) or absolute/functional iron deficiency along with its sequels such as anaemia of chronic disease (ACD). Further, we examine new therapeutic avenues to treat hemochromatosis or anaemia of chronic diseases by targeting the expression of iron regulatory hormones, modulating transcellular iron trafficking or affecting iron regulated immune effector pathways; the latter being based on our longstanding research on regulatory interactions between iron and immune function and their role in infections, auto-immunity and cancer.

In 2013 we identified a novel pathway by which macrophages combat resistance to infection with intracellular bacteria. We found that these cells increase transcellular iron export via nitric oxide mediated induction of the central iron export protein ferroportin. This reduces the availability of the growth factor iron for microbes while at the same time increases antimicrobial immune effector functions (Nairz *et al.,* J Exp Med 2013; Fig. 1). To study microbe specific metabolic and immunological host pathogen responses at the cellular and systemic level we have established various infection models including S. typhimurium, C. pneumoniae, L. monocytogenes, S. aureus and E. coli (Bellmann-Weiler, Immunobiology 2013) and generated mammalian systems with deletions of specific genes being of importance for the delivery of metals/metabolites or establishment of protective host immune responses.

In an attempt to identify regulatory pathways of iron homeostasis and erythropoiesis during hypoxia we uncovered a new mechanism by which platelet derived growth factor-BB inhibits the expression of the iron regulatory hormone hepcidin thus securing a sufficient supply of iron for the synthesis of red blood cells (Sonnweber *et al.,* Gut 2014).

Using a well-established animal model of ACD we identified serum hepcidin levels to be a good predictive marker for the response to erythropoiesis stimulating agents (ESA). We could further demonstrate that pharmacological inhibition of hepcidin formation improves the therapeutic efficacy of ESAs, which may favour a reduction of ESA dosages, costs and side effects (Theurl *et al.,* Haematologica 2014). We also used our mammalian model of ACD to explore and investigate new hepcidin and ferroportin modifying drugs to successfully treat this type anaemia based on our previous proof of principle studies (Theurl *et al.,* Blood 2009 and 2011), and some of these drugs are currently already in phase I and II clinical trials.

Over the last two years we also became interested in stress and inflammation induced erythrophaghocytosis (Fig. 2), a condition often seen in ACD. We realized that this process is much more complex than described in textbooks and uncovered a previously unknown mechanism of how erythrophagocytosis is regulated (Theurl *et al.,* in submission). Using different genetically modified reporter mice we are currently exploring the location of stress erythrophagocytosis and the ontogeny of involved macrophages. We realized that during stress erythrophagocytosis locally proliferating macrophages are supported by on demand-recruited macrophages that are highly specialized for iron handling which enables them to avoid iron mediated toxic tissue damage.

Immunometabolism

Atherosclerosis is still the leading cause of death in industrialized countries, and novel therapies that can lower low-density lipoprotein cholesterol (LDL-C) are needed. Any approach promoting the transport of excess cholesterol from atherosclerotic plaque macrophages back to the liver via plasma high-density lipoprotein (HDL) for biliary and final faecal excretion is expected to prevent atherosclerosis, a mechanistic concept called reverse cholesterol transport. We have recently reported that arachidonic acid (AA)-derived bioactive lipid mediators including leukotrienes and lipoxins critically influence whole body cholesterol homeostasis in mammals (Demetz *et al*., Cell Metabol 2014). We discovered that pharmacological and genetic alteration of AA metabolism aimed at increasing lipoxin levels in the liver promotes reverse cholesterol transport and leads to increased clearance of LDL-C (Fig. 3).

In another project, we discovered that fibrates, drugs used to lower plasma lipids, ameliorate the survival rate of septic mice by positively influencing neutrophil migration, which represent a major constituent of innate immunity (Tancevski *et al.,* EMBO Mol Med 2014). Taken together, our research at the intersection between lipid metabolism and immunology will help to pave the way not only for the development of novel lipid-lowering drugs, but may also serve as an innovative treatment approach in sepsis.

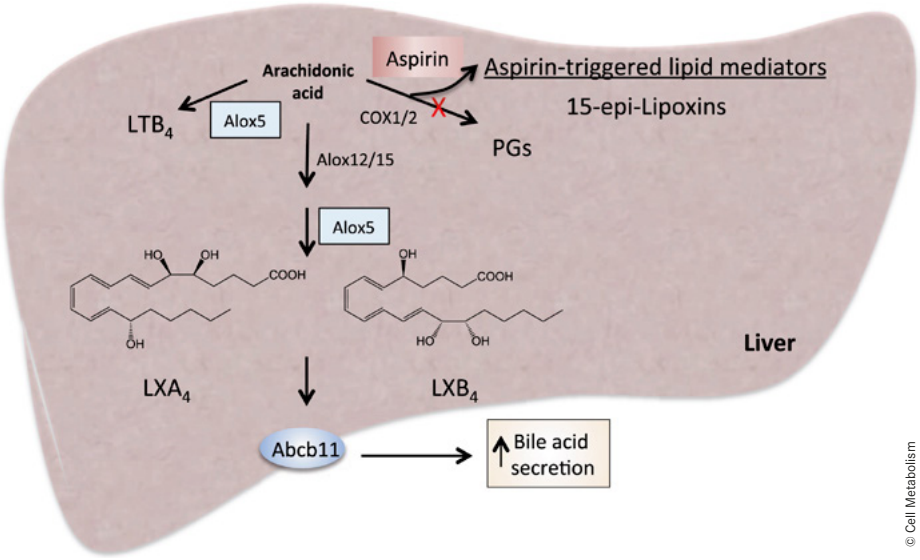


Fig. 3: Regulation of Cholesterol Metabolism by Lipid Mediators
Arachidonic acid (AA) is converted to prostaglandins (PGs) by cyclooxygenase (COX) enzymes. Aspirin inhibits the production of PGs and results in substrate diversion of AA to lipoxygenase (LOX) pathways in the liver and also promotes the generation of 15-epimeric lipoxins. Arachidonate 5-lipoxygenase (Alox5) is involved in the biosynthesis of leukotriene B4 (LTB4) and the lipoxins, LXA4 and LXB4. Aspirin treatment enhances reverse cholesterol transport in part by increasing the production of Alox5-derived mediators and subsequent bile acid secretion through ATP-binding cassette subfamily b member 11 (Abcb11). These protective actions are recapitulated by administration of stable analogs of LXB4 (i.e. 5-R/S-methyl LXB4). Adapted from: Spite M., Cell Metab. 2014 Dec 2;20(6):935–7

Biomarker Research, Diagnostics and Biobanking

These studies focus on the identification of diagnostic and prognostic parameters in infectious diseases including sepsis and auto-immune disorders. The idea is to identify new biomarkers or combinations thereof to enable rapid and pathogen specific diagnosis of infectious diseases in order to differentiate between viral and bacterial infections, and to assist clinicians in the differentiation between an exacerbation of an auto-immune disease and infectious complication in subjects with systemic inflammatory disorders or in an immune-compromised host. Such markers include small molecules derived from innate immune cells, metabolic products such as lipids, amino acid degradation compounds, anti-microbial peptides and volatile gases. Along this line we aim to improve the quality of state of the art diagnostics for infectious diseases and auto-immune disorders along with establishment of clinically needed diagnostic tests for rare diseases and immuno-compromised patients. In addition, clinical studies are undertaken to evaluate the usefulness and effectivity of clinical practices and therapy standards.

Biobanking has been systematically performed at our institution for many years and is of central importance for ongoing and future clinical studies and research in infectious, immunological, rheumatological and pulmonary as well as in rare diseases.
Rheumatological research

Our clinical rheumatological research is focused on the evaluation of a new referral tool for primary care physicians and specialists to our outpatient unit, diagnostic issues (with specific impact on sonography), validation of new classification criteria (e.g. for polymyalgia rheumatica and Behcet's disease) and outcome of rheumatic diseases (e.g. by supporting the international evaluation of the new ASAS-health index). Our current work on a structured disease-specific clinical database together with a clinical biobank will further support translational research.

In the lab we work on pathophysiological mechanisms, especially in large vessel arteritides (including abdominal aortic aneurysm) and spondyloarthritis (Dejaco *et al.,* Ann Rheum Dis 2014). Specifically we focus on a mouse model for spondyloarthritis and pro-inflammatory cytotoxic T-cells, which use alternate stimulatory pathways since they lack the co-stimulatory molecule CD28, show signs of early aging and are considered as long-lived with reduced apoptosis.

Among our major achievements are the initialisation of the new International Criteria for Behçet's Disease, establishment of NKG2D as part of a co-stimulatory pathway for CD4+CD28- T cells in giant cell arteritis and polymyalgia rheumatica and the proposal of antiphospholipid antibody therapy. For abdominal aortic aneurysms.

Furthermore we have extended patient cohorts for clinical and pathophysiological studies and pathophysiological studies in spondyloarthritis and large vessel arteritides. Hyperuricaemia is a frequent clinical condition eventually leading to gout (Fig. 4). While local urate deposition results in activation of the immune system via the NALP3 inflammasome, hyperurecemia also causes systemic metabolic effects, and increased circulating uric acid levels are a known risk factor for coronary heart

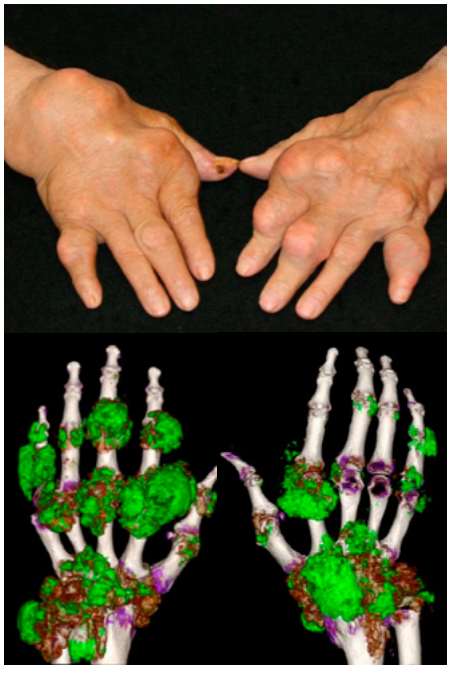


Fig. 4: Severe form of gout and identification of urate deposition by dual energy computer tomography

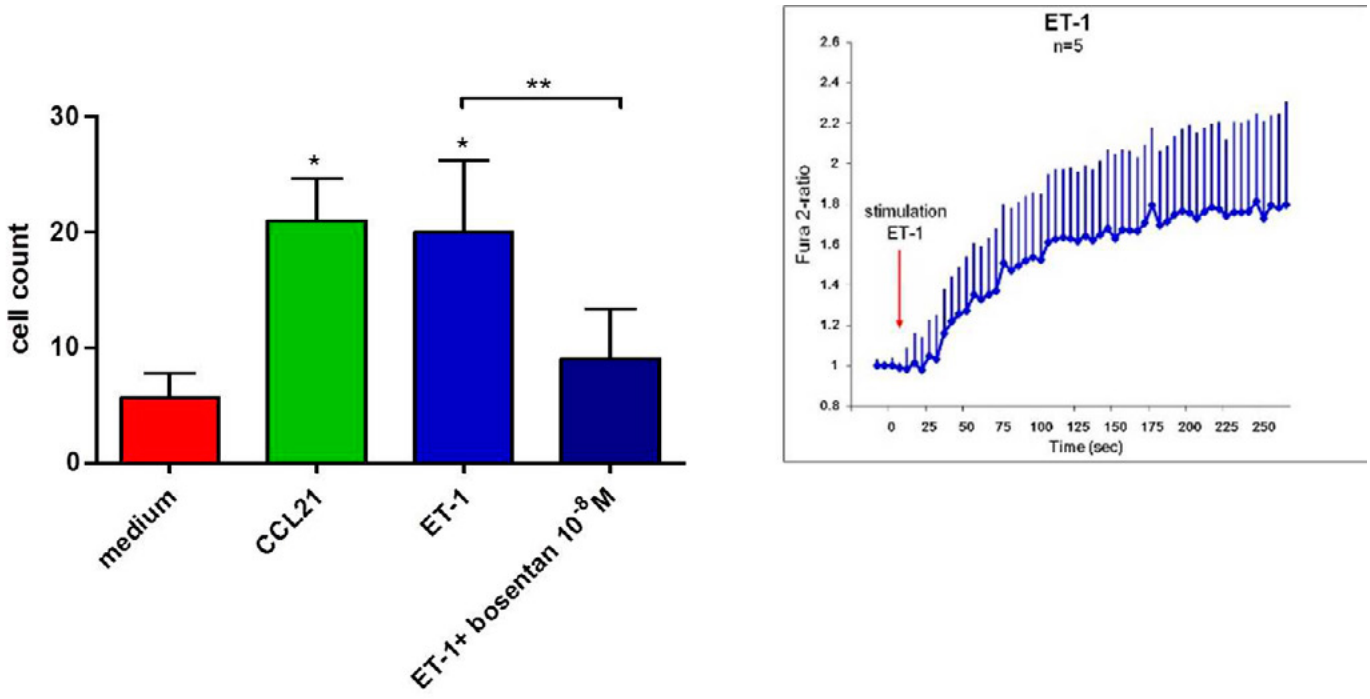


Fig. 5: Enhancing and suppressing effects of endothelin-1 and the endothelin-receptor blocker bosentan on outmigration of Langerhans cells from murine epidermal skin explants (left). Live cell imaging confirming ET-1 induced calcium mobilisation (right).

disease. In a fruitful collaboration with the clinic of radiology this association has been investigated by the combination of state of the art ultrasound and computer tomography (DECT) imaging along with investigations into the effects of immune-modulatory drugs on the course of gout *in vitro* and *in vivo*.

An ongoing clinical study currently investigates the prevalence and nature of anaemia in systemic rheumatic diseases, its impact on disease activity, morbidity and mortality along with its alteration by disease modifying drugs.

Rare Pulmonary Diseases

The orphan lung diseases comprise many disorders, and assessment as well as treatment of affected patients is a great challenge, because of the lack of adequate guidelines. Therefore, present research is focused on a systematic approach to these diseases along with translational research projects. Patients with pulmonary rare diseases are registered within a database and a biobank with biological specimens will be established. Patients with pulmonary arterial hypertension (PAH) represent the major cohort of patients and efforts for improved screening within high risk populations (e.g. patients with connective tissue disease), mutational analysis for BMPR2, ALK-2 and endoglin, analysis of the iron status in these patients and improved imaging with MRI studies are ongoing projects. Among the more rare diseases, patients with sarcoidosis, idiopathic lung fibrosis, CF- and non-CF bronchiectasis as well as polycystic lung diseases are registered. The latter includes pulmonary Langerhans cell histiocytosis, a disease that may also result in PAH. We already tested the presence of PAH drug targets in the inflammatory cells of these patients and concluded that blockade of endothelin-1 signalling might prevent outmigration of Langerhans cells (Fig. 5).

Selected Publications

NKG2D stimulated T-cell autoreactivity in giant cell arteritis and polymyalgia rheumatica. Dejaco C, Duftner C, Al-Massad J, Wagner AD, Park JK, Fessler J, Aigelsreiter A, Hafner F, Vega S, Sterlacci W, Grubeck-Loebenstein B, Tzankov A, Ness T, Boiardi L, Salvarani C, Schirmer M.
ANN RHEUM DIS. 2013 Nov;72(11):1852–9.

The Arachidonic Acid Metabolome Serves as a Conserved Regulator of Cholesterol Metabolism. Demetz E, Schroll A, Auer K, Heim C, Patsch JR, Eller P, Theurl M, Theurl I, Theurl M, Seifert M, Lener D, Stanzl U, Haschka D, Asshoff M, Dichtl S, Nairz M, Huber E, Stadlinger M, Moschen AR, Li X, Pallweber P, Scharnagl H, Stojakovic T, März W, Kleber ME, Garlaschelli K, Uboldi P, Catapano AL, Stellaard F, Rudling M, Kuba K, Imai Y, Arita M, Schuetz JD, Pramstaller PP, Tietge UJ, Trauner M, Norata GD, Claudel T, Hicks AA, Weiss G, Tancevski I.
CELL METABOLISM. 2014 Nov 4;20(5):787–98.

Nitric oxide-mediated regulation of ferroportin-1 controls macrophage iron homeostasis and immune function in Salmonella infection. Nairz M, Schleicher U, Schroll A, Sonnweber T, Theurl I, Ludwiczek S, Talasz H, Brandacher G Moser PL, Muckenthaler MU, Fang FC, Bogdan C, Weiss G.
J Exp. Med. 2013, 210: 855–873.

Hypoxia induced downregulation of Hepcidin is mediated by platelet derived growth factor BB. Sonnweber T, Nachbaur D, Schroll A, Nairz M, Seifert M, Demetz E, Haschka D, Mitterstiller AM, Kleinsasser A, Burtscher M, Trübsbach S, Murphy AT, Wroblewski V, Witcher DR, Mleczko-Sanecka K, Vecchi C, Muckenthaler MU, Pietrangelo A, Theurl I, Weiss G.
Gut. 2014; 63: 1951–59.

Fibrates ameliorate the course of bacterial sepsis by promoting neutrophil rectruitment via CXCR2. Tancevski I, Nairz M, Duwensee K, Auer K, Schroll A, Heim C, Feistritzer C, Hoefer J, Gerner RR, Moschen AR, Heller I, Pallweber P, Li X, Theurl M, Demetz E, Wolf AM, Wolf D, Eller P, Ritsch A, Weiss G.
EMBO Mol Med. 2014 Apr 22;6(6):810–20.

Selected Funding

- European Union 7th Framework, Project: Eurocalin (Günter Weiss)
- FWF- TRP-188: Role of Iron for Atherosclerosis (Günter Weiss)
- FWF-23853-MED: Thyreomimetika und Statine: Einfluß auf Reversen Cholesterintransport & Atherosklerose (Ivan Tancevski)
- FWF-24749-MED: Hepcidin in Diagnose und Therapie verschiedener Anämieformen (Igor Theurl)
- FWF- 25338: Toll like receptors and innate immunity in axial spondyloarthritis: A TH1-prone mouse model and human studies, Austrian Research Foundation (Michael Schirmer)

Collaborations

- Prof. Dr. Christian Bogdan, Univ. of Erlangen, Germany
- Doz. Dr. Christian Datz, Obernsdorf, Austria
- Prof. Dr. Thomas Decker,M Perutz Laboratory, Vienna
- Prof. Dr. Ferric Fang, Univ of Washington, Seattle, USA
- Prof. Dr. Matthias Hentze, EMBL, Heidelberg, Germany
- Prof. Dr. Martina Muckenthaler, Univ. of Heidelberg, Germany
- Prof. Dr. Sylvia Knapp, CeMM, Vienna
- Prof. Dr. Klaus Schuemann, Technical Univ of Munich, Germany
- Prof. Dr. Phil Swirski, Harvard Medical School, Boston, USA
- Prof. Dr. Eric Mattheson, MAYO Clinic and Foundation, Rochester (MN), USA
- Prof. Dr. Carlo Salvarani, Arcispedale S.Maria Nuova, Reggio Emilia, Italy
- Prof. Dr. Fereydoun Davatchi, University of Teheran, Iran
- Prof. Dr. Christos C. Zouboulis, Klinikum Dessau, Germany

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Keywords

Acute kidney injury, sepsis, cardio pulmonary resuscitation, biomarkers, microvesicles, secretoneurin, chronobiology, plasma pharmacokinetics, target-site pharmacokinetics, pharmacodynamics

Research Focus

- Applied clinical as well bench-to-bedside research covering several aspects of critical illness with special emphasis on acute kidney injury (AKI), sepsis, cardiopulmonary resuscitation (CPR)
- Definition and clinical validation of biomarkers for diagnosis and prognosis of AKI and CPR
- Identification and characterisation of microvesicles in severe sepsis
- Chronobiology
- Intensive care specific pharmacodynamics and pharmacokinetics

General Facts

The Joint Institution for Emergency Medicine and Critical Care Medicine was established in December 2012.
Clinically, it was designed as a core facility for the Department of Internal Medicine providing a high level of Intensive Care and Emergency Medicine. It comprises a level three intensive care unit and the medical emergency room including a short stay (maximum 24 hours) ward located in the Medizinzentrum Anichstrasse (MZA). Administratively, the unit is affiliated to the Department of Internal Medicine I (Director: Prof. Dr. Herbert Tilg).

The unit is involved in several clinical multicentre trials investigating early diagnosis and treatment of acute kidney injury, treatment of severe infections and sepsis as well as antimicrobial pharmacokinetics. Complementary *in vitro* models are used to investigate inflammatory mechanisms of renal injury.

The research unit comprises the laboratory of Inflammation Research (U-1-015) hosting two research groups: the Intensive Care Medicine group (Viktoria Haller, Ulrich Harler, Julia Hasslacher, Georg Lehner) led by Michael Joannidis and the Clinical Pharmacokinetics group (Rene Welte) led by Romuald Bellmann.

Internal collaboration partners include all University Clinics (I-VI) of the Department of Internal Medicine, the Neurological Intensive Care Unit and the Surgical/ Trauma Intensive Care Unit as well as the Division of Hygiene and Medical Microbiology, the Division of Molecular and Cellular Pharmacology and the Department of Medical Psychology.

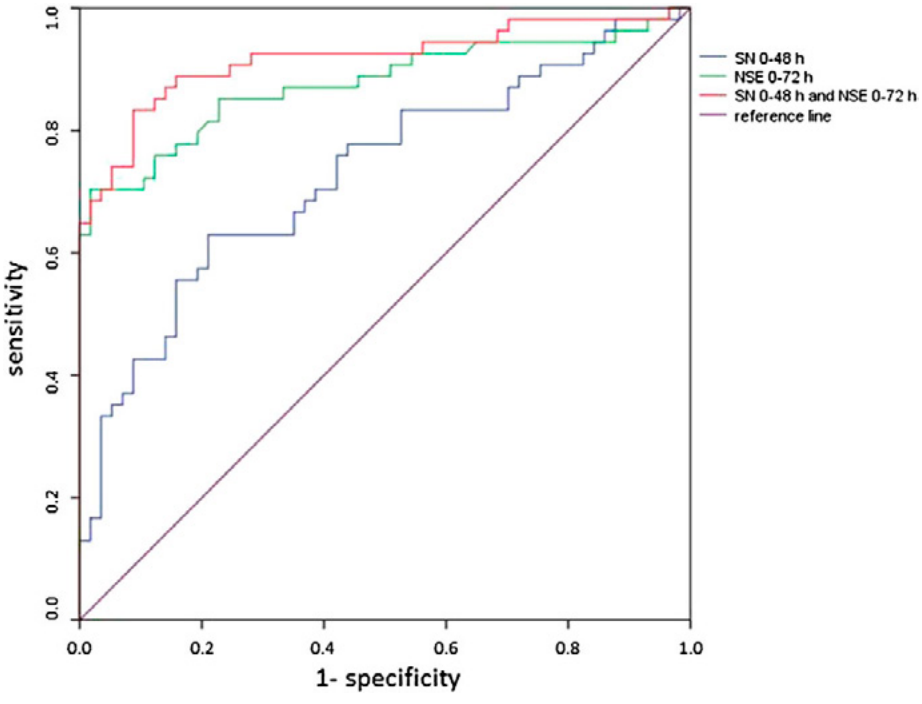

Fig. 1: ROC analysis for prediction of poor neurological outcome at 72 h after CPR. SN secretoneurin, NSE neuron-specific enolase.

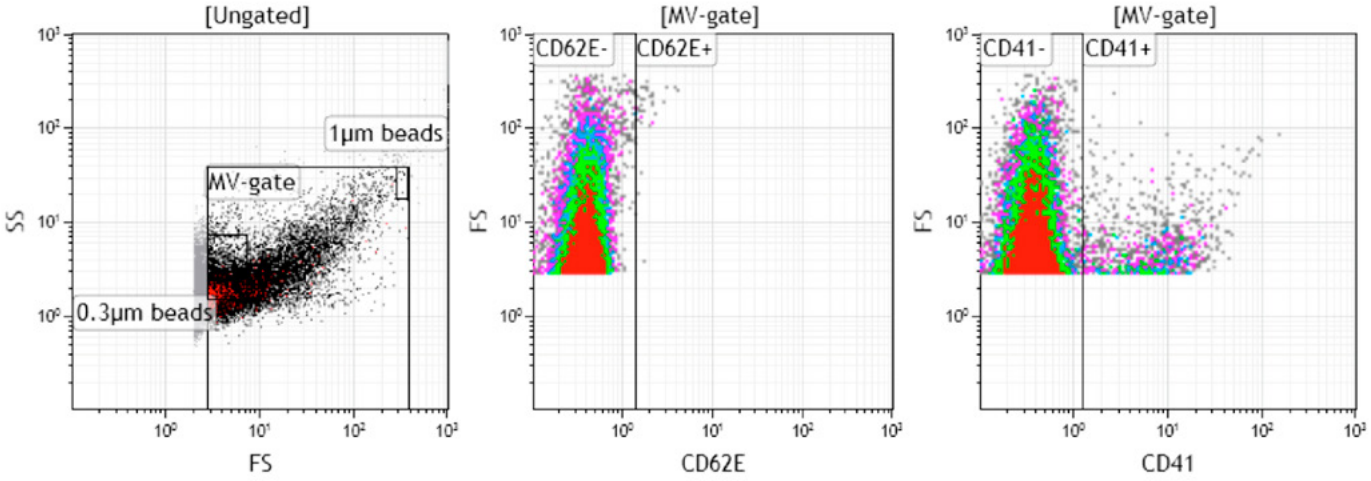

Fig. 2: Characterisation of microvesivles in septic shock applying high-sensitivity flow cytometry (0.3 µM resolution).

Research

Intensive Care Medicine
Michael Joannidis

This group is involved in biomarker research in critical illness with a major interest in acute kidney injury and cardiopulmonary resuscitation. A second major focus is investigation of microvesicles in sepsis. Chronobiology is the third field of interest.

Acute Kidney Injury (AKI)

AKI in the critically ill is associated with significant mortality and long term morbidity including end stage renal disease. Based on a prior project (OeNB Anniversary Fund, project 12094) we analysed conventional criteria for AKI, i.e. dynamic changes in serum creatinine and urinary output significantly triggering the development of the current AKI criteria (KDIGO Clinical Practice Guideline for Acute Kidney Injury, 2012, http://kdigo.org/home/guidelines/acute-kidney-injury/).

Furthermore, several renal tubular proteins were evaluated as biomarkers to achieve an earlier and more specific diagnosis of AKI aiming at improved prevention strategies. Participating in two large prospective cohort trials, cellular arrest markers, tissue inhibitor of metalloproteinsases 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) were investigated. Their presumed mechanism of action is depicted in Fig. 3. The SAPPHIRE and OPAL studies demonstrated diagnosis of moderate or severe AKI (KDIGO stage 2 or 3) at least twelve hours earlier than conventional biomarkers. The achieved AUC > 0.8 was higher than that of previously investigated biomarkers for AKI and prediction was independent of the aetiology of AKI or the underlying disease. Additionally to the clinical approach, function and release kinetics of several biomarkers are characterised in a renal epithelial-endothelial co-culture system developed by our laboratory to simulate interstitial inflammation.

Hypoxic Brain Damage after Cardio-pulmonary Resuscitation (CPR)

Cardiac arrest is one of the major causes of death in cardiovascular disease, frequently associated with long-term neurological deficits in case of survival. Neuron specific-enolase (NSE), the recommended biomarker for outcome prediction since 2006, has been questioned recently because of being influenced by therapeutic hypothermia as well as haemolysis frequently occurring after CPR. Secretoneurin (SN), a 33 amino acid neuropeptide is specifically expressed in endocrine, neuroendocrine and neuronal tissues with a wide spread distribution in the brain. SN exerts a variety of biological functions like induction of angiogenesis and is markedly upregulated by hypoxia. For the first time we could demonstrate, in a large prospective cohort of 150 patients admitted to our ICU after successful CPR, that SN enables outcome prediction within the first 24 hours, significantly earlier than NSE.

SN was not influenced by therapeutic hypothermia. Combining SN and NSE in the first 72 hours after CPR resulted in an AUC of 0.881 (95% CI: 0.815-0.946) to predict poor neurological outcome (Fig. 1).

Microvesicles in Severe Sepsis and Septic Shock

Severe sepsis has a worldwide annual incidence of around 3/1000 inhabitants and a mortality rate > 50% when proceeding to septic shock. This syndrome is frequently complicated by devastating coagulation disturbances leading to disseminated intravascular coagulation (DIC). Microvesicles (MV) are capable of mediating pleiotropic inflammatory signals during sepsis and may play a key role in the propagation of thrombin generation via phosphatidylserine exposure as well as in the initiation of blood coagulation by specific epitopes such as tissue factor. In a project funded by the OeNB Anniversary Fund (project 13861), we investigated the hypothesis that increased levels of endothelial derived MV reflect endothelial dysfunction which is considered a key element in the pathophysiology of sepsis. Developing a specific high-sensitivity flow cytometry approach enabled us to measure previously undetectable smaller MV until 0.3 µm (Fig. 2). We found that increased levels of MV detected in patients with septic shock predominantly originate from circulating cells indicating excessive leukocyte and platelet activation especially in lethal septic shock.

Only single patients exhibited markedly increased amounts of endothelial derived MV. Moreover, our findings indicate that CD31+/CD41- (i.e. platelet endothelial cell adhesion molecule positive and integrin alpha-IIb negative) MV, formerly frequently considered to be mostly endothelium derived, might originate predominantly from leukocytes. These results triggered a subsequent project funded by the OeNB

in which we currently address the role of distinct MV subtypes during DIC trying to identify the specific stimuli that cause their release. To achieve this goal we establish coagulation assays that allow us to investigate the interactions between MV, the endothelium and the coagulation system in a translational approach. This system will be capable of reflecting the key role of the activated endothelium during sepsis and DIC.

Chronobiology Research

Continuous disruption of wake-sleep cycle and chronic sleep deprivation have been implicated to contribute to cardiovascular disease as well as malignancy among other health issues. Investigating the effects of physicians' nightshift we previously had described significant cardiac arrhythmias as well increased sympathetic activity during on call duties. In a consecutive study we could demonstrate significant effects of 24 hours on call duty on the neuroendocrine system leading to increased noradrenaline levels as well as significantly reduced concentration ability, however, concealed by an individual overestimation of performance.

Major Achievements:

- Clinical validation cell cycle arrest proteins as biomarkers for AKI
- First time identification of SN as early predictor for severe hypoxic brain damage after CPR
- Establishment of high-sensitivity flow cytometric MV analysis and characterisation of circulating MV as being mainly platelet and leucocyte derived in septic shock

Future Directions:

- Investigating long term outcome prediction of AKI by cell cycle arrest proteins and markers of fibrosis
- Definition of biomarker panels for neurologic outcome prediction after CPR
- Investigating specific effects of MV subtypes on distinct proteolytic processes of the coagulation system in DIC

Clinical Pharmacokinetics
Romuald Bellmann

Severe infections are a common reason for critical illness. Adequate antimicrobial chemotherapy is crucial for the clinical outcome. Sub-therapeutic antimicrobial dosage results in poor response and may promote the emergence of resistant microorganisms. On the other hand, critically ill patients are at an enhanced risk of drug toxicity. Absorption, distribution, metabolism and elimination of drugs can be altered by critical illness depending on the state of disease, type of organ failure and required treatment modality. An increasing number of patients present with profound

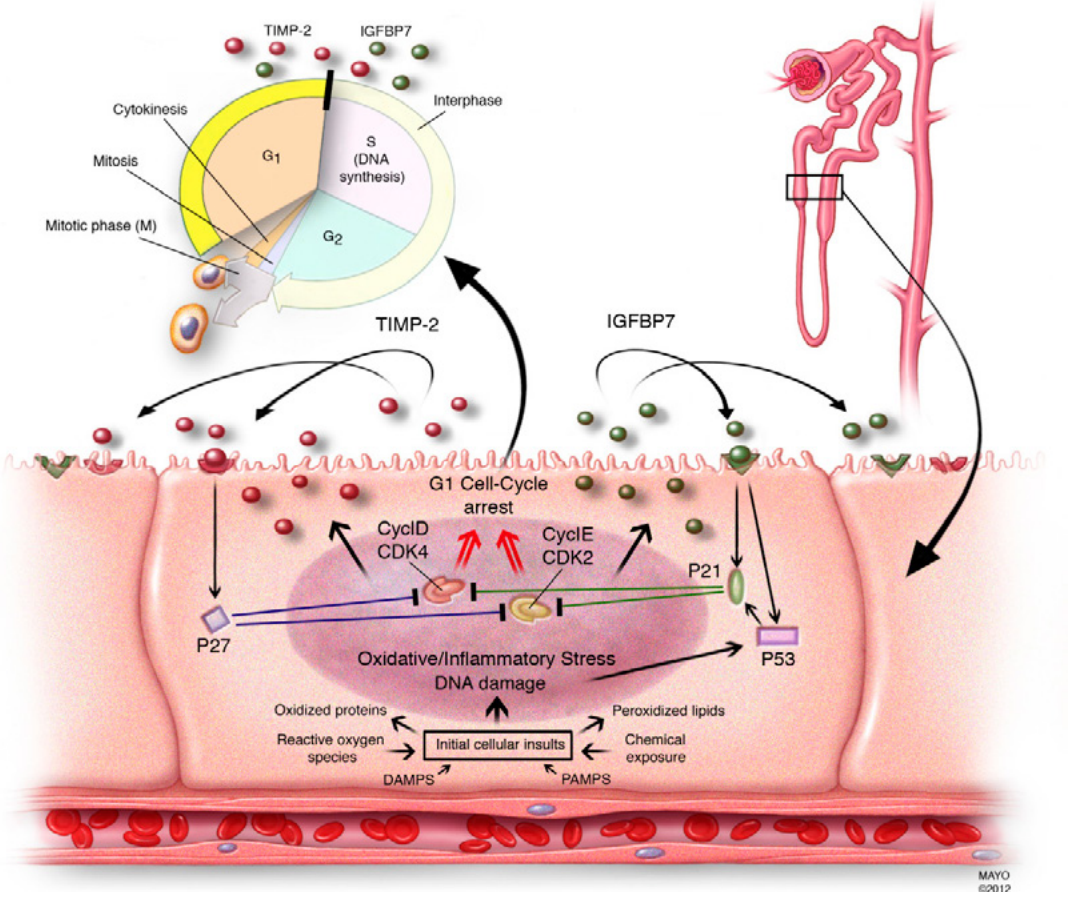

Fig. 3: Proposed mechanistic involvement of the novel biomarkers in AKI: initial tubular cells sustain injury by various insults. In response to DNA and possibly other forms of damage, IGFBP7 and TIMP-2 are expressed in the tubular cells. IGFBP7 directly increases the expression of p53 and p21 and TIMP-2 stimulates p27 expression. These effects are conducted in an autocrine and paracrine manner via IGFBP7 and TIMP-2 receptors. The p proteins in turn, block the effect of the cyclin-dependent protein kinase complexes (CyclD-CDK4 and CyclE-CDK2) on the cell cycle promotion, thereby resulting in G1 cell cycle arrest for short periods of time presumably to avoid cells with possible damage from dividing. AKI, acute kidney injury; IGFBP7, insulin-like growth factor-binding protein 7; TIMP-2, tissue inhibitor of metalloproteinases-2. Ref. Kashani K et al, Critical Care 2013 Feb 6;17(1):R25.

immunological dysfunction facilitating infections by opportunistic pathogens such as invasive fungal infections associated with mortality rate exceeding 50%. Optimum dosage of newly developed broad spectrum azoles and echinocandins guided by pharmacokinetic and pharmacodynamic considerations should contribute to improved outcome.

Therefore we assessed pharmacokinetics of caspofungin, an echinocandin antifungal agent, in critically ill patients requiring continuous renal replacement therapy (CRRT) and in a control group not requiring CRRT. Caspofungin clearance by CRRT was very low and plasma pharmacokinetics almost unaffected by CRRT and comparable to that in healthy volunteers. This study proved that caspofungin can be administered at standard dosage to critically ill patients independent of requirement of CRRT. Since most infections occur in tissue rather than in the blood stream, target-site pharmacokinetics might be even more relevant for clinical outcome than plasma pharmacokinetics. Therefore, biliary AMB pharmacokinetics in patients treated with lipid-formulated AMB and biliary AMB pharmacodynamics by *in vitro* and *ex vivo*-simulations was investigated in another project.

Biliary AMB concentrations were lower and displayed a slower rise and decline than plasma levels. Fungal growth and AMB activity were impaired by bile. Thus, treatment of fungal cholangitis with lipid-formulated AMB is not supported by our data.

Major Achievements:
Determination of pharmacokinetics of caspofungin and target site kinetics of lipid-formulated AMB in the critically ill.

Future Goals:
Plasma and target-site pharmacokinetics and pharmacodynamics of other antifungals and of trimethoprim sulfonamide combinations.

Selected Publications

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Kashani Kianoush, Al-Khafaji Ali, Ardiles Thomas, Artigas Antonio, Bagshaw Sean M, Bell Max, Bihorac Azra, Birkhahn Robert, Cely Cynthia M, Chawla Lakhmir S, Davison Danielle L, Feldkamp Thorsten, Forni Lui G, Gong Michelle Ng, Gunnerson Kyle J, Haase Michael, Hackett James, Honore Patrick M, Hoste Eric AJ, Joannes-Boyau Olivier, Joannidis Michael, Kim Patrick, Koyner Jay L, Laskowitz Daniel T, Lissauer Matthew E, Marx Gernot, McCullough Peter A, Mullaney Scott, Ostermann Marlies, Rimmele Thomas, Shapiro Nathan I, Shaw Andrew D, Shi Jing, Sprague Amy M, Vincent Jean-Louis, Vinsonneau Christophe, Wagner Ludwig, Walker Michael G, Wilkerson R. Gentry, Zacharowski Kai, Kellum John A.
Critical Care. 2013 Feb 6;17(1):R25.

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Selected Funding

Interaction between microvesicles, endothelium and the coagulation system in sepsis and DIC, OeNB Anniversary Fund (project 15708), Michael Joannidis

Collaborations

- Univ.-Prof. Dr. Thomas Staudinger, Intensive Care Unit, Internal Medicine I, Medical University Vienna, Vienna, Austria
- Professor Stefan Kluge, Department of Intensive Care Medicine, Hamburg Eppendorf, Hamburg, Germany
- Prim. Univ.-Prof. Dr. Christian Wiedermann, Department of Internal Medicine, Central Hospital of Bolzano, Bolzano, Italy
- John Kellum, MD, FCCM, FACP, University of Pittsburgh School of Medicine, Pittsburg, PA, USA
- Ravindra L. Mehta, MD, UCSD Medical Centre, San Diego, CA, USA
- Univ.-Prof. Dr. Jaroslav Sterba, Department of Pediatric Oncology, University Hospital Brno and Masaryk University, Brno, Czech Republic
- Dr. Piotr Smuszkiewicz, Department of Anesthesiology, Intensive Therapy and Pain Treatment, University Hospital Przybyszewskiego, Poznan, Poland
- Univ.-Prof. Dr. Markus Müller, Priv. Doz. Dr. Markus Zeitlinger, Universitätsklinik für Klinische Pharmakologie, AKH, Wien, Austria

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Keywords

Addiction, alzheimer, beta-amyloid plaques, cocaine, conditioned place preference, dementia, depression, diagnosis, drug dependence, ECT, electroconvulsive therapy, health related behaviour, magnetic resonance imaging, mild cognitive impairment, platelets, social interaction, substance use disorder, suicide, tau, therapeutic drug monitoring, unipolar, vessels

Research Focus

Age related psychiatric disorders, behavioral and clinical psychology, neuronal signal processing, preclinical substance use research, suicide, therapeutic drug monitoring, treatment of affective disorders

General Facts

The Department of General and Social Psychiatry has a strong focus on clinical research related to the services provided by the in- and outpatient units of the Department, which are located on the campus of the Medical University Innsbruck. This allows for close collaboration with other medical disciplines and the other departments of the Center of Psychiatry, Psychotherapy and Psychosomatics. The latter is especially pertinent with respect to mutual interests shared with the Departments of Biological Psychiatry and Psychosomatics. Preclinical research is mostly of a translational nature and extends and complements the clinical programmes. Within the broad spectrum of research efforts, a few highlights will be briefly summarized in the following.

Research

Selected references, funding sources and collaborations are briefly presented in the Appendix.

Age Related Psychiatric Disorders
Imrich Blasko, Michaela Defrancesco

This research group has its main base in the Memory Clinic of the Department. In addition to providing clinical service for the catchment area, specific areas of scientific interest include the neuropsychological and anatomical underpinnings of mild cognitive impairment (MCI) and Alzheimer dementia. In this context, a strong emphasis is given to predicting the conversion risk from MCI to dementia. To this end, next to findings from well-established neuropsychological tests, anatomical imaging findings and both peripheral and central biomarkers are explored. The Departments of Neuroradiology and the Laboratory for Experimental Alzheimer Research are important collaborating partners. Further to that, Dr. Blasko's research group collaborates with the Vienna Transdanube Aging Study (VITA) spearheaded by Dr. Peter Fischer. This is a large scale population-based epidemiological study evaluating the association of various physical, cognitive and social activities with the risk for dementia. Driving ability of the elderly is a research topic studied in collaboration with Ilsemarie Kurzthaler, who leads the Department's traffic safety in psychiatry group.

Affective Disorders and Suicide
Armand Hausmann, Eberhard Deisenhammer

These two research groups, again, base their work on the clinical services provided by the relevant in- and outpatient units of the Department. Established and experimental treatments for depression, ranging from phase II clinical trials to light therapy and electroconvulsive therapy, are explored.

Depression is associated with a considerable suicide risk, the latter being another long-standing field of research in the Department. The latency between the suicidal impulse and the ensuing action, as well as relationships to previous physician contacts and hospitalization, have been analysed by this group. Biological variables such as oxytocin and cholesterol were also studied in suicide attempters and controls. The work led by Dr. Deisenhammer's group has also led to regional suicide prevention measures, including attaching safety nets to a big highway bridge.

Experimental Alzheimer Research
Christian Humpel

In close collaboration with the clinical researchers, research in the Psychiatric Laboratory of Experimental Alzheimer's disease focusses on investigating the development of beta-amyloid plaques in Alzheimer's disease and their association with brain blood vessels. Furthermore, the migration of blood cells (monocytes and platelets) into the Alzheimer brain is explored. Another research focus is to find and establish novel biomarkers in blood to diagnose Alzheimer's disease and other forms of dementia. In addition to peripheral markers, this lab also scientifically evaluates routinely acquired CSF samples from patients referred either from the Memory Clinic or from the inpatient unit of the Department.

Experimental Psychiatry Unit
Alois Saria, Gerald Zernig

The Experimental Psychiatry Unit is one of the host labs for the international PhD program "Signal Processing in Neurons". Research at the lab focusses on the mechanisms of reward and the mode of action of psychoactive drugs. In addition, the lab offers clinical service for psychiatric patients, i.e. Therapeutic Drug Monitoring (TDM). In this context, blood levels of over 30 antidepressant or antipsychotic drugs are determined daily for the University Hospital Innsbruck and for additional hospitals and physicians in Austria and Northern Italy, by use of liquid chromatography-tandem mass spectrometry. TDM results are also exploited for addressing various research questions, and the lab is the core laboratory for drug monitoring in two large European multi-center studies (OPTiMiZE and EULAST).

The Experimental Psychiatry Unit is also a partner in the Human Brain Project, one of the two flagship research projects funded by the European Commission, involving over 100 partner universities in Europe

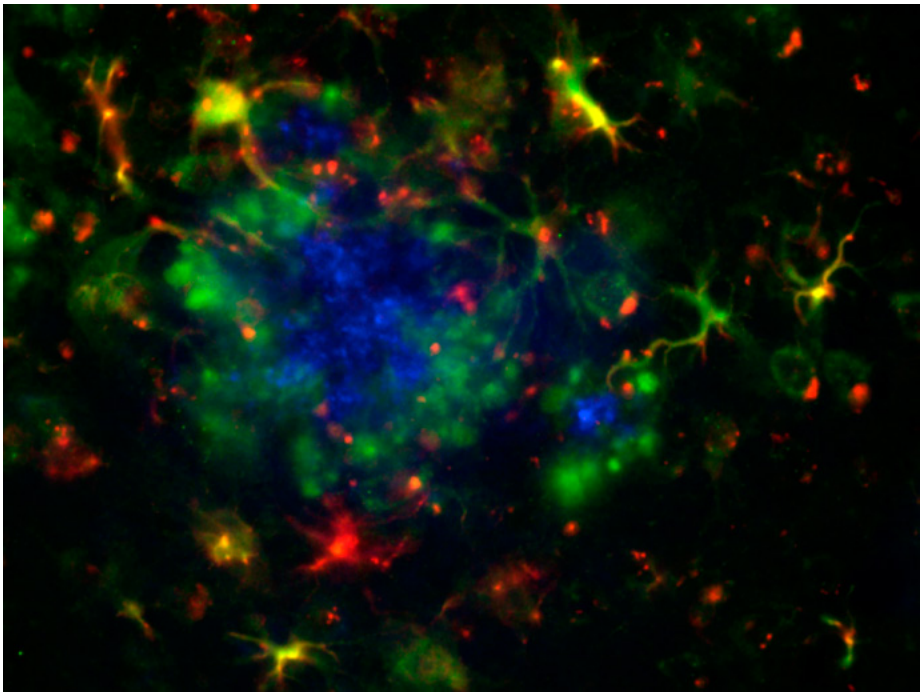

Fig. 1: This picture shows a plaque in an Alzheimer mouse. The plaque (blue) is surrounded by reactive astrocytes (red), most of them express a calcium channel (yellow). Green fluorescence correspond to calcium-channel alpha1 subunit like-immunoreactivity (published in Journal of Alzheimers disease).

and some outside Europe. Alois Saria leads the "Education Program" of this project to coordinate education and training of a large number of PhD students in this multidisciplinary project.

Addiction Research, Preclinical
Gerald Zernig

Impaired social interaction is a hallmark symptom of many psychiatric diseases. This also pertains to substance use disorders. Dr. Zernig's group studies the neural bases of substance-induced social interaction medications, using cocaine as a prototypical drug of abuse, in an experimental model. In addition to behavioural modifications on the impact of potentially beneficial interventions, such as for instance environmental enrichment or paired housing, changes in neurocircuitry and neuroreceptor/neurotransmitter level are investigated.

Behavioral and Clinical Psychology
Verena Günther

Behavioral and Clinical Psychology focusses primarily on cognitive/behavioral aspects of chronically ill-patients (e.g. body image in patients with an insulin pump, psychological aspects of patients with an implantable cardioverter defibrillator...) and on the conceptualization and evaluation of stigma-management-programs and cognitive training programs in psychiatric patients.

Health psychology aims to evaluate our nicotine cessation program and focusses on aspects of body image and body modification (e.g. in blind people).

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Selected Funding

Group Humpel:
- Austrian Science Funds P24734-B24
- Austrian Science Funds P24541-B24
- Austrian Science Funds Sonderforschungsbereich SFB F44

Experimental Psychiatry Unit
- Austrian Science Fund W1206 – Graduate School: Signal Processing in Neurons (PI: Gerald Zernig)
- Austrian Science Fund P 23824-B18: Neurobiology of Social Interaction as Alternative for Drugs of Abuse (PI: Rana El Rawas/Alois Saria)
- Austrian Science Fund P 27852-B21: Does social interaction have an anti-stress effect? (PI: Rana El Rawas)
- European Commission FP7-ICT-2013-FET-F: Human Brain Project (PI Alois Saria)

Collaborations

Group Humpel
Seven publications resulted from collaborations within and outside the MUI. External collaborators were
- Prim. Prof. Josef Marksteiner (Psychiatry, Landekrankenhaus Hall/Tirol),
- PD Dr. Walter Kaufmann (IST, Klosterneuburg) and
- Prof. Ingrid Strömberg (Umea, Sweden).

Experimental Psychiatry Unit
- Henry Markram (coordinator, Human Brain Project), EPFL Lausanne, Switzerland
- Anu Tammiste, Estonian Genome Center, University of Tartu, Estonia
- Claudia Klier, Medical University Vienna, Austria

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Keywords

Addiction, alcohol, antipsychotics, bipolar disorder, bone mineral density, cognition, cognitive-behavioural therapy, compliance, depot, patient related outcomes, prosody, patient recognition, psychooncology, quality of life, resilience, schizophrenia, stigma, substance abuse disorder, therapeutic drug monitoring, transcultural psychiatry

Research Focus

alcoholism, drug safety, psychopharmacology, schizophrenia, substance abuse disorder

General Facts

Embedded into the clinical services of the center, the Department of Biological Psychiatry's research groups have a long standing tradition of dealing with various topics hovering around schizophrenia. These are supported by a number of international collaborators and funded by grants from the European Union, the Austrian Science Foundation, the European Group for Research in Schizophrenia and the pharmaceutical industry, the latter through both investigator initiated grants as well as classical industry sponsored phase II and phase III trials. In addition, international collaborators include Keio University in Tokyo, the University of Bergen in Norway and Zucker Hillside Hospital in New York as well as local collaborators within the Department and also other medical disciplines of the Medical University Innsbruck. Psychooncology research also has strong international connections including among others the European Organisation for Research and Treatment in Cancer (EORTC) which also partially funds quality of life and patient related outcomes research.

Research

Selected references, funding sources and collaborations are briefly presented in the Appendix.

Schizophrenia Research
Wolfgang Fleischhacker, Alex Hofer

Clinical Psychopharmacology
Past and ongoing studies focus on antipsychotics, ranging from early drug development in phase II clinical trials all the way to large-scale international pragmatic effectiveness studies. The underlying theme is always enhancing treatment options for patients with schizophrenia. The European First Episode in Schizophrenia Trial (EUFEST) was the first large-scale independent comparative first episode study worldwide, evaluating treatment outcomes in close to 400 patients in 14 European countries and Israel. In its wake, Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) FP-7 funded program and the European long-acting in Schizophrenia Trial (EULAST) pursue related research questions with advanced methodology. The group is also involved in global efforts to improve clinical trial design in order to ease the translation from rigorous randomized controlled clinical trial standards into every day clinical practice. In this context, the issues of treatment attitudes, compliance and drug safety have been given particular emphasis, a prospective therapeutic drug monitoring program in schizophrenia patients treated with new generation antipsychotics being one example of these efforts.

Patients with schizophrenia starting monotherapy with a new-generation antipsychotic (NGA) in a naturalistic treatment setting are prospectively followed up for three months. Using a pharmacokinetic simulation program, we calculate the ratio of observed versus expected plasma levels of the prescribed NGA and investigate its relationship with changes in psychopathological symptoms. In addition, the relationship between attitudes toward drug therapy as an indirect indicator of adherence and NGA plasma levels is studied.

Cognition
Both neuro- and social (affective) cognition present another focus of this research group. More recently the investigation of social cognition in symptomatically remitted patients suffering from serious mental illness has received much attention. To this end, a number of studies investigating facial emotion recognition and affective prosody as well as Emotional Intelligence are conducted in patients suffering from schizophrenia or bipolar disorder, their healthy siblings as well as healthy control subjects, to identify social cognitive deficits as potential trait markers for these disorders.

These studies also explore the potential role of cognitive impairment on various levels as an endophenotype for schizophrenia and/or bipolar disorder.

Resilience
Three ongoing studies investigate resilience and its biological correlates in patients with schizophrenia and bipolar disorder with a focus on religion and culture. The primary aim of these studies is to investigate transcultural differences in resilience across patients from two different geographical regions, Austria and Japan, that have different religious and cultural backgrounds (i.e. Christianity and Buddhism).

Another study investigates the degree and quality of resilience as well as its correlates (e.g. hope, self-esteem, social support) across 200 female and 200 male students from local universities. Using 3 T-MRI and fMRI and focusing on sex differences, we will subsequently examine potential structural and functional cerebral differences in subjects with a high degree of resilience compared to subjects with a low degree of resilience.

Psychooncology, Quality of Life, Outcomes Research
Bernhard Holzner
In close collaboration with the Department of Psychosomatics, this group studies psychological outcomes in cancer patients,

applying late breaking statistical and technical methodology. Health related quality of life is the main outcome variable and hand held computer based self-assessments analysed by item response theory are used to develop computer-adapted questionnaires, adding a detailed subjective (patient-related outcome) assessment of the psychological health status of cancer patients. Some of this work is done under the aegis of EORTC and with a support of the oncology units in the Departments of Hematology and Gynecology of the MUI.

Substance use Disorder, Clinical
Sergei Mechtcheriakov - Claudia Rupp

A 27 bed alcohol rehabilitation inpatient unit as well as a large outpatient clinic for patients suffering from substance-related and addictive disorders from the illegal spectrum are the base for research in this clinical field. Much emphasis is devoted to neuropsychological deficits in patients suffering from chronic alcoholism and their impact on the development and sustenance of alcoholism as well as their relevance with respect to treatment outcomes. Individually tailored cognitive training measures are employed to support structured treatment programs.

The effect of chronic alcohol intake on bone metabolism is another area of interest in this research group. In collaboration with the Department of Endocrinology the influence of alcohol on bone mineral density and various biomarkers involved in it is explored.

With respect to illegal drugs, patients in methadone and opiate substitution programs constitute a large group of interest. Currently, preferences for the different drugs available in substitution programs and the relevance of subjective attitude are studied.

Selected Publications

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Selected Funding

- Improving usability of the EORTC questionnaires in daily clinical practice by elaborated QoL result presentation in CHES-EORTC, EORTC Quality of Life Group, 2012–2014
- Web-based patients reported outcome monitoring in cancer patients (WEB-PROM), Austrian National Bank (ÖNB), 2011–2014
- Determination of European utility weights for a cancer-specific preference-based quality of life measure derived from the EORTC QLQ-C30, EORTC, 2014–2016
- Validation and scoring of the EORTC CAT measures, FWF, 2014–2017
- "Moodinflame" (Early diagnosis, treatment and prevention of mood disorders targeting the activated inflammatory response system), EU, finished 2013
- Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE)
- Alex Hofer, FWF Projektnummer: KLI-366
- Berndhard Holzner, FWF Projektnummer: P 26930 Einzelprojekte
- Johannes Giesinger, FWF Projektnummer: J 3353 Schrödinger-Programm

Collaborations

- Henning Flechtner, Magdeburg University Hospital
- Susanne Singer, Leipzig University Hospital (Stepped care project)
- Fabio Efficace, GIMEMA Group, Roma, Italy
- Hiroyuki Uchida, Keio University School of Medicine, Department of Neuropsychiatry, Tokyo, Japan
- Roger Pycha, Hospital of Brunico, Department of Psychiatry, Brunico, Italy
- European Alliance against Depression
- pro mente tirol
- University of Bergen, Norway
- University Medical Center Utrecht, Netherlands
- Zucker Hillside Hospital, New York
- European Group for Research in Schizophrenia (EGRIS)
- Keio University, Tokyo, Japan

Psychosomatic Medicine

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Keywords

Psychoimmunology, stress, depression, eating disorders, patient-reported outcome

Research Focus

- Interdisciplinary psychosomatic research: using the field of "psychoimmunology" to study psychosomatic and somatopsychic co-morbidities
- Research in eating disorders
- Research in patient-reported outcome

General Facts

Research in the field of psychosomatic medicine:
- Is concerned with the complex interactions between physical, mental and social conditions that can contribute to psychosomatic and somatopsychic comorbidities
- Is characterized by interdisciplinary approaches
  - In co-operation with the Psychiatric/ Psychotherapeutic Consultation-Liaison Service
  - In co-operation with other clinical units outside the department of Psychiatry and Psychotherapy

One major issue encountered during routine clinical work as well as in research is the subjective judgement of individual patients with regard to their mental and physical well-being. We consider this as "basic knowledge" essential for the evaluation of therapeutic concepts.

Research

Research in Psychoimmunology
Priv.-Doz. Dr. Katharina Hüffner

Psychoimmunology provides the opportunity to study the interacting biological systems that might contribute to psychosomatic and somatopsychic co-morbidities. In this context chronic stress conditions are used as a research paradigm for the investigation of individual stress reactions and related changes in neurotransmitter-pathways and immune activation.

Several immunological mechanisms might link chronic somatic disease such as breast cancer and psychological distress. One possibility is that inflammatory stimuli can influence the neurotransmitter pathways known to be important in the pathogenesis of depression. Specifically, the serotonin pathway can be influenced by cytokines which enhance the activity of the indole amine 2,3-dioxygenase (IDO) or stress hormones which can activate tryptophan 2,3-dioxygenase (TDO). Both enzymes are involved in the break-down of tryptophan (TRP) to kynureine (KYN).

The resulting TRP depletion results in lower levels of serotonin (5-HT) which could in turn increase the risk for depressive symptoms (Fig. 1). In addition to influencing the serotonergic neurotransmitter pathway, inflammatory stimuli can also affect catecholamine synthesis via the enzyme co-factor, tetrahydrobiopterin (BH4) or cytokines may reduce the availability of

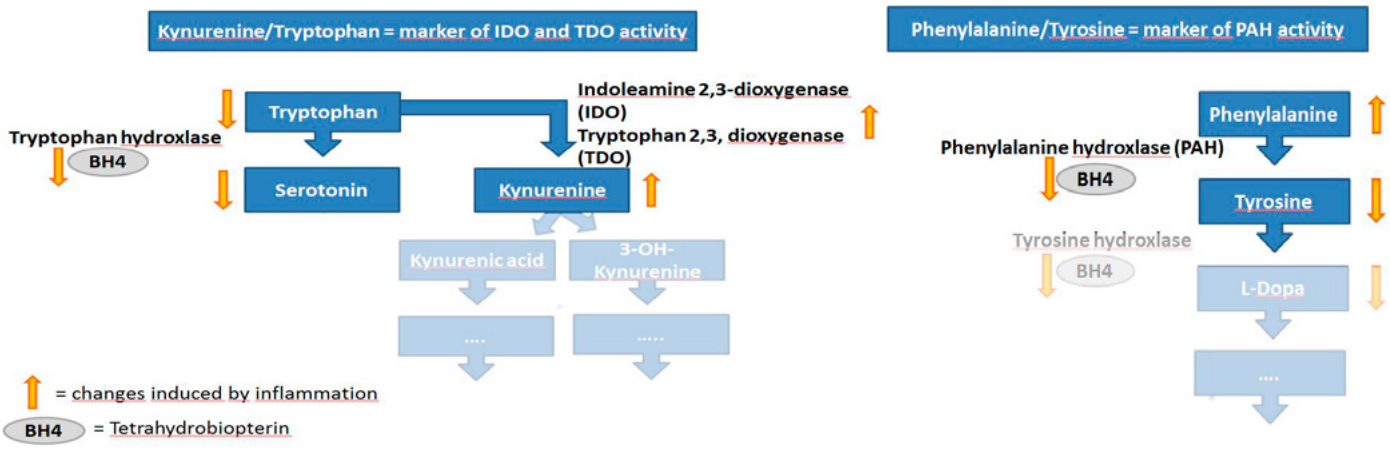

Fig. 1: Graphical depiction of the amino acid derived neurotransmitter biosynthesis pathways analyzed in our current studies. Changes induced by inflammation are indicated with an arrow.

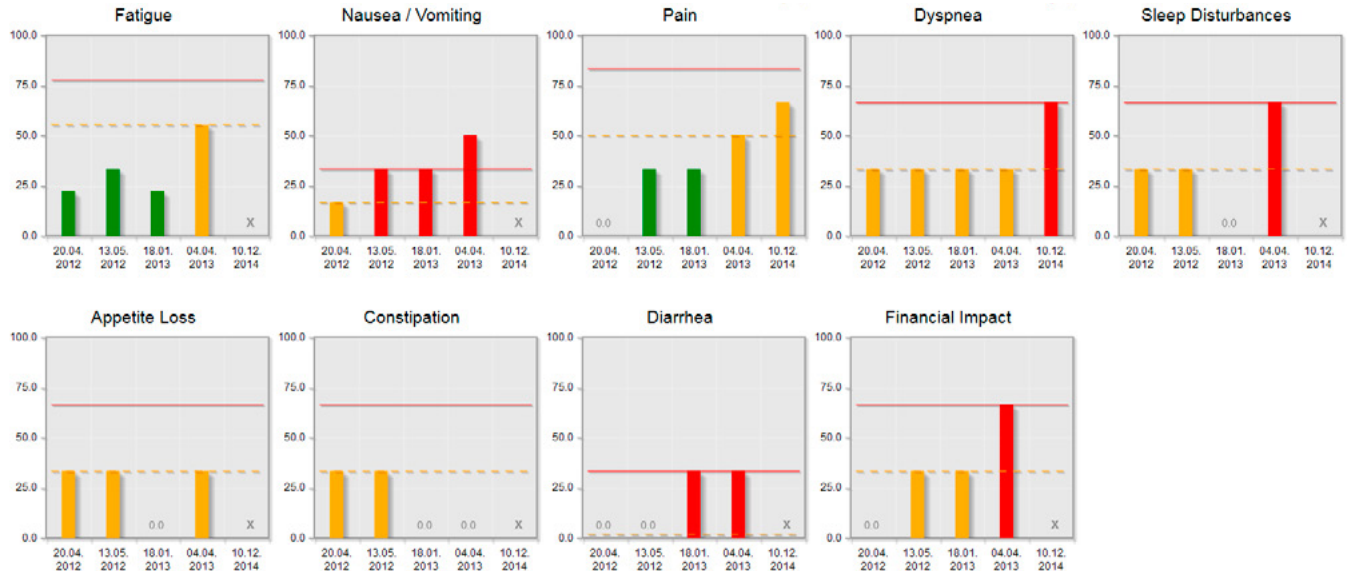

Fig. 2: Patient-reported outcome profile of an individual patient's quality of life trajectory

BH4, which is necessary for the conversion of phenylalanine ((PHE) to tyrosine/TYR) by phenylalanine hydroxylase (PAH). Tyrosine hydroxylase which converts TYR into L-3, 4-dihydroxyphenylalanine (Levodopa) is also dependent on BH4. PHE/TYR ratio is used as an estimate of PAH activity (Fig. 2).

Notably, also tryptophan hydroxylase, an enzyme that converts TRP to 5-HT, is dependent on BH4. Currently, we study healthy probands as well as patients with depression and depressive adjustment disorder with and without chronic somatic disorders (e.g. cancer). These projects are being carried out together with various cooperation partners within the Medical University Innsbruck such as the Division of Biological Chemistry at the Biocenter and the Department of Gynaecology and Obstetrics and are supported by the EU grant "moodinflame" (Early diagnosis, treatment and prevention of mood disorders targeting the activated inflammatory response system – finished 2013) and an ongoing ÖNB grant (Platelet function as a biomarker for depression – Can acute mental stress increase the diagnostic value?, 01.01.2013 –31.12.2015).

Research in Eating Disorders
Univ.-Prof. Mag. Dr. Barabara Mangweth-Matzek

Present research is focused on various aspects of clinical eating disorders: We currently study a) addictive symptoms in anorexic and bulimic patients, b) cultural differences and traumatic childhood in obese patients who undergo bariatric surgery. We also perform epidemiological studies, e.g. middle aged males; and between female and male fitness-centre-sports activists with regard to eating behaviour, quality of life, and mood.

Patient-Reported Outcome
Univ.-Doz. Dr. Bernhard Holzner

A major research focus of our group in 2013 and 2014 was the evaluation of medical treatments and the impact of chronic diseases from a patient's perspective. We have conducted a number of patient-reported outcome (PRO) studies in cancer patients investigating clinical as well as methodological research questions. Currently, we are extending our PRO research activities beyond oncology and are planning and conducting studies in further medical fields in addition to those performed in- and outpatient groups from the Division of Psychosomatic Medicine.

Selected Publications

The menopausal transition–a possible window of vulnerability for eating pathology. Mangweth-Matzek Barbara, Hoek Hans W, Rupp Claudia, Kemmler Georg, Pope Harrison G-Jr, Kinzl Johannes. INTERNATIONAL JOURNAL OF EATING DISORDER. 2013; 46(6): 609–616.

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Bioprofiling of plateletes in medicated patients with depression. Hüfner Katharina, Kandler Christina, Koudouovoh-Tripp Pia, Egeter Jonas, Hochstrasser Tanja, Stemer Bettina, Malik Peter, Giesinger Johannes, Humpel Christian, Sperner-Unterweger Barbara.
JOURNAL OF AFFECTIV DISORDERS. 2014; 172: 81–88.

Pathological eating and body dissatisfaction in middle-aged and older women. Mangweth-Matzek Barbara, Hoek Hans W, Pope Harrison G.
Jr. CURRENT OPINION PSYCHIATRY. 2014; 27(6): 431–435.

Getting the whole picture: adding patient-reported outcomes to adjuvant endocrine treatment evaluation in premenopausal breast cancer patients. Oberguggenberger Anne, Goebel Georg, Beer Beate, Oberacher Herbert, Meraner Verena, Sztankay Monika, Sperner-Unterweger Barbara, Zeimet Alan G, Marth Christian, Hubalek Michael, Holzner Bernhard.
THE BREAST JOURNAL. 2014; 20(5): 555–557.

Selected Funding

- "Moodinflame" (Early diagnosis, treatment and prevention of mood disorders targeting the activated inflammatory response system), EU, finished 2013
- Platelet function as biomarker of depression – Can acute mental stress increase the diagnostic value? Österreichische Nationalbank, 01.01.2013 – 31.12.2015
- Sexual health during endocrine-treatment for breast cancer, Austrian Cancer Aid, 2013–2015

Collaborations

- Harrison G. Pope, MD; Biological Psychiatry Laboratory, McLean Hospital/Harvard Medical School, Boston, USA
- Hans W. Hoek, MD; Parnassia Psychiatric Institute, The Hague/ Department of Psychiatry, Groningen University, The Netherlands / Department of Epidemiology, Columbia University, New York, USA
- Dr. K.M. Giesinger; Kantonsspital St. Gallen (Dept. of Orthopedia), St. Gallen, Schweiz
- Univ.-Prof. Dr. Henning Flechtner; Magdeburg University Hospital
- Univ.-Prof. Dr. Susanne Singer; Leipzig University Hospital (Stepped care project)
- Prof. Dr. Fabio Efficace, GIMEMA Group, Roma, Italy

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Keywords

Bio-psycho-social aspects of diseases, doctor-patient-relationship, psychotherapy

Research Focus

- Psychoneuroimmunology: investigation of psychosomatic/psychoneuroimmunological complexity
- Patient reported outcomes
- Quality of life, health psychology, well-being, psychometric assessment, questionnaire development, positive psychology
- Transplant psychology: psychosocial evaluation, treatment protocols
- Cognitive Neuroscience: neuronal processing for cognitive processes e.g. language
- Psychotraumatology and Trauma Therapy
- Psychotherapy research concerning emotions, diagnosis, efficacy and delivery

General Facts

The **Psychoneuroimmunology Laboratory** run by ao.Univ.-Prof. DDr. Christian Schubert was founded in 1995. Currently, there is strong collaborative activity with the Division of Biological Chemistry, Biocentre, Innsbruck Medical University, Innsbruck, Austria (ao.Univ.-Prof. Dr. Dietmar Fuchs).

The **Center for Advanced Psychology in Plastic and Transplant Surgery (CAPPTS)** represents a psychological center of excellence that is dedicated to the psychosocial evaluation of different transplant candidates, particularly of living kidney donors and recipients as well as other candidates undergoing reconstructive or solid organ transplantation.

The research group **Cognitive Neuroscience** cooperates locally and internationally. The facility "Lab for Cognitive Neurosciences Innsbruck" is fully equipped with electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS), and behavioural measuring methods suitable for studies in infants, children, adults, and patients.

The working group **"Psychotraumatology and Trauma Therapy"** examines the effects of specific trauma-therapeutic treatment in patients with complex post-traumatic stress disorders (cPTSD) and in patients with dissociative disorders. In this project the group works together with European research groups.

A **broad training of medical students in doctor-patient-relationship and communication** is one major task. A psychotherapeutic inpatient and mainly outpatient clinic gives the opportunity for research in this clinical field. In 2014, a highly competitive grant from the Austrian Science Foundation (P 27228-G22) was received to focus on the health and wellbeing of

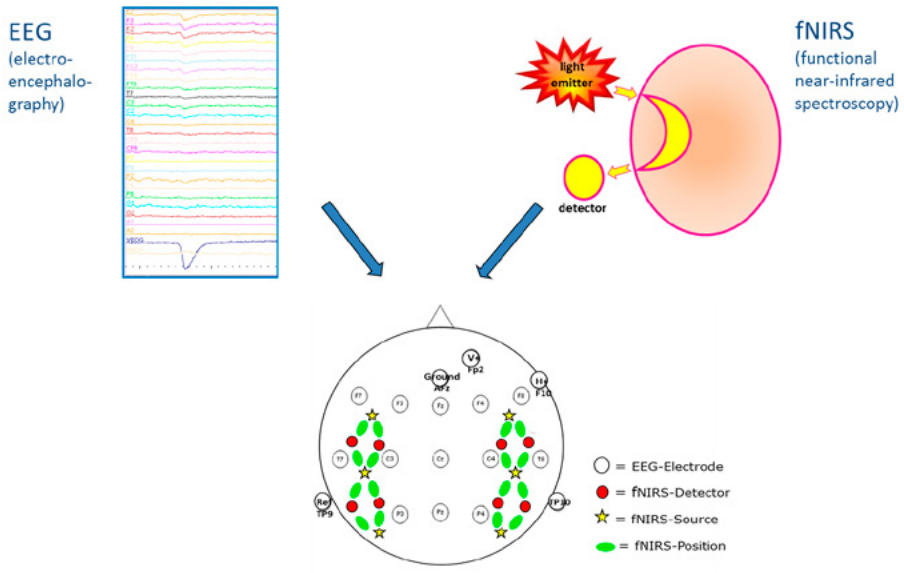

Fig. 1: Simultaneous assessment of electrophysiological and vascular signals by means of the electroencephalography and the functional near-infrared spectroscopy.

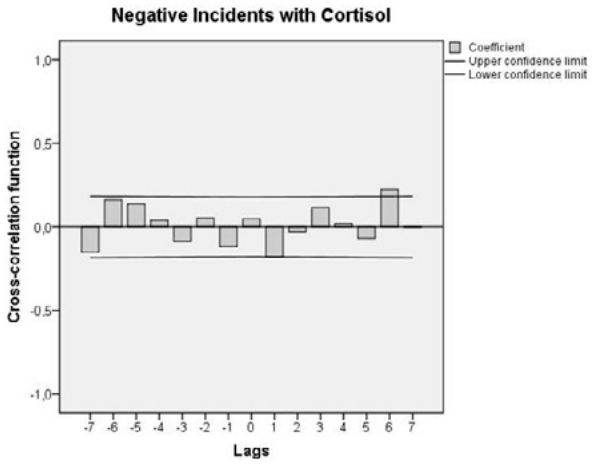

Fig. 2: Negative Incidents with Cortisol.

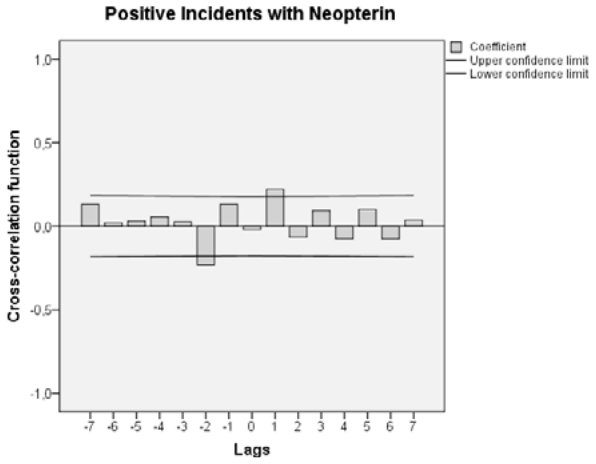

Fig. 3: Positive Incidents with Neopterin.

medical students and practitioners. In particular health professionals in the medical field are prone to burnout. This research project focuses on identifying key factors to promote health and wellbeing throughout the medical curricula. The unique approach is to investigate environmental (work- and organisational psychology) as well as personal factors (health psychology, positive psychology) together to determine pathways to health and wellbeing throughout the professional life.

Research

Psychoneuroimmunology
Christian Schubert

Stress system dynamics during "life as it is lived": integrative single-case studies on healthy women and women with LE, breast cancer, depression *et al.*

Transplantation Psychology
Martin Kumnig

Psychological assessments are crucial for the evaluation and optimization of the suitability of transplant patients, considering solid organ or vascularized composite allotransplantation (VCA). Psychological assessment is mandatory for living kidney donation.

Lab for Cognitive Neurosciences
Sonja Rossi

The research group "Cognitive Neuroscience" focuses primarily on neuronal processing mechanisms during first and second language acquisition in infancy and adulthood. Neuronal markers are assessed by means of the electroencephalography (EEG) and the near-infrared spectroscopy (fNIRS), both adoptable also simultaneously.

Health Psychology
Stefan Höfer

Research focuses on two key areas: the fist key area is the development of international patient reported outcome measures in different areas (i.e. heart disease) and different languages worldwide (i.e. Swedish, Danish, Norwegian). The application of health psychological theories to enhance the quality of life and wellbeing of patients and the general population is the second key area. Recently together with the European Health Psychological Society and the Federation of Austrian Associations of Psychologists Prof. Höfer hosted the 28th Conference of European Health Psychology Society with over 800 participants.

Psychotraumatology and Trauma Therapy
Astrid Lampe

In addition to the main task of trauma therapy, the effects of training measures to sensitize medical professionals for domestic violence are reviewed and possible negative consequences of traumatic events are surveyed regarding the prevalence for illnesses. Within the project "The experience and the stress processing of executives in emergency organisations" two measure packages have been developed; on one hand a self-management tool for executives which helps the affected executives to efficiently adjust their stress load, on the other hand a guide for psychosocial experts for the professional support of stress-loaded executives. The annual meeting of the Society for Psychotraumatology (DeGPT) 2015 took place in Innsbruck. The focus was on the health consequences of severe stress in childhood, epigenetics, and brain development after traumatic stress in childhood.

Selected Publications

OPD-2 – Operationalisierte Psychodynamische Diagnostik: Das Manual für Diagnostik und Therapieplanung. (Ed.; u.a. G. Schüßler), Hans Huber. Arbeitskreis OPD. 2014.

The first step is the hardest – emotion recognition in patients with somatoform disorders. Beck Thomas, Breuss Margit, Kumnig Martin, Schüßler Gerhard.
ZEITSCHRIFT FÜR PSYCHOSOMATISCHE MEDIZIN UND PSYCHOTHERAPIE. 2013; 59: p. 385–390.

Psychoneuroimmunologie des Lebenslaufs: Einfluss von Stress in der Kindheit auf Immunfunktionsstörung und entzündliche Erkrankung im weiteren Leben. Schubert Christian.
PSYCHOTHER PSYCHOSOM MED PSYCHOL. 2014; 64: p. 171–180.

Is there a link between physical activity and alcohol use?. Kopp Martin, Burtscher Martin, Kopp-Wilfling Prisca, Ruedl Gerhard, Kumnig Martin, Ledochowski Larissa, Rumpold Gerhard.
SUBST USE MISUSE. 2015; 50: p. 546–51.

[Patterns of dysfunctional parenting styles and psychological disturbances in offspring]. Kumnig Martin, Höfer Stefan, Alexandra Huber, Messner Carmen, Renn Daniela, Mestel Robert, Klingelhöfer Jürgen, Kopp Martin, Dören Stephan, Schüßler Gerhard, Rumpold Gerhard.
PSYCHOSOMATISCHE MEDIZIN UND PSYCHOTHERAPIE. 2013; 59: p. 356–368.

An overview of psychosocial assessment procedures in reconstructive hand transplantation: The past, present, and future in psychosocial assessemnt of patients undergoing for reconstructive hand transplantation. Kumnig Martin, Jowsey-Gregoire Sheila G, Morenao Elisa, Brandacher Gerald, Azari Kodi, Rumpold Gerhard.
TRANSPLANT INTERNATIONAL. 2013; 27: p. 417–427.

Electrophysiological evidence for modulation of lexical processing after repetitive exposure to foreign phonotactic rules. Rossi Sonja, Hartmüller Tobias, Vignotto Micol, Obrig Hellmuth.
BRAIN AND LANGUAGE. 2013; 127: p. 404–414.

Selected Funding

- Optimizing patient/doctor interaction at the breast cancer unit at the LKH/Tirol, Land Tirol Qualitätsförderungsprogramm 2011–2013, Christian Schubert
- Language learning in monolingual and bilingual infants, 2013–2015 Marie Curie Intra-European Felloship awarded by the European Commission, Sonja Rossi
- Austrian Science Foundation 2014–2017, Stefan Höfer

Collaborations

- Multiple international cooperations, s.a.

Child and Adolescent Psychiatry

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Keywords

Child and adolescent psychiatry, child and adolescent psychology, clinical psychiatry, psychopathology, psychotherapy, personality disorders, eating disorders, attachment research, internet addiction, cyber-mobbing

Research Focus

Assessment and Course of Personality Disorders in Adolescence
The diagnosis of personality disorders (PD) in adolescence has long been controversially discussed in the research literature. Major concerns include the validity and stability of diagnosing PD, the heterogeneity of the psychopathological profile and stigmatisation in that age group.

Even though studies on temperament and personality provide evidence that the main ingredients of adult PD are present during puberty, only very little is known about the course of these disorders in adolescents. Therefore, the purpose of this study is to examine underlying dimensions (e.g. attachment patterns, emotion regulation, integration level of mental structure) mediating the course and outcome of PD in adolescents. Furthermore, we are interested in examining possible links between attachment representations, symptom severity, comorbid disorders, course and outcome in adolescent patients with PD.

Attachment and Eating Disorders in Adolescence
The emerging body of attachment research in patients with eating disorders (ED) provides a promising insight into the interplay between environmental, social and individual factors and how they contribute to the development of this complex and painful condition. The aim of our research is to assess attachment representations in adolescent patients with Anorexia Nervosa or Bulimia Nervosa. We will analyze attachment themes concerning parent-child relationships and experiences of separation, abuse and loss in the attachment narratives of our adolescent ED patients.

Additionally, we are interested in the links between attachment representations, symptom severity, comorbid disorders and personality pathology. One of the most challenging directions taken by attachment researchers focuses on the influence of attachment representations on the course and outcome of mental disorders. To date, there is no study investigating that influence in adolescent patients with ED. Thus, we want to examine the influence of attachment representations on the outcome and also, for the first time, analyse how far attachment can change after treatment.

General Facts

New research unit with a special focus on personality pathology and attachment research in child and adolescent psychiatry

Collaborations inside MUI:

Neuropsychoimmunology in Adolescent Patients with Eating Disorders
ao.Univ.-Prof. Dr. Dietmar Fuchs, Section for Biological Chemistry, Biocenter Innsbruck
Neural correlates and personality pathology in adolescents with eating disorders (Univ.-Prof. Dr. Elke Gizewski, Department of Radiology, Medical University of Innsbruck)

Dr. Astrid Bock, Postdoc Researcher

Dr. Manuela Gander, Postdoc Researcher

Dr. Martin Fuchs, Specialist for Child and Adolescent Psychiatry

Research

Assessment and Course of Personality Disorders in Adolescence
Prof. Dr. Kathrin Sevecke,
Dr. Manuela Gander, Dr. Astrid Bock
The purpose of this study is to examine underlying dimensions (e.g. attachment patterns, emotion regulation, integration level of mental structure) mediating the course and outcome of PD in adolescents.

Furthermore, we are interested in examining possible links between attachment representations, symptom severity, comorbid disorders, course and outcome in adolescent patients with PD.

Attachment and Eating Disorders in Adolescence
Prof. Dr. Kathrin Sevecke,
Dr. Manuela Gander, Dr. Astrid Bock
The aim of our research is to assess attachment representations in adolescent patients with Anorexia Nervosa and Bulimia Nervosa and analyse their influence on the outcome.

Neuropsychoimmunology in Adolescent Patients with Eating Disorders
Prof. Dr. Dietmar Fuchs, Prof. Dr. Kathrin Sevecke
To examine relevant neurotransmitters in plasma samples of patients with Anorexia Nervosa.

Neural Correlates and Personality Pathology in Adolescents with Eating Disorders
Prof. Dr. Elke Gizewski,
Prof. Dr. Kathrin Sevecke
To investigate neural correlates of adolescents with eating disorders while watching visual food cues in an fMRI environment.

Emotional and Structural Indicators of Psychopathological Development in Adolescence
Dr. Astrid Bock
The aim of this study is to examine factors like affect regulation and emotion recognition that might contribute to the early onset of psychopathology in adolescence.

Internet-Addiction and Cyber-Mobbing in Psychiatric Patients
Dr. Martin Fuchs,
Prof. Dr. Kathrin Sevecke
The major aim of this study is to analyse the prevalence rates of internet-addiction and cyber-mobbing experiences in psychiatric in- and outpatients.

Assessing Trauma in Children and Adolescents
Univ.-Prof. Dr. Barbara Juen,
Prof. Dr. Kathrin Sevecke
This study aims to improve the assessment of trauma and analyse consequences of traumatic experiences in children and adolescents.

Selected Publications

Autismus oder „Psychopathy"? Roberz J, Lehmkuhl G, Sevecke K Forensische Psychiatrie, Psychologie, Kriminologie. 2013, 7:282–289.

Tierquälerei als Symptom von Callous-Unemotional Traits bei inhaftierten Jungen und Mädchen. Sevecke K, Franke S, Krischer M Kindheit und Entwicklung. 2013, 22(3):165–173.

Schulabsentismus bei Kindern und Jugendlichen – Beilage zum Fachjournal „neuropsychiatrie – vereinigt mit psychiatrie und psychotherapie". Sevecke K; 2014.

Grenzfall ADHS – Diagnose und Differentialdiagnose im Volksschulalter: A Review. Bonatti E, Küng A, Sevecke K.
Zeitschrift Neurologie Psychiatrie. Jatros 2014 (12–14).

Das dimensional-kategoriale Hybridmodell für Persönlichkeitsstörungen im DSM-5 aus jugendpsychiatrischer Perspektive – Kritik und Ausblick. Sevecke K, Schmeck K, Krischer M. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie. 2014, 42 (4), 279–283.

Persönlichkeitspathologie und Psychopathie bei verhaltensauffälligen, delinquenten Jugendlichen. Sevecke K, Maya K, Krischer und Gerd Lehmkuhl.
Buch: Kriminologie-Jugendkriminalrecht-Strafvollzug. Herausgeber Frank Neubacher, Michael Kubink. Band 59 Drucker & Humblot. Berlin 2014.

Borderline-Störungen und selbstverletzendes Verhalten. Sevecke K, Krischer M, In G Lehmkuhl, F Poustka, M Holtmann & H Steiner. Praxishandbuch Kinder- und Jugendpsychatrie. Hogrefe, ISBN: 978-3-8017-2538-9 (2014).

Die Psychoptahy-Checkliste für Jugendliche. Sevecke K, Krischer M. Hogrefe. 2014.

Attachment classification, psychophysiology and frontal EEG asymmetry across the lifespan. Gander M & Buchheim A.
Frontiers in Human Neuroscience. 9 (79): 1–16.

Eating disorders in adolescence: Attachment issues from a developmental perspective. Gander M, Sevecke K & Buchheim A. Frontiers in Psychology. 2015;6: 1–12.

Collaborations

- Univ.-Prof. Dr. Anna Buchheim, Institute of Psychology at the University of Innsbruck, Austria
- Univ.-Prof. Dr. Barbara Juen, Institute of Psychology at the University of Innsbruck, Austria
- Univ.-Prof. Dr. Svenja Taubner, Institute of Psychology at the Alpen-Adria University of Klagenfurt, Austria
- Dr. Florian Juen, KBO Child Center Munich, Germany
- Prof. Dr. med. Dipl. Psych. Klaus Schmeck, KJPK Basel, Switzerland
- PD Dr. Maya Krischer, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Cologne, Germany

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Keywords

Stroke research, multiple sclerosis (MS), neurocritical care, parkinson's disease (PD), multiple system atrophy (MSA), REM sleep behavior disorder, RBD, RLS, computational neuroscience

Research Focus

The clinical Department of Neurology at the Medical University of Innsbruck has an internationally established research focus in the fields of epidemiology and pathophysiology of ischemic stroke, neurocritical care (including infectious diseases of the nervous system), Parkinson's Disease, MSA and degenerative movement disorders. In addition, the department is the only academic institution in Austria with an internationally recognized and certified sleep laboratory with a focus on research into the field of sleep-related movement disorders. The Division of Neurobiology is focused on animal modelling of neurodegeneration with an emphasis on multiple system atrophy. A recently established professorship for computational science is concerned with establishing novel image analysis algorithms for MRI datasets.

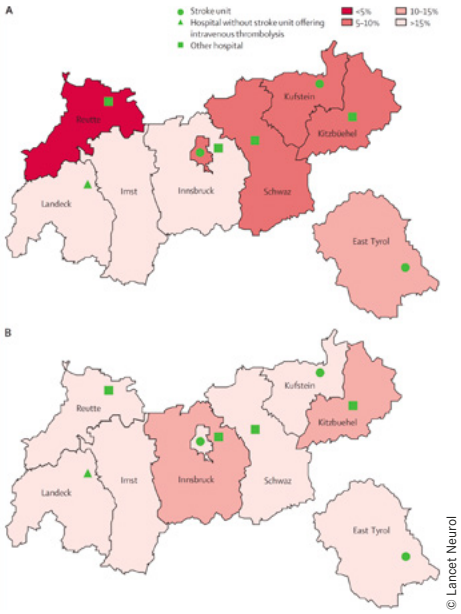

Fig. 1: Thrombolysis administration in the nine countries of Tyrol in 2010 (A) and 2013 (B).

General Facts

The Department of Neurology at Innsbruck Medical University has a total of 114 in-patient beds including a stroke unit (8 beds), a neurocritical care unit (10 fully-ventilated beds, 6 post-immediate care beds), an epilepsy monitoring unit (4 beds) and a dedicated sleep laboratory (6 beds). The department acts as a referral center for the entire spectrum of neurological diseases encompassing the entire area of the state of Tyrol and neighbouring areas. Furthermore, the department receives referrals on an Austria-wide scale when second opinions and specialized diagnostic and therapeutic procedures are required. The large number of patients received into the department each year (more than 6,000 in-patient admissions per year, close to 40,000 out-patient contacts per year) results in a significant clinical routine workload. Key collaborations in the field of clinical routine include joint programs with the Department of Neurosurgery, in particular vascular surgery, neurooncology, epilepsy surgery and deep brain stimulation for movement disorders. Equally close collaborations exist with the Departments of Neuroradiology and Vascular Surgery and Cardiology in the field of stroke medicine. Research collaborations in the field of neuroimaging are centered upon the Department of Neuroradiology and Nuclear Medicine. Dedicated research infrastructures within the clinical department include the Division of Neurobiology (animal modelling of neurodegeneration), the neurological research laboratory (focus on biomarker research and neuroimmunology), as well as the recently established computational neuroscience unit for the development of novel image analysis algorithms.

Research

Research Group Stroke
Group leaders:
Univ.-Prof. Johann Willeit
Univ.-Prof. Stefan Kiechl,
Priv.-Doz. Michael Knoflach

Research priorities of the neurovascular research group include acute and post-acute stroke care, cardiovascular risk prediction as well as cardiovascular ageing. Based on the internationally well-respected Bruneck Study, a population based longitudinal cardiovascular health study that has been running for 25 years, state of the art biomarker research is conducted in an international cooperation with a focus on the lipidome and the role of micro RNAs in atherogenesis. The neurovascular research group participates in in large international research and meta-analysis consortia (steering/writing committee: FSC, ERFC, LSC, NPSC, IMT-PROG, GBD, various GWA studies).

The evaluation of the effect of the optimization of the Tyrol wide stroke treatment pathway received broad international acclaim (Fig. 1). Risk prediction after TIA as well as impact of differences in stroke unit management on treatment

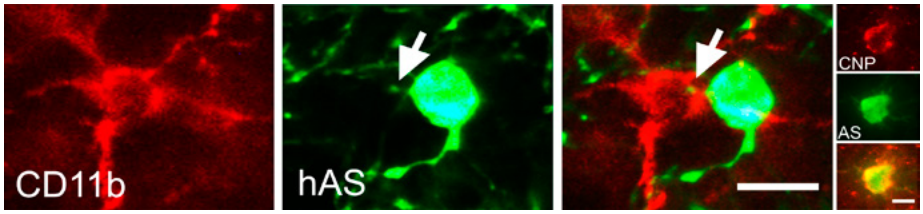

Fig. 2: Involvement of microglia (CD11b) in the clearance of α-synuclein (hAS) in a model of MSA with accumulation of AS in oligodendroglia (CNP).

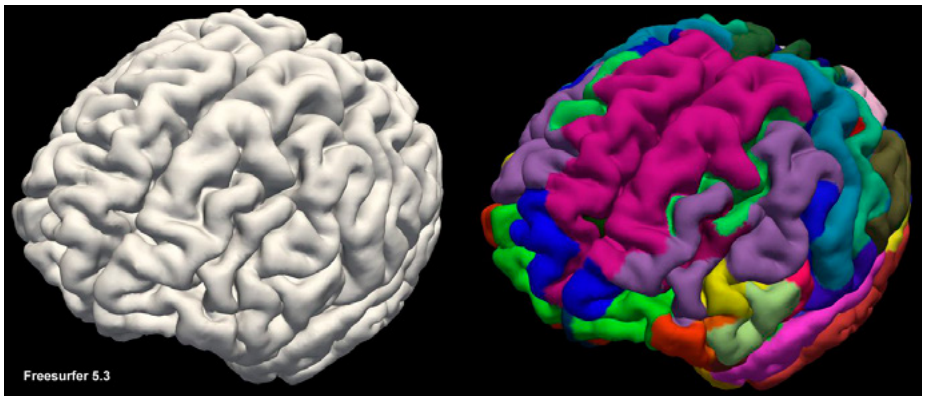

Fig. 3: Three-dimensionally reconstructed human brain based on a T1-weighted MRI sequence using FreeSurfer brain-analyzing tool. The silver-coloured image represents the calculated surface model of a human cerebral cortex with its detailed gyrification. Colour-coded cortical labels of both hemispheres reflecting various anatomical regions are illustrated in the left image. Data can be used to investigate regional and tissue specific neuroanatomical variations.

delays are addressed as part of the Austrian Stroke Unit Collaboration and Registry. Different approaches to post stroke care are currently tested in a large scale randomized disease management project (Stroke Card). Johann Willeit and Stefan Kiechl head the 'Research Center of Excellence in Vascular Ageing – Tyrol' which has its headquarters in Innsbruck (4.3 Mio €) (Fig. 1).

Research Group Multiple Sclerosis and Neuroimmunology
Group leaders:
Univ.-Prof. Thomas Berger,
Univ.-Prof. Florian Deisenhammer,
Univ.-Prof. Markus Reindl
Grounded in long-lasting and excellent research collaborations the main research topics are related to pathomechanisms, clinical and therapeutic aspects of autoimmune CNS and PNS disorders: multiple sclerosis (MS), antibody-associated neurological disease (neuromyelitis optica [NMO], acute disseminated encephalomyelitis or NMDAR-encephalitis) and immune neuropathies. Thus, scientific foci are the role of human autoantibodies directed against different CNS tissue antigens (mainly MOG, AQP4 and NMDA-R) and neutralizing antibodies in the monitoring of various MS treatments. These research activities are complementary to and translatable to our neurological laboratory diagnostics. In addition, extensive databases for MS and NMO have been established, which are of paramount importance for past and current national and international research activities.

Research Group Neurocritical Care and Infectious Diseases of the Nervous System
Group leaders:
Univ.-Prof. Erich Schmutzhard*,
Priv.-Doz. Ronny Beer,
Priv.-Doz. Raimund Helbok*
The study group focuses both on clinical and translational research. Invasive multimodal neuromonitoring, covering structural (imaging), metabolic (microdialysis, pbtiO2, CBF), functional monitoring (electrocorticography – COSBID) and the clinical aspects of neurocritical care (blood pressure management, nosocomial infections, ventilator associated pneumonia etc.) are major foci in the departments research. Murine aneurysmatic subarachnoid haemorrhage and murine cerebral malaria are the basis for translational research. Beyond that, infectious diseases of the nervous system and tropical neurology (cerebral malaria, helminthic diseases of the brain, epilepsy in tropical countries) are a major focus of this research group.
**state funded position (TirolKliniken) with active research grants in MUI*

Research Group Movement Disorders
Group leaders:
o. Univ.-Prof. Werner Poewe,
Priv.-Doz. Sylvia Bösch*,
Univ.-Prof. Christoph Scherfler,
Univ.-Prof. Klaus Seppi,
Univ.-Prof. Gregor Wenning
Movement disorder groups at the Department of Neurology and their partners at MUI have established an internationally recognized clinical research programme focusing on degenerative movement disorders including Parkinson's disease and related syndromes. Major contributions have been made in the field of clinical trials in PD, rating scale development for PD and MSA, natural history and imaging studies in parkinsonian syndromes and other movement disorders, with key papers in major journals such as Neurology, Brain or Lancet Neurology.

The research group is involved in multiple international research consortia and networks and between 2013 and 2014 has authored and co-authored a total of 86 papers in peer-reviewed journals. Recent clinical research projects have focused on the epidemiology, genetics and natural history of PD, MSA and other movement disorders including HD and ataxias, on the validation of imaging and biomarker studies for PD, MSA, ataxias and related disorders, on the development, clinimetrics and validation of new rating scales for PD, MSA and ataxias and on clinical trials in PD and related movement disorders. Present aims are to validate biomarkers for early diagnosis and progression of PD, MSA and other movement disorders inlcuding HD and ataxias as well as to introduce clinical trials of novel therapies for these disorders including an immunisation trial against alpha-synuclein. Major achievements to date include the identification of risk factors and prodromal markers for the development of Parkinson's disease and a natural history study of multiple system atrophy. Future goals of the department encompass a better characterization of premotor PD and clinical trials on novel therapeutics for PD, MSA and other movement disorders.
**state funded position (TirolKliniken) with active research grants in MUI*

Research Group Sleep Medicine
Group leader:
Univ.-Prof. Birgit Högl,
Univ.-Doz. Birgit Frauscher
The Sleep Disorders Research Group and Sleep Disorders Clinic at the Department of Neurology have a highly modernized clinical sleep laboratory and a large sleep disorders outpatient clinic. The unit serves the whole spectrum of clinical sleep medicine including insomnia, sleep breathing disorders, narcolepsy and other hypersomnia syndromes, circadian disorders, parasomnias (such as sleep walking and REM sleep behavior disorder) and other sleep disorders, namely restless legs syndrome (RLS).

Fig. 4: SINBAR Study Group / Department of Neurology.

For specific clinical questions regular and expanded polysomnography are performed (expanded refers to, among others, additional EMG or EEG channels, transcutaneous capnography, etc.) as well as multiple sleep latency tests, maintenance of wakefulness tests, actigraphy, pupillographic sleepiness test, DLMO etc. The Sleep Research Group and Sleep Disorders Clinic have three board certified expert neurologists/sleep specialists and one board certified sleep technician, and additional highly trained staff. The RLS outpatient clinic has been recognized as a Willis-Ekbom disease quality care Center by the Willis-Ekbom disease/RLS foundation. In addition, the sleep research group at the Department of Neurology is entertaining a long-standing collaboration with the sleep group at Barcelona University (SINBAR Study Group) which has resulted in more than 10 high-level publications over the past few years (Fig. 3).

Division of Neurobiology
Group leaders:
Univ.-Prof. Gregor K. Wenning,
Priv.-Doz. Nadia Stefanova

The research programme at the Division of Neurobiology focuses on multiple system atrophy (MSA), a neurodegenerative disorder associated with autonomic failure, ataxia and parkinsonism. Over the last decade our research group has made important contributions regarding clinical presentation, diagnostic tools and pathogenesis of MSA. We are especially interested in α-synuclein mediated oligodendroglial pathology that includes protein misfolding and aggregation as well as cell-to-cell propagation. We identified fundamental interactions between MSA pathology and mitochondrial or proteolytic stress. The latter contribute to the specific neuronal vulnerability in MSA and represent powerful interventional targets. We were the first to demonstrate that the toll-like receptor 4 (TLR4) promotes α-synuclein clearance by microglia (Fig. 2).
More recently our work also involved preclinical screening of candidate neuroprotective and neuroregenerative strategies that are currently being evaluated for safety and efficacy in controlled clinical trials

Computational Neuroscience:
Group leader:
Univ.-Prof. Christoph Scherfler

The research unit for Computational Neuroscience was established at the Department of Neurology in October 2014 to accommodate and support existing research groups in the field of MRI and PET image analysis. The unit is tightly intertwined with the Department of Neuroradiology and has broad access to the MRI core facility, equipped with a dedicated 3 Tesla research tomograph. Members of the laboratory are developing and exploring mathematical models of structural and functional image analysis that will be translated into routine neurological and radiological assessment of patients with CNS disorders. Due to a long-lasting expertise in the field of movement disorders the main focus of our research is in the area of neurodegenerative parkinsonian disorders and has recently been extended to neurodegenerative dementias, sleep disorders and intracranial hemorrhages.

Selected Publications

Research Group Stroke:
1. Thrombolysis and clinical outcome in patients with stroke after implementation of the Tyrol Stroke Pathway: a retrospective observational study. Willeit J, Geley T, Schöch J, Rinner H, Tür A, Kreuzer H, Thiemann N, Knoflach M, Toell T, Pechlaner R, Willeit K, Klingler N, Praxmarer S, Baubin M, Beck G, Berek K, Dengg C, Engelhardt K, Erlacher T, Fluckinger T, Grander W, Grossmann J, Kathrein H, Kaiser N, Matosevic B, Matzak H, Mayr M, Perfler R, Poewe W, Rauter A, Schoenherr G, Schoenherr HR, Schinnerl A, Spiss H, Thurner T, Vergeiner G, Werner P, Wöll E, Willeit P, Kiechl S. (2015);
Lancet Neurol. 14:48–56.

2. Prediction of cardiovascular disease risk with lipoprotein(a): prospective 15-year outcomes. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, Xu Q, Mayr A, Willeit J, Tsimikas S (2014);
In the Bruneck Study. JACC 2014;64:851–60.

3. Lipidomics profiling and cardiovascular disease risk in the prospecitive population-based. Stegemann C, Pechlaner R, Willeit P, Langley S, Santer P, Rungger G, Willeit J, Kiechl S, Mayr M (2014); Bruneck Study. Circulation 129:1821–31.

4.Blockade of receptor activator of nuclear factor-kB (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. Kiechl S, Wittmann J, Giaccari A, Knoflach M, Willeit P, Bozec A, Moschen A, Muscogiuri G, Sorice GP, Kireva T, Summerer M, Wirtz S, Luther J, Mielenz D, Billmeier U, Egger G, Mayr A, Oberhollenzer F, Kronenberg F, Orthofer M, Penninger J, Meigs JB, Bonora E, Tilg H, Willeit J, Schett G (2013);
Nature Medicine. 19:358–63.

5. Circulating microRNAs as novel biomerkers for platelet activation. Willeit P, Zampetaki A, Dudek K, Kaudewitz D, King A, Kirkby NS, Crosby-Nwaobi R, Prokopi M, Drozdov I, Langley S, Sivaprasad S, Markus HS, Mitchell JA, Warner T, Kiechl S, Mayr M (2013);
Circ Res 112:595–600.

Research Group Multiple Sclerosis and Neuroimmunology
1. Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. Titulaer MJ, Hoeftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, Benson LA, Shu H, Irioka T, Hirano M, Singh G, Cobo C, Alvaro K, Kenichi Morales PS, Wirtz PW, Yamamoto T, Reindl M, Rosenfeld MR, Graus F, Saiz A, Dalmau J. Ann Neurol. 2014; 75: p. 411–428.

2. Guidelines for uniform reporting of body fluid biomarker studies in neurologic disorders. Gnanapavan S, Hegen H, Khalil M, Hemmer B, Franciotta D, Hughes S, Hintzen R, Jeromin A, Havrdova E, Tumani H, Bertolotto A, Comabella M, Frederiksen J, Alvarez-Cermeno JC, Villar L, Galimberti D, Myhr KM, Dujmovic I, Fazekas F, Ionete C, Menge T, Kuhle J, Keir G, Deisenhammer F, Teunissen C, Giovannoni G.
Neurology. 2014; 83: p. 1210–1216.

3. Antigen-Specific Tolerance by Autologous Myelin Peptide-Coupled Cells: A Phase 1 Trial in Multiple Sclerosis. Lutterotti A, Yousef S, Sputtek A, Stuerner KH, Stellmann JP, Breiden P, Reinhardt S, Schulze C, Bester M, Heesen C, Schippling S, Miller SD, Sospedra M, Martin R.
Science Translational Medicine. 2013; 5.

4. The spectrum of MOG autoantibody-associated demyelinating diseases. Reindl M, Di Pauli F, Rostasy K, Berger T.
Nature Reviews Neurology. 2013; 9: p. 455–461.

Research Group Neurocritical Care and Infectious Diseases of the Nervous System:
1. Higher brain extracellular potassium is associated with brain metabolic distress and poor outcome after aneurysmal subarachnoid hemorrhage. Antunes AP, Schiefecker AJ, Beer R, Pfausler B, Sohm F, Fischer M, Dietmann A, Lackner P, Hackl WO, Ndayisaba JP, Thomé C, Schmutzhard E, Helbok R.
Crit Care. 2014 Jun 11;18(3):R119.

2. Addressing neurologic needs in sub-Saharan Africa: An opportunity for multisociety cooperation. Bower JH, Diop AG, Gouider R, Schmutzhard E.
Neurology. 2014 Sep 23;83(13):1207–9.

3. Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. Intracranial pressure and cerebral perfusion pressure monitoring in non-TBI patients: special considerations. Helbok R, Olson DM, Le Roux PD, Vespa P.
Neurocrit Care. 2014 Dec;21 Suppl 2:S85–94.

4. The speed of ultraearly hematoma growth in acute intracerebral hemorrhage. Sato S, Arima H, Hirakawa Y, Heeley E, Delcourt C, Beer R, Li Y, Zhang J, Jüettler E, Wang J, Lavados PM, Robinson T, Lindley RI, Chalmers J, Anderson CS, INTERACT Investigators.
Neurology 2014; 83:2232–2238.

5. Nitric oxide synthase inhibition with the antipterin VAS203 improves outcome in moderate and severe traumatic brain injury: a placebo-controlled randomized Phase IIa trial (NOSTRA). Stover JF, Belli A, Boret H, Bulters D, Sahuquillo J, Schmutzhard E, Zavala E, Ungerstedt U, Schinzel R, Tegtmeier F, NOSTRA Investigators.
J Neurotrauma 2014; 31:1599–606.

6. A longitudinal study on nodding syndrome–a new African epilepsy disorder. Winkler AS, Wallner B, Friedrich K, Pfausler B, Unterberger I, Matuja W, Jilek-Aall L, Schmutzhard E.
Epilepsia. 2014; 55:86–93.

Research Group Movement Disorders
1. Correlation of dopaminergic terminal dysfunction and microstructural abnormalities of the basal ganglia and the olfactory tract in Parkinson's disease. Scherfler C1, Esterhammer R, Nocker M, Mahlknecht P, Stockner H, Warwitz B, Spielberger S, Pinter B, Donnemiller E, Decristoforo C, Virgolini I, Schocke M, Poewe W, Seppi K.
Brain. 2013 Oct;136(Pt 10):3028–37.

2. Substantia nigra hyperechogenicity as a marker for Parkinson's disease: a population-based study. Mahlknecht P, Seppi K, Stockner H, Nocker M, Scherfler C, Kiechl S, Willeit J, Schmidauer C, Gasperi A, Rungger G, Poewe W.
Neurodegener Dis. 2013;12(4):212–8.

3. Changing the research criteria for Parkinson's disease: obstacles and opportunities. Berg D, Lang AE, Postuma RB, Maetzler W, Deuschl G, Gasser T, Siderowf A, Schapira AH, Oertel W, Obeso JA, Olanow CW, Poewe W, STern M.
Lancet Neurol. 2013;12(5):514–24.

4. European Multiple System Atrophy Study Group. The natural history of multiple system atrophy: a prospective European cohort study. Wenning GK, Geser F, Krismer F, Seppi K, Dürr S, Bösch S, Köllensperger M, Goebel G, Pfeiffer KP, Barone P, Pellecchia MT, Quinn P, Koukouni V, Fowler CJ, Schrag A, Mathias CJ, Giladi N, Gurevich T, Dupont E, Ostergaard K, Nilsson CF, Widner H, Oertel W, Eggert KM, Albanese A, del Sorbo F, Tolosa E, Cardozo A, Deuschl G, Hellriegel H, Klockgether T, Dodel R, Sampaio C, Coelho M, Djaldetti R, Melamed E, Gasser T, Kamm C, Meco G, Colosimo C, Rascol O, Meissner WG, Tison F, Poewe W.
Lancet Neurol. 2013;12(3):264–74.

5. Movement disorders: new insights into disease mechanisms and treatment. Poewe W, Mahlknecht P.
Lancet Neurol. 2014; 13(1):9–11.

Research Group Sleep Medicine:

1. A Prospective Video-Polysomnographic Analysis of Movements during Physiological Sleep in 100 Healthy Sleepers. Stefani A, Gabelia D, Mitterling T, Poewe, W, Högl B, Frauscher B.
SLEEP MEDICINE. Sleep, 2014

2. Sleep and Respiration in 100 Healthy Caucasian Sleepers – A Polysomnographic Study According to American Academy of Sleep Medicine Standards. Mitterling T, Högl B, Schonwald V, Hackner H, Gabelia D, Frauscher B.
SLEEP. 2014 38(6):867–875.

3. Validation of an integrated software for the detection of rapid eye movement sleep behavior disorder. Frauscher B, Gabelia D, Biermayr M, Stefani A, Hackner T, Mitterling T, Poewe W, Högl B.
SLEEP. 2014; 37: p. 1663–1671.

4. Quantitative assessment of isolated rapid eye movement (REM) sleep without atonia without clinical REM sleep behavior disorder: clinical and research implications. Sasai-Sakuma T, Frauscher B, Mitterling T, Ehrmann L, Gabelia D, Brandauer E, Inoue Y, Poewe W, Högl B.
SLEEP MEDICINE. 2014; 15: p. 1009–1015.

5. Motor events during healthy sleep: a quantitative polysomnographic study. Frauscher B, Gabelia D, Mitterling T, Biermayr M, Bregler D, Ehrmann L, Ulmer H, Högl B.
SLEEP. 2014; 37: p. 763–73, 773A-773B.

Division of Neurobiology – key papers:

1. Multiple-system atrophy. Fanciulli A, Wenning GK (2015);
N Engl J Med. 372:249–263.

2. Toll-like receptor 4 is required for alpha-synuclein dependent activation of microglia and astroglia. Fellner L, Irschick R, Schanda K, Reindl M, Klimaschewski L, Poewe W, Wenning GK, Stefanova N (2013);
Glia. 61:349–360.

3. Systemic proteasome inhibition triggers neurodegeneration in a transgenic mouse model expressing human alpha-synuclein under oligodendrocyte promoter: implications for multiple system atrophy. Stefanova N, Kaufmann WA, Humpel C, Poewe W, Wenning GK (2012);
Acta Neuropathol. 124(1):51–65.

4. Toll-like receptor 4 promotes alpha-synuclein clearance and survival of nigral dopaminergic neurons. Stefanova N, Fellner L, Reindl M, Masliah E, Poewe W, Wenning GK (2011);
Am J Pathol. 179:954–963.

5. Multiple system atrophy: a primary oligodendrogliopathy. Wenning GK, Stefanova N, Jellinger KA, Poewe W, Schlossmacher MG (2008);
Ann Neurol. 64:239–246.

Selected Funding

Research Group Stroke:
In 2013 and 2014 funding was also derived from the FWF (Translational Research Project TRP 188-B12, 360 K€). The neurovascular research group participates in in large international research and meta-analysis consortia (steering/writing committee: FSC, ERFC, LSC, NPSC, IMT-PROG, GBD, various GWA studies).

Research Group Multiple Sclerosis and Neuroimmunology:
- 2013: HSRM Project, Austrian Federal Ministery of Science "BIG-WIG MS" (Markus Reindl and Thomas Berger)
- 2013: #I916-B13, Austrian Science Foundation (FWF) ERANET ERARE "Eugene Devic European Network (EDEN)" (Markus Reindl)
- 2007: #DK W1206, Austrian Science Foundation (FWF) "Doctoral program SPIN", Re-evaluation 2013 (Markus Reindl, deputy speaker and PI)

Research Group Neurocritical Care and Infectious Diseases of the Nervous System:
- "Novel Biomarkers for DCI after SAH: Microparticles Revisited", FWF(Austrian Science Fund (Project KLI 375-B00), Ronny Beer

Research Group Movement disorders:
- D. Berg: MJFF – Prospektive validation of risk markers for the development of PD. Biomarkers 2007
- C. Goetz. MJFF – Validation of Dyskinesia Rating Scales. EudraCT no. 2009-017968-17. 2009
- CHRUL (Coordinating Center Lille, France) – FAIR-PARK II – HORIZON 2020– Research agreement no. 633190. 2015

Research Group Sleep Medicine:
- I 21 20 B 27 01/2015-01/2018: Safer Screening for RBD, funding from FWF Bilateral Austria/Argentina. Project Leader: Birgit Högl
- 11/2012-10/2016: RLS-Iron: Investigation of iron metabolism in patients with idiopathic RLS, funding from the Government of Tyrol, translational research fund. Global project Leader Birgit Högl
- KLI 236 (former KLI 112) 2012–2016: Motor activity during sleep in health and disease Funded by FWF, Project Leader Birgit Frauscher. formally transferred to Gregor Wenning in 2012
- 2007–2011: Motor characterization of augmentation in restless legs syndrome, funding from the Austrian Nationalbank, Anniversary Funds. 12594 Project Leader Birgit Högl

Division of Neurobiology
- Progression of microglial activation in a mouse model of MSA. FWF Doctoral Programme SPIN DK W1206-08 (Nadia Stefanova);
- Cardiovascular phenotyping of a transgenic mouse model of multiple system atrophy, MUI-Start 2014-05-005 (Daniela Kuzdas-Wood)

Computational Neuroscience
- Hochschulraumstrukturmittel-Projekt: Neuroimage Wien Innsbruck Graz (WING)

Collaborations

Research Group Neurocritical Care and Infectious Diseases of the Nervous System:
- Craig Anderson, The George Institute for Global Health, Sydney, Australia
- John Stover, Zürich, Switzerland: NOSTRA trialists
- Peter Kremsner: Tübingen, Germany and Lambarene, Gabun: SMAC trialists
- Peter Le Roux: Wynnewood, PA, USA, International Multidisciplinary Consensus Conference on Multimodality Neuro-Monitoring.
- JH Zhang: Loma Linda, CA, USA
- Sarah Gabriel, Cystinet-project, Antwerp, Belgium
- Nino Stocchetti, Milano, Italy: SyNAPSE trialists

Research Group Sleep Medicine:
- Oscar Gershanik, University of Buenos Alres, Argentina
- SINBAR, Sleep Innsbruck Barcelona
- Joan Santamaria and Alex Iranzo, Hospital Clinic of Barcelona, Barcelona, Spain
- Claudia Trenkwalder, Paracelsus-Elena Clinic, Kassel, and University of Goettingen Germany
- University of Barcelona, Harvard University, Stanford University, Johns Hopkins University, the Rush Medical Center, and other universities in Japan, Latin America etc.

The strong international imbedding and connections of the sleep research group is also apparent from the fact, that the group leader holds several current EC positions in international groups, e.g. the International RLS study group IRLSSG, and the International RBD study group (current secretary in both groups) and is the current chair of the medical advisory board of the RLS/WED foundation.

International guests, students, specialists and visiting professors visited the Sleep Group came from Israel, Georgia, Argentina, Brazil, The Netherlands, Germany, Finland, Thailand, Japan, etc. Birgit Högl, the Head of unit has in turn been invited as a Visiting Professor to Harvard Medical School, the Federal State University of Sao Paulo and the University of Chicago.

The strong international network and collaborations are also visualized through the pubmed publication track report of the Sleep Research Group, which comprises more than 100 international collaborative studies, for the most part published in high ranking peer-reviewed international journals. These publications include results from bicentric, oligocentric or multicentric studies, academic research projects, and guideline papers.

Research Group Multiple Sclerosis and Neuroimmunology:
- Hans Lassmann, Monika Bradl, Romana Höftberger, Fritz Leutmezer and Alexander Zimprich: Medical University of Vienna, Vienna, Austria
- Michael Khalil, Christian Enzinger and Franz Fazekas: Medical University of Graz, Graz, Austria
- Kevin Rostasy: Childrens Hospital Datteln, Datteln, Germany
- Edgar Meinl: LMU Munich, Munich, Germany
- Bernhard Hemmer: TU Munich, Munich, Germany
- Sven Jarius and Brigitte Wildemann: University of Heidelberg, Heidelberg, Germany
- Orban Aktas and Hanspeter Hartung: University of Düsseldorf, Düsseldorf, Germany
- Christine Stadelmann and Wolfgang Brück: Univ. of Göttingen, Göttingen, Germany
- Andreas Lutterotti, Mireia Sospreda, Jan Lünemann and Roland Martin: University of Zürich, Zürich, Switzerland
- L. Kappos: University of Basel, Basel, Switzerland
- Romain Marignier: University of Lyon, Lyon, France
- Albert Saiz, Frances Graus, Josep Dalmau and M. Comabella: University of Barcelona, Barcelona, Spain
- Paddy Waters, Jackie Palace, Isabel Leite and Angela Vincent: University of Oxford, Oxford, UK
- Anne Fogdell-Hahn: Karolinska Institute, Stockholm, Sweden
- Eva Havrdova: University of Prague, Prague, Czech Republic
- Jeffrey Bennett: University of Denver, Denver, Colorado
- Douglas Sato, Tatsuro Misu and Kazuo Fujihara: Tokohu University, Sendai, Japan

Computational Neuroscience:
- Neuroimage Wien Innsbruck Graz (WING)
- EU Horizon 2020, FAIRPARK II
- PRODEM AUSTRIA

Miscellaneous

Neurological Research Laboratory:
The main goals of the Neurological Research laboratory (headed by Univ.-Prof. Markus Reindl) are clinically orientated neuroscience, teaching and the development of novel methods for laboratory testing in neurology. In 2013 the Neurological Research Laboratory moved, together with the Institute of Neuroscience and the Neurosurgery Research Laboratory to Innrain 66, 2nd and 3rd floor. In July 2003 and again in 2006, 2009 and 2012 the Neurological Research and Routine Laboratories were certified for the International Standard EN ISO 9001:2008

Neurosurgery

Director:
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Keywords

Neuro-oncology, cerebrovascular, neurointensive care, neuromonitoring, neurotrauma, spine surgery, spinal implants, disc degeneration, regenerative medicine

Research Focus

- Characterization of myelin-associated neurite growth inhibitors and their cognate receptors in the central nervous system.
- Signal transduction of neurite growth inhibitors in the brain with special emphasis on effects on cytoskeletal changes in neuronal growth cones.

General Facts

The Department of Neurosurgery actively hosts investigator-driven academic studies and is participating in multinational trials in different fields of our daily practice. Clinical research is paralleled with experimental work in our laboratory. We pursue the idea of leading innovative concepts from “bench to bedside”, exemplarily shown in the case of chondrocyte cell transplantation after surgical treatment of lumbar disc herniations. Besides ongoing research focusing on tumor cell infiltration into healthy brain tissue, we implemented different pre- and postoperative routines to determine the “functional status” of patients after treatment of intracranial pathologies. Our main clinical research focuses are divided into three (interacting) groups.

Research

Tumor

The neuro-oncology program of our department is focusing on two main fields of interest, “infiltration” and “optimization of functional outcomes” of patients after brain tumor surgery. Infiltration is always present in gliomas, whereas metastatic disease of solid cancers was believed to be circumscript lesions in the brain. The surrounding tissues of metastatic disease and primary gliomas are currently under investigation with 31-Phosphorus-MR-Spectroscopy and precise biopsies are taken from these regions to demonstrate that infiltrative behavior in brain tumors (metastasis and gliomas) can be found by state-of-the-art MR-imaging. The borders and surroundings of resected metastases are examined immunohistochemically. Operative techniques are currently under investigation, as in cases of gliomas, fluorescence guided resections and intraoperative imaging with CT is evaluated through posthoc image rendering with prototypic algorithms. The aim of this collaborative project with industrial partners is to predict the extent of tumor resection through intraoperative CT-imaging.

<u>Selected Trials:</u>

- Elastic Fusion: intraoperative CT is rendered by prototypic algorithms to generate a “virtual” MRI. Extent of resection is evaluated by neuroradiology (proof of principle)
- 31P-MR-Spectroscopy: several tumor entities undergo 31P-MR-Spectroscopy to determine chemical shift imaging based profiles of tumor tissue
- Biopsy: regions of high phosphorus concentration (high ATP-levels) are precisely examined through a targeted biopsy to correlate P-concentration with histologic patterns

Vascular/Neurotrauma/Intensive Care

In addition to prospective analysis of treatment results of vascular pathologies (aneurysms, arteriovenous malformations and stroke) and the ongoing improvements in technical standards and operative techniques, the use of hypoxic preconditioning and serum biomarkers

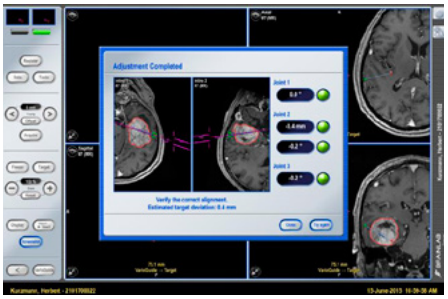

Fig. 1: Multimodal treatment plan for the resection of a solid brain tumor.

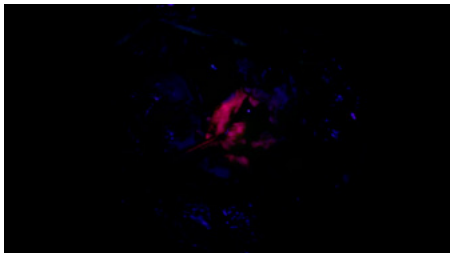

Fig. 2: Intraoperative fluorescence of a malignant brain tumor to delineate the lesion from healthy brain tissue.

are investigated to beneficially influence patient treatment. The Department of Neurosurgery is participating in several international registries and is in close collaboration with the Department of Neurology. Invasive multimodal monitoring of brain oxygenation, metabolism and blood flow, in combination with intracranial pressure is performed to evaluate the use of these invasive techniques on patient outcome after severe head trauma and subarachnoid hemorrhage. Researchers of the Department are currently abroad in joined projects with the Mayo Clinic in Rochester, Minnesota and in Loma Linda, California.

Severe head injury is a common medical condition at our department. In addition to multimodal monitoring and pathophysiological investigations, a monocentric study was launched in close collaboration with the Departments of Neuroradiology and Neurology to determine the use and interpretation of early MRI data and their correlation to serum biomarkers of brain injury. Furthermore, treatment of chronic subdural hematomas, a widely underestimated disease predominantly arising in the elderly, was analyzed based on a monocentric randomized protocol.

Selected Trials:

- RIPAT: hypoxic preconditioning is applied (randomized) to patients before elective treatment of aneurysms. Serum biomarkers and neuropsychological outcomes are recorded pre- and postoperatively
- TIBI: multimodal invasive neuromonitoring in patients with severe head trauma in combination with early MRI data and serum biomarkers of neuronal injury

Spine

In accordance with our experimental research of spinal pathologies, our spine group is leading ongoing regenerative studies such as the N-DISC trial. Human (autologous) chondrocytes are cultivated from herniated disc material and reinjected 3 months after standard surgery. This is the first clinical trial also investigating prophylactic treatment of degenerated discs. Another main (clinical) research interest is based on minimally invasive surgery using state-of-the-art neuronavigation systems and imaging technology. Recurrent pathologies (i.e. re-herniation of lumbar discs) might be reduced by closure of substance defects in the annulus fibrosus. We collaborate with industrial partners to approve the use of closure devices to reduce recurrences (Barricaid) and have conducted experimental studies to elucidate the benefits of regenerative approaches. Clinical studies on corpectomies and instrumentation procedures are supplemented with biomechanical studies to determine the stability and durability of spinal implants needed for surgical stabilization of the human spine in close collaboration with the Department of Trauma Surgery.

Selected Trials:

- N-DISC: autologous chondrocyte cells to be reinjected in the patient's intervertebral disc several weeks after surgery to prevent ongoing degeneration
- Barricaid: a composite material annulus closure device is implanted during standard surgery for lumbar disc herniation
- DynorFuse: a multinational trial to investigate the effectiveness of rigid vs. dynamic fusion techniques in patients with spinal stenosis and mild signs of instability
- ForaC: a multicenter randomized trial on anterior versus posterior approaches for cervical foraminal stenosis with radiculopathy

The experimental focus of the spine group is biological treatment approaches for intervertebral disc degeneration (IVD). IVD, often accompanied by inflammatory and patho-immunological processes, has been described as structural failures of disc tissues. Current treatment approaches are restricted to symptomatic therapies and do not address the option of biological repair of the discs. Intervertebral disc cells play a central role in the maintenance of discs by coordinating the expression of anabolic, catabolic, anti-catabolic and inflammatory cytokines affecting the extracellular matrix. Our electronic database search has identified several target genes that could have a significant impact on disc matrix anabolism and catabolism.

By combinatorial relative mass value evaluations of the identified target proteins in degenerative lumbar and cervical discs, we have ascertained imbalanced protein expression patterns of certain anabolic, catabolic, anti-catabolic and inflammatory cytokines. Our progressive characterization of the target genes gives us the opportunity to develop new therapeutic approaches. Currently, we are establishing an adeno-associated virus (AAV) based gene therapeutic system as a new biological treatment approach for degenerative disc diseases. So far, AAV serotypes with human IVD tissue tropism have not been identified and characterized. The use of AAV-mediated gene therapy for human intervertebral disc research has not yet been investigated.

Selected Publications

Effectiveness of posterior decompression techniques compared with conventional laminectomy for lumbar stenosis. Overdevest GM, Jacobs W, Vleggeert-Lankamp C, Thomé C, Gunzburg R, Peul W. Cochrane Database Syst Rev. 2015 Mar 11;3:CD010036.

Imbalanced protein expression patterns of anabolic, catabolic, anti-catabolic and inflammatory cytokines in degenerative cervical disc cells: new indications for gene therapeutic treatments of cervical disc diseases. Mern DS, Beierfuß A, Fontana J, Thomé C, Hegewald AA.
PLoS One. 2014 May 7;9(5):e96870.

Enhancing tissue repair in annulus fibrosus defects of the intervertebral disc: analysis of a bio-integrative annulus implant in an in-vivo ovine model. Hegewald AA, Medved F, Feng D, Tsagogiorgas C, Beierfuß A, Schindler GA, Trunk M, Kaps C, Mern DS, Thomé C.
J Tissue Eng Regen Med. 2015 Apr;9(4):405–14.

Perfusion characteristics of Moyamoya disease: an anatomically and clinically oriented analysis and comparison. Schubert GA, Czabanka M, Seiz M, Horn P, Vajkoczy P, Thomé C.
Stroke. 2014 Jan;45(1):101–6.

Distance to the neurooncological center: a negative prognostic factor in patients with glioblastoma multiforme. An epidemiological study. Kerschbaumer J, Freyschlag CF, Bauer R, Obwegeser AA, Schubert GA, Thomé C, Seiz M.
Anticancer Res. 2012 Dec;32(12):5515–9.

Selected Funding

Diverse Industry sponsored and academic clinical trials

Collaborations

Numerous research collaborations with institutions in Austria and neighboring countries in the fields of neurooncology (i.e. Vienna, Regensburg, Heidelberg), cerebrovascular neurosurgery (i.e. Aachen, Düsseldorf, Berlin) and regenerative medicine (i.e. Berlin, Mannheim). The multicenter clinical trials involve numerous partners throughout Europe. Researchers are currently staying at the Mayo Clinic, Rochester, MS/USA and in Loma Linda, CA/USA within the scope of ongoing cooperations.

Obstetrics and Gynecology

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Keywords

Clinical studies, gynecologic oncology, senology, biobanking translational research, biomarker-identification

Research Focus

- Clinical and pre-clinical studies in women specific cancer in regard to prevention, diagnostics, therapy and follow-up care
- Translational research
- Collection of biological samples (tissues, serum, ascites, …,3)
- Biomarker identification in breast and gynecological malignancies
- Special interest in understanding the development of women specific cancer
- Pregnancy Research

General Facts

The clinical trials conducted in the department are coordinated by AGO Studienzentrale as trial office of the non-profit organization AGO Austria (Association of gynecologic oncology in Austria) since 2002. The main aim is to enable gynecologic cancer patients to receive advanced and innovative therapies in this field, as well as to contribute to research in order to improve therapy options. The AGO Studienzentrale is not only responsible for trial conduct within the department, but also for the coordination of AGO trials in other Austrian sites (i.e. manages applications to ethics committees and other competent authorities etc.). Furthermore, the department has a trial office for breast cancer trials with several study nurses dedicated to support the patients in trials at the department.

The pre-clinical studies are conducted mainly in the Laboratory of Clinical Biochemistry (Head: Heidi Fiegl) and in the Morphological Laboratory (Head: Elisabeth Müller-Holzner until her death in July 2014; Afschin Soleiman since July 2014). Both laboratories are certified according to ISO 9001:2008 and house the bio bank of this department, which contains FFPE tissue samples from nearly 6,500 patients, fresh frozen tissue samples from over 1,000 patients, ascites samples from over 1,500 patients and serum samples (pre-therapeutic samples and samples drawn during the follow-up period from over 3,000 patients).

Biobanking has been performed in the department since the 1980s and optimized over the years. The serum-, tissue- and tumour data applications are registered in the Data Processing Registry of the Austrian Data Protection Commission. The clinical and personal data are stored separately in a clinical database, which is also registered in the Data Processing Registry.

Research

Clinical Trials: Gynaecologic Oncology
Christian Marth

A selection of the most important trials is shown below:

A number of gynecological cancer trials (surgical and therapeutic trials) are being conducted to assess efficacy and safety of different types of therapies.

Selected trials are described below.

- The antiangiogenic treatment of advanced epithelial ovarian, primary peritoneal or fallopian tube cancer with AMG386 or placebo was evaluated in the first-line setting with carboplatin and paclitaxel (AGO 30 Trinova 3) and in the recurrent partially platinum-sensitive or -resistant setting with pegylated liposomal doxorubicin (PLD) (AGO 28 Trinova 2) as Phase III randomized double-blind trials to determine whether AMG386 is superior to placebo in either setting.
- In the randomized open-label AGO 39 Ovar 2.21 trial, two standard-of-care chemotherapies (Carboplatin+Gemcitabine vs. Carboplatin+PLD) in combination with antiangiogenic treatment (Bevacizumab) are compared to measure efficacy in patients with first recurrence of platinum-sensitive epithelial ovarian, primary peritoneal or fallopian tube cancer.
- The Phase III randomized double-blind AGO 40 NOVA trial evaluates the efficacy of the PARP inhibitor Niraparib compared to placebo as maintenance therapy in patients with platinum-sensitive ovarian cancer, evaluated in a cohort of patients with germline BRCA mutation and high-grade serous or high-grade predominant-

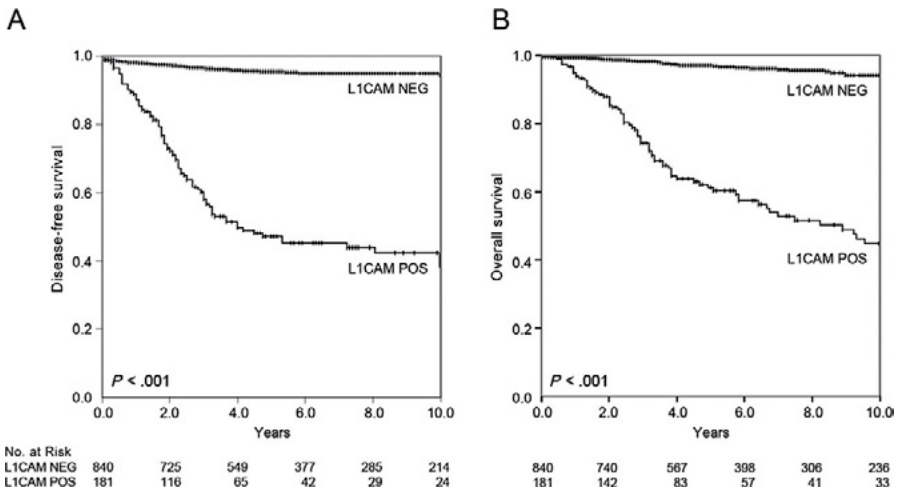


Fig. 1: Univariate survival analyses according to L1CAM expression in 1021 patients with FIGO stage I, type I endometrial cancers. A) Disease-free survival. B) Overall survival.

ly serous histology but without germline BRCA mutation. The aim is to assess whether maintenance with Niraparib will extend the progression-free survival (PFS) in these patients.

Major Achievements:
Inhibition of Angiopoietins 1 and 2 with Trebananib in women with recurrent epithelial ovarian cancer (EOC) provided a clinically meaningful prolongation in PFS.

Clinical Trials: Breast Cancer
Christian Marth
In the following, a selection of the most important clinical trials is shown:
- The department is currently successfully participating in a Phase III trial (Belle 3) which is investigating BKM120 with Fulvestrant in HR+/HER2- breast cancer (BC) patients, who progressed on or after mTOR inhibitor based treatment. We are at the moment the worldwide top recruiter in this trial.
- Treatment options for triple-negative BC patients are still limited. Therefore, clinical trials are of special interest in this setting. Two promising trials in this setting are currently being conducted in our department. These are the tnAcity (Gemcitabine/Carboplatin) and the placebo controlled, randomized Olympia Trial with the PARP-inhibitor Olaparib.
- We are also involved in innovative chemotherapy trials. For example, the Phase II AGMT-MBC 6 Trial evaluates Capecitabine in combination with Bedamustine in women with pre-treated locally advanced or metastatic Her2-negative BC; or the Kathrine Trial investigates the anti-body drug conjugate Trastuzumab Emtansine in patients with HER2-positive primary BC.

L1CAM Expression
Alain Zeimet
L1CAM is a 200 to 220k Dmembrane glycoprotein of the immunoglobulin superfamily and is crucially involved in neurogenesis. Moreover, L1CAM is expressed in a variety of tumours, where its presence is associated with poor clinical outcome.
- In a retrospective, international multicentre cohort study, the L1CAM expression was analysed by immunohistochemistry in 1021 endometrial cancer specimens. L1CAM has been shown to be the best prognostic factor in Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage I, type I endometrial cancers and shows clear superiority over the standardly used multifactor risk score. L1CAM expression in type I cancers indicates the need for adjuvant treatment. This molecule might serve as a treatment target for the fully humanized anti-L1CAM antibody currently under development for clinical use.

Major Achievements:
Identification of miR-21-3p as a positive L1CAM regulator in several human carcinomas and miR-34a as a L1CAM suppressor in endometrial carcinoma. Establishment of a standardized staining protocol for L1CAM on formalin-fixed, paraffin-embedded tissues using automated platforms.

Future Goals:
Validation of the clinical usefulness of L1CAM in a prospective randomized trial.

Identification and Targeting of Ovarian Cancer Stem Cells
Alain Zeimet and Daniel Reimer
In general the majority of patients with FIGO stage III/IV EOC initially responds to initial surgery and standard chemotherapy but ultimately undergo relapse, probably due to the survival of small populations of cells with tumour-repopulating potential, also termed cancer stem cells (CSC). It is a hallmark of CSC to survive anti-cancer treatment, which primarily target rapidly dividing tumour cells. They can give rise to recurrences of tumours that are usually more chemo-resistant and aggressive. Thus, it would be desirable to develop additional therapeutic modalities that could target ovarian CSC to complement conventional treatment options, ultimately enabling complete eradication or at least long term growth arrest of the disease.

- In an Oncotyrol funded project, EOC cell lines were screened for putative CSC to identify specific markers and to select targets suitable for *in vivo* CSC depletion or inhibition strategies.

Major Achievements:
The side population of ovarian cancer cells defines a heterogeneous compartment exhibiting stem cell characteristics.

GANNET53 (EU Project)
Nicole Concin
Epithelial ovarian cancer (EOC) is the most lethal gynecological malignancy. The predominance of aggressive type II tumours, which are characterized by a high frequency of p53 mutations, and primary or acquired resistance to platinum-based chemotherapy profoundly contribute to the high mortality rate. Addressing this need for more effective treatment strategies to improve the dismal survival in these patients, the GANNET53 trial (Ganetespib in metastatic, p53 mutant, platinum-resistant ovarian cancer) was initiated. GANNET53 is a Europe-wide, multi-centre Phase I and randomized Phase II clinical trial, targeting mutant p53, via an innovative new Hsp90 (heat shock protein 90) inhibitor in platinum-resistant EOC patients.

The consortium consists of clinical trial groups in gynecological oncology, university centres as well as noted p53 scientists and three innovative enterprises. We aim to substantially improve overall survival (OS) in EOC patients with metastatic type II platinum-resistant tumours. On the molecular level, we aim to identify the tumours mutational status in all GANNET53 study patients.

Biomarker Identification in Gynaecologic Cancer
Nicole Concin
A selection of the most important projects is shown:
- The gamma-glutamyltransferase (GGT) modulates crucial redox-sensitive functions in the cell. It has also been shown that GGT plays a role in tumour progression, invasion and drug resistance. Therefore, the significance of preoperative serum GGT levels as a prognostic marker is evaluated in gynecological cancers.
- Circulating tumour cells (CTCs) have been demonstrated to have prognostic value in several tumour types. Recently identified new molecular markers for the CTC-detection are analysed in blood of EOC patients to evaluate their diagnostic usefulness.

Major Achievements:
Identification of an association of elevated GGT levels with poor survival rates among endometrial cancer and EOC patients.

Identification of HIF1 alpha as an independent prognostic factor for OS in advanced primary EOC.

Impact of Aluminium on Breast Cancer
Nicole Concin
There is a need for research clarifying recently raised issues relating underarm antiperspirants containing aluminium salts with BC. Therefore we established the most comprehensive study in biological samples of BC patients and controls.

Parallel Mechanisms between Embryo- and Carcinogenesis
Nicole Concin
The aim of this study is to analyse the spatiotemporal distribution of relevant biomarkers expressed in mesenchymal and epithelial structures within the developing female secondary sexual organs and to identify diagnostically and/or therapeutically markers.

Biomarker Identification in Cancer
Heidi Fiegl
A selection of the most important projects is shown below:

- Despite years of intensive study and substantial progress in identifying new biomarkers and creating new therapies for BC, this disease remains the most common cause of cancer-related death in women. The aim of an Oncotyrol funded project was the improvement of recurrence-risk prediction in BC patients based on the analyses of the epigenome, genome, transcriptome and metabolome in blood samples from BC patients. In a large-scale blood specimen collection in breast cancer centres in Austria (Innsbruck, Salzburg, and Vienna) and South-Tyrol (Brixen and Meran) blood samples from over 2,000 BC patients have been collected so far.
- A central aim of preventive oncology is the identification of patients with a heritable predisposition to cancer. Identification of common founder mutations in certain ethnicities allows integration of genetic testing strategies in the routine care of all cancer patients. In collaboration with the Division of Human Genetics, we analysed specimens from breast and ovarian cancer patients treated in our Department and identified a Tyrolean *BRCA1* founder mutation.
- Much of the risk for endometrial cancer development is influenced by the environment and lifestyle. In an international collaboration, we analysed the functional role of epigenetic factors in endometrial cancer development.

Major Achievements:
Identification of a highly prevalent *BRCA1* founder mutation in the Lower Inn Valley that correlates to a local increase in the breast and ovarian cancer risks.

Identification of *HAND2* DNA methylation as a biomarker for early detection of endometrial cancer and as a predictor of treatment response.

DNA Demethylation Agents
Heidi Fiegl
Anaesthetic management of cancer surgery may influence tumour recurrence. Previous results in our laboratory showed that at clinically relevant concentrations, Lidocaine, a prototype amide-type local anaesthetic, demethylates DNA of BC cell lines *in vitro*. This modification of epigenetic information may be of therapeutic relevance in the perioperative period, because a decrease in methylation can reactivate tumour suppressor genes and inhibit tumour growth.

Major Achievements:
Demonstrates that Ropivacaine exert demethylating effects on specific BC cell lines.

Development and Validation of Pan-High-Risk E7 ELISA
Andreas Widschwendter
Persistent infections by high-risk human papillomaviruses (HPV) are the main etiological factor for the development of cervical cancer. A subgroup of the 12 HPV-types, referred to as high-risk HPVs, is associated with cervical carcinoma in situ and invasive cancers. High-risk HPV persistence is associated with the increased expression of the high-risk HPV E7 oncoproteins, the major transforming proteins of such viruses, which is highly specific for the induction of cervical carcinogenesis.

- In collaboration with the Institute for Biomedical Aging Research, a project was initiated to establish a novel ELISA assay for the detection and quantification of E7 oncoproteins of high-risk HPV types for the detection of cervical precancers and cancers. Additionally, a validation of the clinical performance diagnostic kit with cervical smears from 2000 patients was conducted.

Analysis of Afamin in Serum Samples
Michael Hubalek
Afamin is a human glycoprotein with an

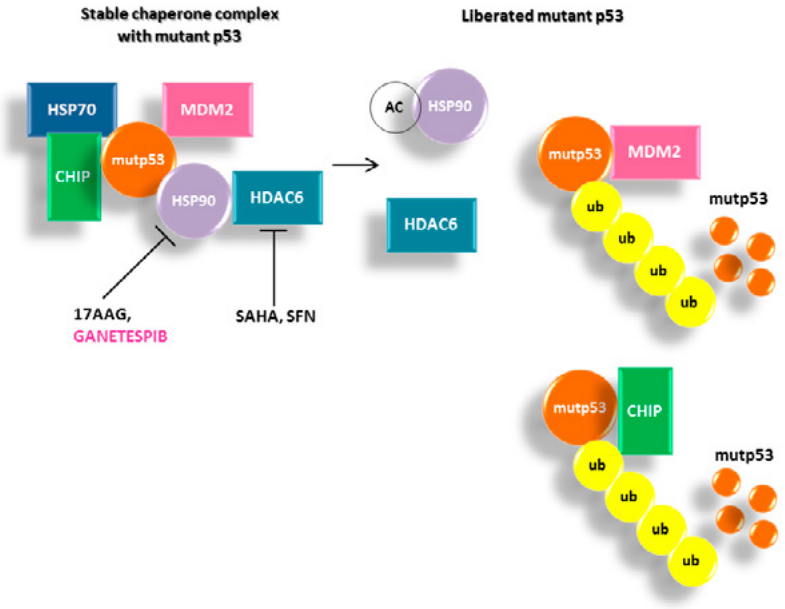


Fig. 2: Scientific principle of the GANNET53 trial. (Li et al, Cell Death& Diff 18:1904-13, 2011; Li et al, Mol Cancer Res 9:577–88, 2011). Destabilisation of mutant p53 protein by inhibition of the Hsp90 chaperone causes subsequent degradation by MDM2 or CHIP E3 ligases: Stable complex formation with Hsp90 causes aberrant stabilisation of mutp53 in cancer cells. MDM2 and CHIP, which in principle are capable of degrading mutp53, are unable to degrade mutp53 as long as it is protected by the complex ('caging'). Stabilised mutp53 exerts oncogenic gain-of-function (GOF). Acute depletion of mutp53 in tumour cells is strongly cytotoxic in all tested mutp53 solid cancer cell types tested (ovarian, breast, colon, and prostate). Small molecule inhibitors of the Hsp90 ATPase (such as the highly potent second generation Hsp90inhibitor Ganetespib, or the weaker first generation 17AAG + SAHA) acutely deplete mutp53, which is strongly cytotoxic in mutp53 harbouring tumour cells.

apparent molecular weight of 87 kDa with specific binding properties for vitamin E. Comparative proteomics has identified Afamin as a potential biomarker for ovarian cancer.

- In collaboration with the Division of Genetic Epidemiology has shown that Afamin serum concentrations were measured in women with uncomplicated pregnancies in a retrospective cohort study at different gestational ages and a prospective observational study in the first, second and third trimester.
- In a second project, Afamin levels were measured in serum samples of BC patients and patients with benign breast diseases.

Major Achievements:
Identification of linearly increased of Afamin levels in maternal serum during pregnancy.

Association between Body Mass Index and Anastrozole Plasma Levels
Michael Hubalek
The efficacy of adjuvant endocrine treatment with aromatase inhibitors, inhibiting the conversion of androgens to oestrogen in adipose tissue, might depend on the overall volume of adipose tissue. In collaboration with the Department of Psychiatry and Psychotherapy, the interaction between body mass index (BMI) and Anastrozole treatment as well as estrogenic was analysed.

Major Achievements:
Identification of positive association between BMI and Anastrozole plasma levels.

Human Epididymis Protein 4 (HE4) Levels in Serum of Endometrial Cancer Patients and Pregnant Women
Irene Mutz-Dehbalaie
Human epididymis protein 4 (HE4) is a secretory protein that is overexpressed in patients with serous and endometrioid epithelial ovarian and uterine cancers. HE4 has proven utility as a serum biomarker in EOC and is approved as an aid in monitoring recurrence or progressive disease in EOC patients. Recently, our Department identified HE4 as an independent prognostic marker in endometrial cancer patients.

- In collaboration with the University of Queensland, HE4 was analysed in sequential serum samples from endometrial cancer patients to analyse the HE4 kinetics between the time point of diagnosis and the time point of recurrence or freedom from recurrence.
- In another project HE4 serum levels were evaluated in comparison to CA 125 (cancer antigen 125) levels in the course of pregnancy to assess the influence of pregnancy-associated conditions/ diseases.

Major Achievements:
Identification of HE4 as a biomarker to detect recurrent endometrial cancer in patients undergoing routine clinical surveillance.

Future Goals:
Initiation of a prospective analysis of HE4 in endometrial cancer patients in the setting of a randomized control trial.

Pregnancy Research
Several different Members of the Department
Selections of the most important studies are shown:

Working group of Irene Mutz-Dehbalaie and Matthias Scheier
In industrialized countries a growing number of women delay reproduction until later in life. The impact of advanced maternal age on the rate of perinatal mortality was analysed in a retrospective cohort study in the state of Tyrol, Austria.

Working group of Angela Ramoni
The incidence of abnormally invasive placentation is rising. Massive, potentially life-threatening blood loss during delivery is the most feared complication. Prenatal diagnosis via ultrasound, followed by appropriate peripartum management of this condition, may help reduce morbidity and mortality. In a study four cases of placenta percreta and the chosen form of treatment were described.

Working group of Susanne Jerabek-Klestil and Matthias Scheier
The incidence of fetal portosystemic anastomoses is unknown, and it is presumed that many cases remain undetected. However, portosystemic anastomoses are associated with fetal growth restriction due to a diminished oxygen supply to hepatocytes and hence, downregulation of liver function. In a study three cases and the used form of treatment were described.

Major Achievements:
Identification of an increased risk for stillbirth in women older than 40 years and description of obesity and poor antenatal care as important amendable risk factors. Recommendation for a detailed examination of the fetal liver using color flow mapping to exclude portocaval anastomoses in cases of unexplained growth restriction.

Selected Publications

Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, Ray-Coquard I, Provencher DM, Karlan BY, Lhommé C, Richardson G, Rincón DG, Coleman RL, Herzog TJ, Marth C, Brize A, Fabbro M, Redondo A, Bamias A, Tassoudji M, Navale L, Warner DJ, Oza AM.
LANCET ONCOLOGY. 2014;15:799–808.

Role of miR-34a as a suppressor of L1CAM in endometrial carcinoma. Schirmer U, Doberstein K, Rupp AK, Bretz NP, Wuttig D, Kiefel H, Breunig C, Fiegl H, Müller-Holzner E, Zeillinger R, Schuster E, Zeimet AG, Sültmann H, Altevogt P.
ONCOTARGET. 2014;5;462–472.

Suppression of acetylpolyamine oxidase by selected AP-1 members regulates DNp73 abundance: mechanistic insights for overcoming DNp73-mediated resistance to chemotherapeutic drugs. Bunjobpol W, Dulloo I, Igarashi K, Concin N, Matsuo K, Sabapathy K.
CELL DEATH AND DIFFERENTIATION. 2014; 21:1240–1249.

L1CAM in Early-Stage Type I Endometrial Cancer: Results of a Large Multicenter Evaluation. Zeimet AG, Reimer D, Huszar M, Winterhoff B, Puistola U, Azim SA, Müller-Holzner E, Ben-Arie A, van Kempen LC, Petru E, Jahn S, Geels YP, Massuger LF, Amant F, Polterauer S, Lappi-Blanco E, Bulten J, Meuter A, Tanouye S, Oppelt P, Stroh-Weigert M, Reinthaller A, Mariani A, Hackl W, Netzer M, Schirmer U, Vergote I, Altevogt P, Marth C, Fogel M.
JOURNAL OF THE NATIONAL CANCER INSTITUTE. 2013;105; 1142–1150.

Role of DNA Methylation and Epigenetic Silencing of HAND2 in Endometrial Cancer Development. Jones A, Teschendorff AE, Li Q, Hayward JD, Kannan A, Mould T, West J, Zikan M, Cibula D, Fiegl H, Lee SH, Wik E, Hadwin R, Arora R, Lemech C, Turunen H, Pakarinen P, Jacobs IJ, Salvesen HB, Bagchi MK, Bagchi IC, Widschwendter M.
PLOS MEDICINE. 2013;10; e1001551.

Selected Funding

GANNET53 European Union Seventh Framework Program (FP7) is planned for 5.5 years with a funding of 6 million Euros (Prof. Dr. Nicole Concin).

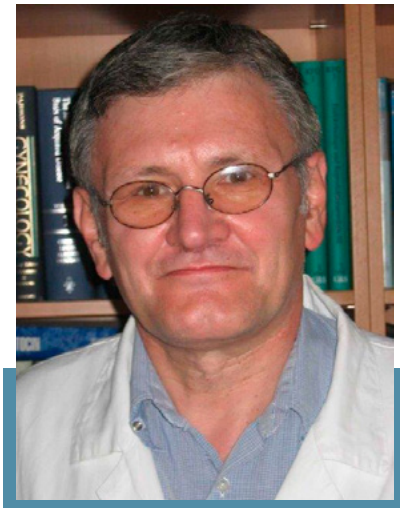
Collaborations

- Prof. Dr. Robert Zeillinger, Medical University Vienna, Vienna, Austria
- Prof. Dr. Ignace Vergote, Katholieke Universiteit Leuven, Leuven, Belgien
- Dr. Neda Slade, Ruđer Bošković Institute, Zagreb, Croatia
- Priv.-Doz. Dr. Roland Reitsamer, Paracelsus Medical University, Salzburg, Austria
- Primar Dr. Arthur Scherer, Medical Services Hospital, Bressanone, Italy
- Primar Dr. Herbert Heidegger, Medical Services Hospital, Meran, Italy
- Prof. Dr. Andreas Obermair, University of Queensland, Brisbane, Australia
- Prof. Dr. Martin Oehler, University of Adelaide, Adelaide, Australia
- Prof. Dr. Martin Widschwendter, University College London, London, United Kingdom
- Dr. Heinrich Roehder, Biodesix, Colorado, USA
- Dr. Peter Schulz-Knappe, Protagen AG, Dortmund, Germany

Collaborations in Clinical Trials with (inter)national research groups:
- AGO Austria – Arbeitsgemeinschaft Gynäkologische Onkologie
- ENGOT – European Network for Gynecological Oncological Trial groups (Cooperation with 19 trial groups)
- GCIG – Gynecologic Cancer InterGroup (Cooperation with 25 international trial groups)
- ABCSG – Austrian Breast & Colorectal Cancer Study Group

International collaboration with trial groups outside of ENGOT, GCIG or ABCSG trials:
- Prof. Dr. Jalid Sehouli, Charité Berlin, Germany
- Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO e.V.)
- EORTC – European Organization for Research and Treatment of Cancer

Gynecological Endocrinology and Reproductive Medicine



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Keywords

Endocrinology, reproductive biology and medicine, fertility preservation, endometriosis, PCOS, early pregnancy, menstrual cycle dependent disorders, uterine fibroids gender identity disorders.

Research Focus

The main research topics of the Department of Gynecological Endocrinology and Reproductive Medicine are physiology and pathology of ovarian function, fertility preservation, polycystic ovarian syndrome, adenomyosis/endometriosis, early pregnancy and recurrent pregnancy loss, uterine fibroids, cycle dependent disorders, contraception and disorders of gender identity.

General Facts

All our research projects are performed in intense cooperation between the research laboratory, the clinical units and the IVF-laboratory of the Department. This allows translation of experimental medicine to direct patient care, for example, in the case of ovarian tissue cryopreservation in patients facing loss of fertility due to malignant disease. We collaborate closely with the Department of Gynecology and Obstetrics and the Morphologic Laboratory of this department, the central laboratory of the LKI, General Pathology Division, Division of Clinical Biochemistry, Departments of Genetics and Genetic Epidemiology, Department of Neuroradiology, Departments of Neurology, Department of Nuclear Medicine, Division of Endocrinology of the Department of Internal Medicine, Divisions of Endocrinology and Metabolism of the Department of Paediatrics and the Department of Otolaryngology.

Research

Fertility Preservation

Katharina Winkler-Crepaz, Susanne Hofer, Sarrah Ayuandari, Wolfgang Biasio and Ludwig Wildt

One side effect of many of the commonly used chemotherapies, as well as pelvic irradiation, is its deleterious effect on the gonads. In women this can lead to premature menopause with its related diseases and sterility. In addition, ovarian tumours, chromosomal disorders such as Turner Mosaic or fragile X Premutation can lead to a premature loss of ovarian function and fertility.

One possible strategy to preserve female fertility is the cryopreservation of ovarian tissue prior to the gonadotoxic treatment. Once the patient is cured, ovarian function can be restored by autotransplantation of the tissue. The Department of Gynecological Endocrinology and Reproductive Medicine was the first center to perform ovarian tissue cryopreservation in Austria. Oncologic patients from all over Austria, South Tyrol and Southern Germany were referred to Innsbruck. In order to improve the success rate of cryopreservation and transplantation, xenotransplantation is an important approach to assess the quality of ovarian tissue prior to transplantation, as well as to investigate the mechanism behind follicular development after transplantation.

The fertility preservation unit of our clinic is primarily interested in studying follicular growth and functionality as well as to analyse molecular mechanisms involved in follicular growth initiation and follicular loss. This is done by *in vitro* assays, by immunohistochemistry and by transplantation and stimulation experiments in SCID-mice. Furthermore, we aim to optimize the existing fertility preservation techniques by developing specific stimulation and preservation protocols. The concept followed at our Department is shown in Fig. 1.

Physiology and Pathology of the Menstrual Cycle and Early Pregnancy

Bettina Boettcher, Christoph Brezinka, Valeria Colesselli, Agung Dewanto, Katharina Feil, Verena Porto, Beata Seeber, Ludwig Wildt (alphabetical order)

The main research interests concern the regulation of the menstrual cycle, the assessment of ovarian reserve and the large area of menstrual cycle dependent (katamenial) disorders such as dysmenorrhea, endometriosis/adenomyosis and, as additional examples, katamenial epilepsy and premenstrual syndrome. With regard to the pathophysiology of menstrual disorders, our main interest is in hyperandrogenemic disorders (PCO-syndrome).

Physiological Changes During the Menstrual Cycle

It has been known for a long time that women hyperventilate during the luteal phase of the menstrual cycle and during pregnancy. We could show that hyperventilation starts already during the beginning of the rise of serum estradiol indicating final maturation of the preovulatory follicle and the start of the fertile phase of the menstrual cycle. Thus, determination of the decline of endexspiratory pCO2 pressure may be used for determining the fertile phase of the cycle. After developing a highly sensitive device for easy determination of endexspiratory pCO2, studies are initiated to evaluate the usefulness of this method in the context of natural family planning. Moreover, our findings indicate that some symptoms of the premenstrual syndrome may be caused by excessive hyperventilation during the luteal phase of the cycle.

Adenomyosis and Endometriosis

Adenomyosis and Endometriosis are common disorders of human females during the middle and late reproductive period of life. They are characterized by dysmenorrhea, pelvic pain and infertility. We developed a new model of the pathogenesis of endometriosis/adenomyosis based on morphological and molecular biology data called TIAR (Tissue injury and repair). This concept views adenomyosis and endometriosis as the consequence of constant autotraumatisation of the uterus caused by exaggerated uterine contractions followed by local injury, induction of prostaglandin synthesis and aromatase activity and in turn a further estrogen-induced increase in the force of contractions. Pharmacological studies now underway are the logical consequence of this concept, examining the effects of aromatase inhibitors and

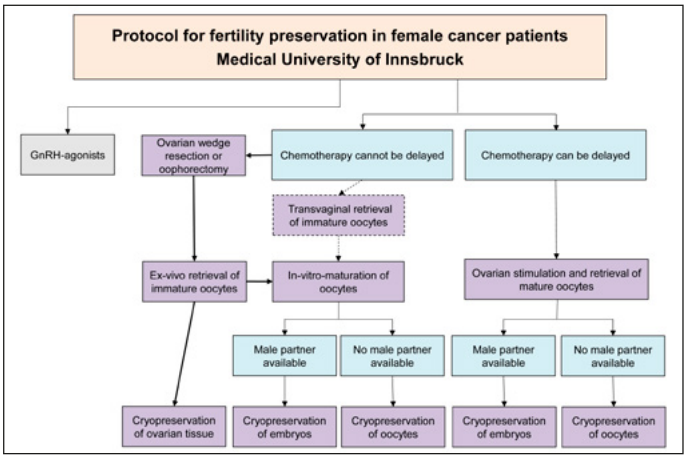

Fig. 1: The Innsbruck protocol for fertility preservation in female cancer patients.

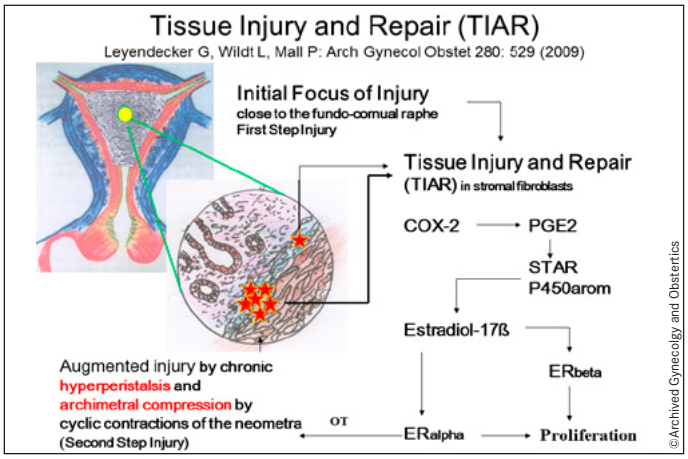

Fig. 2: TIAR-Tissue injury and Repair

novel prostaglandin antagonists on pain in patients suffering from endometriosis. Pain perception, which may also be profoundly altered in endometriosis, is examined using functional MRT in a model of pelvic pain. Along a similar line, the induction of pain fiber growth in endometriotic lesions by neurotrophins and their receptors are examined using quantitative immunohistochemistry and molecular biology. Further studies examined some metabolic disturbances in endometriosis as indicated by Afamin serum levels.

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome is the most frequent endocrine disorder of women of early to mid reproductive life associated with signs of androgenization, irregular cycles and infertility. It is frequently, although not always associated with insulin resistance and symptoms of metabolic syndrome. In our studies we have focused on diagnostic aspects of PCOS (highly sensitive assays for androgens in serum, diagnosis of insulin resistance and the diagnosis of heterozygous forms of C-21 Hydroxylase deficiency.

Early Pregnancy Failure

Early pregnancy failure (e.g. missed abortion) has traditionally been treated by dilatation and curettage. This is a surgical procedure and may have adverse effects on the function of the endometrium with respect to future pregnancies. We tried to optimize the medical management of women with early pregnancy failure. Women are primarily being offered successful yet non-invasive treatment options for early miscarriage. Positive feedback through patient questionnaires has confirmed the safety and acceptability of this treatment. Studies on the efficacy and safety of progestins and aromatase inhibitor intravaginal ring in endometriosis and assessment of safety and efficacy of Vilaprisan in patients with uterine fibroids are currently performed.

Gender Identity Disorders

The Department is a center for treatment of female to male (FtM) and male to female (MtF) transsexuals. So far, our interests were mainly to study the effects of androgens or estrogens, respectively on hormonal and metabolic parameters in transsexual patients. Now a functional MRT-study has been initiated which will examine the effect of visual erotic stimuli on the activity of specific brain regions in FtM transgender patients.

Ultrasound in Gynecological Endocrinology and Reproductive Medicine
Christoph Brezinka

Ultrasound has become a central part of diagnosis in all questions related to fertility and early pregnancy but also to menopause, endometriosis and genital neoplasia. With state of the art equipment that is constantly being updated, the main effort is on training of medical staff of the department particularly in the use of 3D and 4D ultrasound, proper documentation with an online system and a constant quality review process. Outside the department there is strong activity in ultrasound training courses and publication of guidelines and manuals. Christoph Brezinka is a board member of the International Society for Ultrasound in Obstetrics and Gynecology ISUOG and member of the ISUOG ultrasound safety committee, the ultrasound education committee. He is organizing the 2017 ISUOG conference in Vienna which is expected to have 3000 registered participants. He is a fellow of the American Institute of Ultrasound in Medicine and a Seminarleiter of ÖGUM.

Major Achievements: Publication of the "Truffle" study in 2014 and 2015, getting the 2017 ISUOG conference to Austria.

Selected Publications

Novel dynamic culture system to support initiation of primordial follicle growth in prepubertal mouse ovaries. Winkler-Crepaz K, Nederegger V, Ayuandari S, Rosenfellner D, Zervomanolakis I, Hofer S, Wildt L, Ziehr SC. Fertil Steril. 2014 Sep;102(3):864–870.

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Metformin induces a prompt decrease in LH-stimulated testosterone response in women with PCOS independent of its insulin-sensitizing effects. Kurzthaler D, Hadziomerovic-Pekic D, Wildt L, Seeber BE. Reprod Biol Endocrinol. 2014 Oct 11;12.

Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study. Leyendecker G, Bilgiycildirim A, Inacker M, Stalf T, Huppert P, Mall G, Boettcher B, Wildt L.
Arch Gynecol Obstet. 2015 Apr;291(4):917–32.

TRUFFLE study group. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, Calvert S, Derks JB, Diemert A, Duvekot JJ, Ferrazzi E, Frusca T, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E, Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, Valcamonico A, Visser GH, Wolf H.
Lancet. 2015 May 30;385(9983):2162–72.

Selected Funding

- Tyrolean Research Foundation (TWF), project number GZ: UNI-0404-1097, Dr. K. Winkler-Crepaz
- Oesterreichische NAtionalbank, Anniversary Fund (OeNB), project number 14641, Dr. K. Winkler-Crepaz

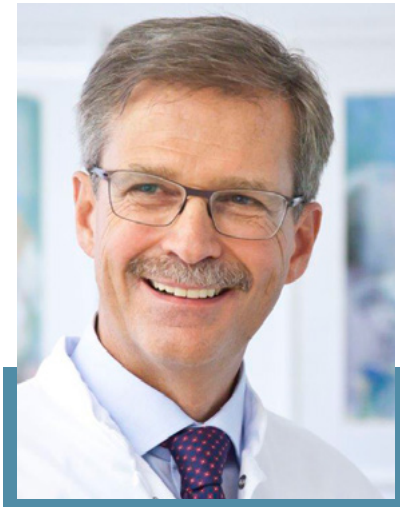
Collaborations

- Fertiprotect Network: Germany, Switzerland and Austria
- C. A. Schreiber, Univ. of Pennsylvania, Penn Medicine, USA
- S. Mechsner, Charitè Berlin, Germany
- T. Woodruff, Northwestern University and the Oncofertility Consortium, USA
- G Leyendecker, Kinderwunschzentrum Darmstadt, Germany

Devices & Services

- Ovarian tissue cryobank
- CL-863 Freeze Control, Cryologic (automated freezer)
- Tecan Reader, Genius Pro, Fluorescence/Luminescence/Absorbance Reader

Otorhinolaryngology



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Keywords

Drug delivery to the inner ear, inner ear morphology, accuracy of computer aided surgery, head & neck neoplasm, epithelial-mesenchymal transition

Research Focus

- The role of Nanoparticles in drug delivery to the inner ear
- Error analyses for computer assisted surgery
- Targeted therapy for head and neck squamous cell carcinoma

General Facts

The major aim of the Department of Otorhinolaryngology is to provide independent basic and clinical research in the field of Otorhinolaryngology to optimize patient treatment. The basic research is provided by three independent laboratories: 1) the Molecular Biology and Oncology Laboratory by PD. Dr. Joszef Dudas; 2) the 4D Visualization Laboratory by Univ.-Prof. Dr. Wolfgang Freysinger; 3) the Inner ear Laboratory by Univ.-Prof. Dr. Annelies Schrott-Fischer. These three major research units are in close cooperation with the clinician scientists enabling translational research projects with clinical impact in three major focuses of Otorhinolaryngology. Furthermore the Department is in close cooperation with the local industry, developing, for instance a laryngeal pacemaker or a vestibular implant. Further clinical research focuses are focused on clinical oncology, rhonchopathy and clinical aspects of hearing implants.

Research

Molecular Biology and Oncology Laboratory
PD. Dr. Joszef Dudas

Cell cycle association and hypoxia regulation of excision repair cross complementation group 1 protein (ERCC1) in tumor cells of head and neck cancer.

Excision repair cross complementation group 1 (ERCC1) protein is considered a prognostic marker in head and neck cancer. In this study, clinical response to mitomycin C (MMC) or cisplatin (CDDP) based radiochemotherapy (RCT) was assessed in 106 head and neck squamous cell carcinoma (HNSCC) patients and compared with cell nuclear immunoreactivity (in % of positive nuclei) of the mouse monoclonal (clone: 8F1) ERCC1-antibody in tumor tissue samples.

The same immunostaining was performed in 26 normal mucosa samples. While ERCC1-immunoreactivity did not differ in normal pharyngeal mucosa and treatment responders, non-responders revealed significantly lower (p=0.0064) ERCC1 representation. Simultaneous *in vitro* studies revealed that under hypoxic conditions, ERCC1-gene expression significantly decreased, whereas ERCC1+ cells might represent radiosensitive cells, which are preferably in G2-phase of cell cycle, and are non-hypoxic. (Fig. 1, Dudas *et al.,* Tumor Biol. 2014)

4D Visualization Laboratory
Univ.-Prof. Dr. Wolfgang Freysinger

Quantitative error analysis for computer assisted navigation: A feasibility study.
The benefit of computer-assisted navigation depends on the registration process, at which patient features are correlated to some preoperative imagery. The operator-induced uncertainty in localizing patient features–the user localization error (ULE)–is unknown and most likely dominating the application accuracy. This initial feasibility study aims at providing first data for ULE with a research navigation system. Active optical navigation was done in CT-images of a plastic skull, an anatomic specimen (both with implanted fiducials), and a volunteer with anatomical landmarks exclusively. Each object was registered ten times with 3, 5, 7, and 9 registration points. Measurements were taken at 10 (anatomic specimen and volunteer) and 11 targets (plastic skull). The active NDI Polaris system was used under ideal working conditions (tracking accuracy 0.23 mm root-mean-square, RMS; probe tip calibration was 0.18 mm RMS). Variances of tracking along the principal directions were measured as 0.18 mm^2, 0.32 mm^2, and 0.42 mm^2. ULE was calculated from predicted application accuracy with isotropic and anisotropic models and from experimental variances, respectively.

The ULE was determined from the variances as 0.45 mm (plastic skull), 0.60 mm (anatomic specimen), and 4.96 mm (volunteer). The predicted application accuracy did not yield consistent values for the ULE. Quantitative data of application accuracy could be tested against prediction models with iso- and anisotropic noise models and revealed some discrepancies.

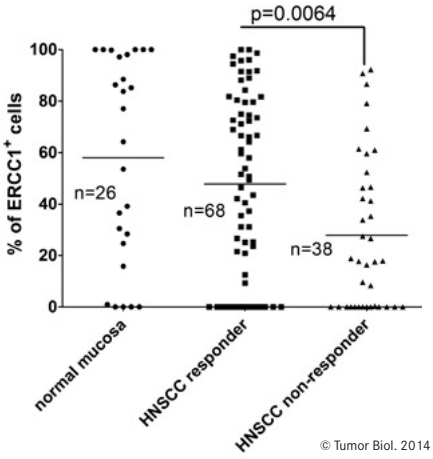

Fig. 1: Twenty-six normal mucosa samples and 106 HNSCC tumor tissue samples have been stained with 8 F1 ERCC1 antibody, and the percentage of stained cells in tumor cell nests or in high power fields of normal mucosa has been evaluated. There was no significant difference between the staining representation of normal mucosa and therapy responder HNSCC, but the therapy nonresponder HNSCC patients have shown significantly lower (p=0.0064) ERCC1 representation compared to the normal mucosa and responder patients.

This could potentially be due to the facts that navigation and one prediction model wrongly assume isotropic noise (tracking is anisotropic), while the anisotropic noise prediction model assumes an anisotropic registration strategy (registration is isotropic in typical navigation systems).

The ULE data are presumably the first quantitative values for the precision of localizing anatomical landmarks and implanted fiducials. Submillimetric localization is possible for implanted screws; anatomic landmarks are not suitable for high-precision clinical navigation (Fig. 2) (Güler *et al.* J. Med. Phys. 2013).

Inner Ear Biology
Univ.-Prof. Dr. Annelies Schrott-Fischer
Nanoparticle mediated drug delivery of rolipram to tyrosine kinase B positive cells in the inner ear with targeting peptides and agonistic antibodies.

Systemic pharmacotherapies have limitation due to blood-labyrinth barrier, so local delivery via the round window membrane opens a path for effective treatment. Multifunctional nanoparticle (NP)-mediated cell specific drug delivery may enhance efficacy and reduce side effects. Different NPs with ligands to target TrkB receptor were tested. Distribution, uptake mechanisms, trafficking, and bioefficacy of drug release of rolipram loaded NPs were evaluated. We tested lipid based nanocapsules (LNCs), Quantum Dot, silica NPs with surface modification by peptides mimicking TrkB or TrkB activating antibodies. Bioefficacy of drug release was tested with rolipram loaded LNCs to prevent cisplatin-induced apoptosis. We established different cell culture models with SH-SY-5Y and inner ear derived cell lines and used neonatal and adult mouse explants. Uptake and trafficking was evaluated with FACS and confocal as well as transmission electron microscopy. Plain NPs show some selectivity in uptake related to the *in vitro* system properties, carrier material, and NP size.

Some peptide ligands provide enhanced targeted uptake to neuronal cells but failed to show this in cell cultures. Agonistic antibodies linked to silica NPs showed TrkB activation and enhanced binding to inner ear derived cells. Rolipram loaded LNCs proved as effective carriers to prevent cisplatin-induced apoptosis.

Most NPs with targeting ligands showed limited effects to enhance uptake. NP aggregation and unspecific binding may change uptake mechanisms and impair endocytosis by an overload of NPs. This may affect survival signaling. NPs with antibodies activate survival signaling and show effective binding to TrkB positive cells but needs further optimization for specific internalization.

Bioefficiacy of rolipram release confirms LNCs as encouraging vectors for drug delivery of lipophilic agents to the inner ear with ideal release characteristics independent of endocytosis.
(Glückert *et al.* Front Aging Neurosci. 2015)

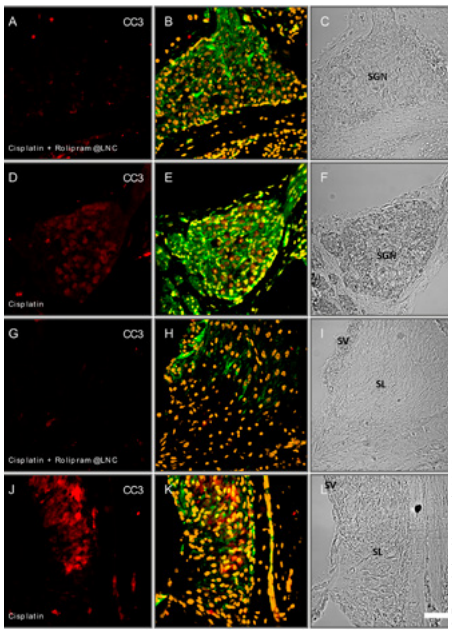

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Fig. 2: Rolipram-loaded lipid nanocapsules (LNCs) partially rescue cisplatin-induced apoptosis in postnatal mouse cochlea cultures (P24). Spiral ganglion neurons (SGN) treated with cisplatin and rolipram-loaded LNCs exhibit less cleaved caspase 3 (CC3-red staining) immune reactivity (A) than controls exclusively treated with cisplatin (D). In the spiral ligament (SL) cisplatin induces increased CC3 reactivity (J) while additional treatment with rolipram-loaded LNCs reduced the CC3-reacitivty (G). (A,D,G,J) CC3 immunolabeling; (B,E,H,K) phalloidine labeling and DAPI staining; (C,F,I,L) bright field. Scale bar 50 µm.

Selected Publications

Nanoparticle mediated drug delivery of rolipram to tyrosine kinase B positive cells in the inner ear with targeting peptides and agonistic antibodies. Glueckert R, Pritz CO, Roy S, Dudas J, Schrott-Fischer A.
Front Aging Neurosci. 2015 May 19;7:71.

Cell cycle association and hypoxia regulation of excision repair cross complementation group 1 protein (ERCC1) in tumor cells of head and neck cancer. Dudás J, Schartinger VH, Romani A, Schweigl G, Kordsmeyer K, Marta PI, Url C, Kral F, Riechelmann H.
Tumour Biol. 2014 Aug;35(8):7807–19.

Quantitative error analysis for computer assisted navigation: a feasibility study. Güler Ö, Perwög M, Kral F, Schwarm F, Bárdosi ZR, Göbel G, Freysinger W.
Med Phys. 2013 Feb;40(2):021910.

Selected Funding

- Echtzeit Resektionskontrolle bei navigierten Operationen an der lateralen Schädelbasis, ÖNB, approved 12 /2014, 100,000.-
- CIGuide, FFG, approved 2014, 420,000.-
- 3D Rekonstruktion des Innenohrs, VAMEL, K-Regio, Land Tirol 197,810.-
- Ion channels in human neurons, MEDEL, 218,000.-
- BDNF – TrcB signaling in Head and Neck Cancer; FWF, 112,623.-

Collaborations

- TU München mit Informatik, Prof. Nassir NABAB
- Universität Bern, HNO, Prof. Marco Caversaccio
- Brigahm & Womens Hospital, Harvard, Boston, MA, USA, Prof. Ron KIKINIS
- Mechatronik, MCI, Innsbruck, DI Dr. Andres MEHRLE Brainlab, München
- iSYS, Kitzbühel, CEO Dr. Michael VOGELE
- ACMIT, Wr. Neustadt, CEO Dr. Gernot Kronreif
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- Semmelweis University Budapest, Inst. Pathology and Experimental Cancer Research Budapest, Hungary
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- http://www.khri.med.umich.edu/research/miller_lab/index.php
- Auditory Anatomy Laboratory,., Laboratory Director, USA Richard Altschuler, Ph.D
- http://www.khri.med.umich.edu/research/altschuler_lab/index.php
- Universität Uppsala, Schweden, Helge Rask-Andersen http://www.medfarm.uu.se/
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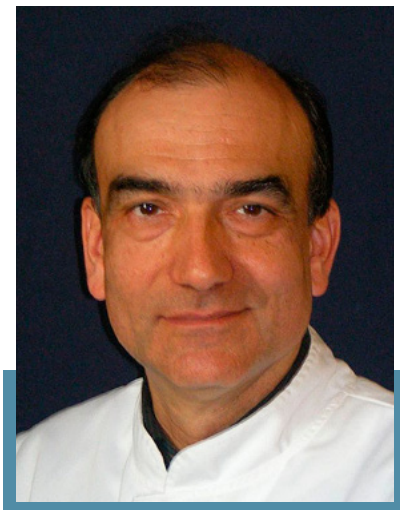
- Department für Anatomie, Histologie und Embryologie , Sektion für Histologie und Embryologie, Kristian Pfaller
- Veterinärmedizinische Universität, VetCore Facility for Research Imaging Unit, Stephan Handschuh
- UMIT Hall Institut für Biomedizinische Informatik, Division für Biomedizinische Bildanalyse, Karl Fritscher, Rainer Schubert
- UMIT Hall, Institut für Elektrotechnik und Biomedizinische Technik,Christian Baumgartner
- MedEl Innsbruck ,Ingeborg Hochmair, Carolyn Garnham, Claude Jolly
- Frank Rattay, Computational Neuroscience and Biomedical Engineering, Institute for Analysis and Scientific Computing, Vienna University of Technology, Austria
- University of Tampere, Finland, Ilmari Pyykko
- University of Angers, France, Saulnier Patrick, Guillaume Bastiat
- University of Southampton, UK, Tracey Newman
- The Bionics Institute, East Melbourne, Australia, Andrew K. Wise
- Inserm U 254 Neurobiologie de l'Audition, Montpellier, France, Eybalin Michel

Devices

- TissueFaxs from TissueGnostics

Hearing, Speech and Voice Disorders



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Keywords

Aural effects of noise, hearing disorders, hearing rehabilitation, sound localisation, sound localisation with hearing implants, speech understanding with hearing implants, tinnitus, voice disorders

Research Focus

- Assessing the auditory performance (e.g. speech understanding, sound source localisation) of patients with hearing implants including cochlea and middle ear implants.
- Assessing the auditory performance of normal hearing people whose hearing is impaired by external factors like helmets or caps.
- Developing objective methods for hearing implant fitting in children (e.g. Stapedius reflex measurement).
- Analysing the effects of noise on hearing health through epidemiological studies of tinnitus and hearing complaints in adolescents

General Facts

The Department HSV was founded in 1974, after a "Chair in Audiology and Phoniatrics" was established at Innsbruck Medical Faculty in 1968. This was the first chair in these specialities in the German speaking countries. Today, the HSV is Austria's largest institution in the fields of Audiology, Pediatric Audiology and Phoniatrics. It offers a full range of clinical services for the diagnosis and treatment of disorders of hearing, speech, language, swallowing and of childhood learning problems. In the 1990s, the Department was significantly involved in implementing Universal Newborn Hearing Screening in Austria.

Equipped with an anechoic chamber and tools for high-precision acoustic measurements, the Department is frequently involved in collaborations with commercial firms (including producers of hearing implants and hearing aids) who seek to test or evaluate their recently developed technology with patients or test persons under suitable acoustic conditions.

Research

Hearing Loss in Cystic Fibrosis (CF)
Markus Rungger
In collaboration with the CF Unit of the Department of Pediatrics III of Innsbruck Medical University.
Patients with Cystic Fibrosis (CF) and chronic airway colonisation with Pseudomonas

Fig. 1: The anechoic chamber is a special room for high-precision psycho-acoustic measurements. The background noise level in the chamber is less than –10 dB Hearing Level at all frequencies between 16 and 20,000 Hz. Loudspeaker boxes are mounted in a horizontal plane for testing a person's sound source localization skills.

aeruginosa receive regular aminoglycoside therapy against their infection. To monitor the ototoxic side-effects of the treatment, the patients undergo hearing tests (audiograms) before and after aminoglycoside application. In this research project, audiograms of the CF patients are retrospectively analysed and changes of their hearing thresholds are statistically linked to parameters of their disease, including genotype of the mutation, cumulative aminoglycoside dose, type of aminoglycoside application, pulmonary function, pancreas insufficiency, and others. In detail, it is analysed which of these parameters is most predictive for a hearing threshold deterioration and which frequencies of the hearing threshold are most vulnerable to the above parameters.

Sound Localisation in Unilateral Deafness

Josef Seebacher

Correct localization of sound sources in a 3D environment requires binaural hearing. In patients with unilateral deafness sound source localisation is impaired; as a consequence their rate of correct localisations is low. Restoring their hearing with a hearing implant (cochlea or middle ear implant) is supposed to improve their localisation skills, however, research has shown that the results remain below expectations: despite restored bilateral hearing the patients perform worse than normally hearing persons. This research project investigates why unilaterally deaf persons with a hearing implant in the deaf side localize worse than normally hearing persons. The hypothesis under investigation is that the processing of the acoustic signal in the speech processor is so fast that the interaural time differences (which sounds normally have) are nearly annihilated. As these differences are an important cue for the auditory system in determining the direction where a sound comes from, their diminishment may be the cause for the deterioration of the localisation performance. If this hypothesis is true, a slight deceleration of the signal processing in the speech processor should improve the localisation performance.

Conceptual modelling of Tinnitus pathogenesis

Viktor Weichbold

There exists a huge mass of theories attempting to explain the pathogenesis of Tinnitus. While most of them integrate data from empirical research in order to confirm their assumptions and hypotheses, none of them uses empirical data for the purpose of falsification of assumptions and hypotheses (as would be logically correct). Moreover, many theories suffer from conceptual uncertainty; others make wrong predictions and again others have implications which are inconsistent with other well-established theories. This research project undertakes a logical and ontological analysis of models of Tinnitus pathogenesis. Its primary goal is to reveal logical and ontological errors included in them and, if possible, to eliminate them and revise the model assumptions. In addition, it will be demonstrated that a lot of empirical research could be saved if, prior to empirical investigation, conceptual uncertainty and logical ambivalence of theories would be remedied.

Aural Effects of Noise

Viktor Weichbold

Loss of hearing sensitivity is a long-known effect of continuous exposure to loud noise. In recent years it has become clear that tinnitus and hyperacusis are also due to inner ear damage from acoustic energy. To induce tinnitus or hyperacusis, sound levels need not be so high as to induce a hearing loss (i.e. >85 dB Sound Pressure Level). Rather, impulse noise is presumed to be the detrimental factor in these pathologies. This study assesses the prevalence of tinnitus and hyperacusis in adolescents who play an instrument in a band and who are regularly exposed to different sorts of noise. It is expected that adolescent musicians who are frequently exposed to impulse noise (e.g. drummers) have more hearing complaints than others who are exposed to more stationary noise.

Stapedius Reflex in Cochlear Implant (CI) Patients

Kurt Stephan

Various studies (incl. from our research group) have shown that the stapedius reflex can be elicited by electrical stimulation via a cochlear implant in deaf ears. The electrical stapedius reflex threshold (ESRT) which can be detected by an objective test procedure was found to correlate with the upper limit of electrical stimulation (maximum comfortable loudness), a quantity which is most important for the fitting of CI speech processors. Based on this correlation an objective fitting procedure was developed which is routinely applied at the HSV Department for the CI fitting of children and of patients who cannot verbally report their loudness sensation when their hearing is stimulated by a CI. Long-term stability of ESRT and clinical application of CI fitting based on ESRT are currently being evaluated and possibilities of extending the clinical applicability of the procedure are being investigated.

High-Speed Visualization of Vocal Cord Vibration Anomalies

Thomas Wöllner

High-speed cameras (>4000 images/second) allow for a detailed and, to some degree, real-time visualization of vocal cord vibrations. With the help of software the recorded images can be analysed and vocal cord movements which are irregular or functionally abnormal can be identified. To detect irregularities which are clinically relevant, the software needs a decision algorithm including criteria for recognizing some movement patterns as normal and others as abnormal. This research project attempts to define such criteria by correlating abnormal movement patterns with clinical parameters of dysphonic voices.

Selected Publications

Effect of Wearing a Ski Helmet on Perception and Localization of Sounds. Ruedl G, Kopp M, Burtscher M, Zorowka P, Weichbold V, Stephan K, Koci V, Seebacher J.
INT J SPORTS MED. 2014, 35(8): p. 645–650.

Evaluation of a minimally invasive surgical fixation technique for young children with the Concerto Pin cochlear implant system. Schnabl J, Wolf-Magele A, Pok SM, Url C, Zorowka P, Sprinzl G. EUR ARCH OTORHINOLARYNGOL. 2014 Mar 23. [Epub ahead of print]

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HNO. 2013, 61(1): p. 25–29.

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EUR ARCH OTORHINOLARYNGOL. 2013, 270(5): p. 1679–1687.

Collaborations

- Fa. Grassmayr Glockengießerei, Innsbruck, Österreich
- SCOTT Sports SA, Givisiez, Schweiz

Devices and Services

- Medical outpatient unit
- Audiology (incl. Anechoic Chamber)
- Pediatric Audiology
- Logopedic unit

Diagnostic Radiology

Director:
o. Univ.-Prof. Dr. Werner Jaschke

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Keywords

Radiology, interventional radiology, MRI, CT, angiography, contrast media, ultrasound, PET-CT, robotics, interventional oncology, radiation protection, digital imaging, PACS, microCT

Research Focus

- ultrasound (elastography, musculoskelettal ultrasound, ultrasound of peripheral nerves, ultrasound guided interventions)
- multiparametric imaging of prostate cancer
- MRI (quantification of fat/iron; cardiac MRI; spectrosopy of muscle/myocardium; musculo skeletal MRI including stress MRI of the hip and knee, MR mammography)
- Cardiac CT
- Dual Energy CT
- Emergency Radiology, especially trauma
- Sports injury
- Interventional Radiology (endovascular/oncology)
- Real time dose monitoring of patients
- Diagnosis and treatment of HCC
- Percutaneous stereotactic RFA
- Digital imaging/PACS/post processing of imaging data
- Clinical trials in oncology

General Facts

For clinical research, the Department is equipped with state of the art imaging equipment including 7 CT scanners (1 Dual source/three 64 row/one 32 row/two 16 row), 3 MRI scanners (3T and 1.5T), 1 PET-CT (in cooperation with the Department of Nuclear Medicine), 3 angio suites (1 biplane) and 15 high end ultrasound systems. One CT with a sliding gantry operating in an OR and an imaging suite is dedicated to stereotaxy and CT guided procedures. The Department operates completely digitally using a comprehensive imaging archive that was installed in the year 1999.
There are 66 staff members including 30 residents (radiologists in training).

The Section of Experimental Radiology is staffed with 6 phycisists with different areas of interest such as MRI, MRS, image data processing,radiation protection and computer applications.

The Department houses research facilities for animals (Small Animals Research Lab). High resolution RF coils for MR imaging of animals are available as well as access to PET imaging. Large animals can be imaged on 1 of the clinical CT scanners (32 rows/Siemens). The Core Facility MicroCT is equipped with 2 MicroCT scanners (vivaCT40/Scanco Medical and XtremeCT II/Scanco Medical) which are operated in cooperation with the Department of Trauma Surgery. Both microCT scanners can be used for the high resolution imaging of small animals (ranging from mice to rabbits). The XtremeCTII is also used for high resolution scanning of extremities of patients, mostly for the evaluation of bone density (Osteoporosis). Our research projects are mostly clinically orientated. We focus on the rapid translation of research results into clinical practice. Also, most research projects are interdisciplinary. The Department of Radiology and the Department of Neuroradiology have a close cooperation regard-ing training, patient care and research.

Research

Atherosclerotic Burden and its Relevance in Case of Different Diseases and Treatment Strategies.
Bernhard Glodny, Johannes Petersen
Cardiovascular and cerebrovascular sequelae of atherosclerotic disease are one of the leading causes of morbidity and mortality in humans, and concerns many different fields of medicine. Atherosclerosis can be detected using different modalities of diagnostic imaging. Moreover, treatments are planned using clinical imaging, and cardiovascular risk profiles can be compiled individually. Computed tomography can be used to quantify the “atherosclerotic burden” of all vascular territories in an objective and reproducible manner. Relationships between oral health and health in general have been suspected since many years. One of the first observations to be made in this area of study was that oral and general health is impacted similarly by certain behavioural, social and environmental factors. In the late eighties, and the nineties of the last century, a causal relationship between marginal periodontitis, and atherosclerosis was established.

This fitted perfectly with the concept of atherosclerosis as an inflammatory disease. The aim of the present studies is to adopt the

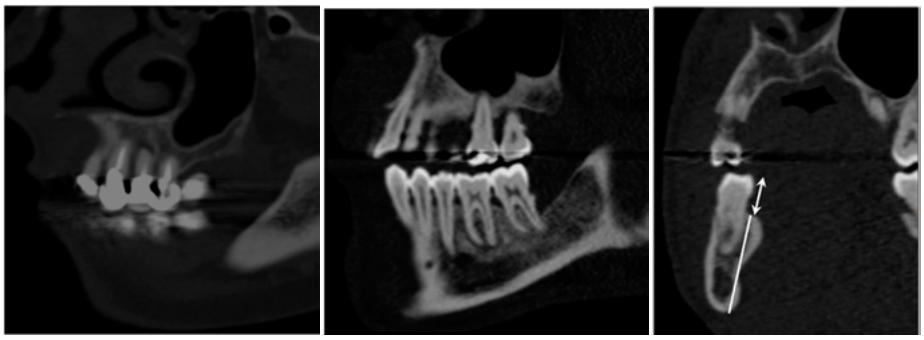

Fig. 1: A typical CAP lesion of a tooth (14) in a semi-coronal reconstruction of a CT. The tooth shows an endodontic filling (a), a CAP lesion of a tooth (46) in a semi-sagittal reconstruction of a CT (b), and a semicoronal reconstruction in the region 46 (c), showing the methods of measurement of the distance between the crown and the alveolar ridge (double arrow) and of measurement of the height of the bone (white line).

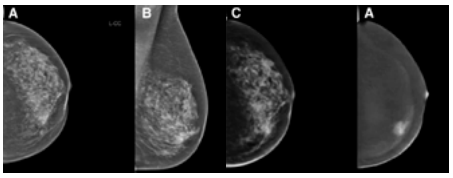

Fig. 2: 65-year-old woman with an invasive ductal carcinoma showing inhomogeneous breast tissue at 9 o'clock as demonstrated by conventional mammography (a, b). Low-energy CESM images (c) are equivalent to conventional mammography, while spectral imaging shows a contrast enhancing mass.

theory of atherosclerosis as inflammatory disease in order to ascertain whether caries may be causative for atherosclerosis as well, especially in cases in which the disease has crossed the enamel. Consequent infections of the dental pulp and apical periodontitis may represent additional causes for atherosclerosis. Dental caries (Fig. 1) turned out to be an independent risk factor for a higher atherosclerotic burden of the aorta. Moreover, dental fillings showed an inverse effect, and were found to be an independent protective factor for aortic atherosclerotic burden (Fig. 2). Chronic apical periodontitis also emerged as a risk factor for higher atherosclerotic burden.

Imaging of Breast Cancer
Martin Daniaux, Tobias De Zordo
Example: Dual-energy contrast-enhanced mammography
Dual-energy contrast-enhanced mammography is one of the latest developments in breast care. Imaging with contrast agents in breast cancer has already been described in previous magnetic resonance imaging and computed tomography studies. However, high costs, limited availability–or high radiation dose–led to the development of contrast-enhanced spectral mammography (CESM). Our most recent research evaluated this novel technique and was supported by GE Health Care (literature below).
The research team focussing on the diagnosis of breast cancer has a vast experience with all of the imaging modalities currently used for evaluating the breast. In case of a suspicious imaging finding we perform fine needle aspiration and/or percutaneous biopsies using stereotaxy or ultrasound guidance. Our unit serves as the largest screening and assessment centre of the national breast-screening programme in Tirol. Approximately 10 000 mammograms and breast ultrasound studies are performed each year making our unit the biggest in Austria.

Non-Invasive Cardiac/Cardiovascular Imaging
Gudrun Feuchtner
CT: 10 Multicenter trials
MRI:Pulse wave velocity (PWV) is the proposed gold-standard for the assessment of aortic elastic properties. It is the aim of this research project to use MR based pulse wave velocity imaging to assess aortic stiffness as a biomarker of myocardial wall stress.

Experimental Radiology
Wolfgang Recheis
Image processing and analysis including Rapid Prototyping based on radiological data represent core interests and tasks of the work group "Experimental Radiology". These projects include multidimensional visualization, quantification of disease patterns based on texture analysis, shape analysis and others (see Fig. 3). Moreover, our new core facility micro-CT allows for the depiction of structures in µm scale in all three spatial dimensions.

Morphological and MR-Imaging
Benjamin Henninger, Christian Kremser
Morphological and functional MR-imaging in all organ systems deveolopment of novel MR-imaging applications and MR sequences
Examples of research projects

a) MRI for the Evaluation of Diffuse Liver Disease: Evaluation of different MRI-methods (relaxometry, chemical-shift imaging, multi-echo approach, screening dixon) for the determination of diffuse liver disease (fat, iron or combined diease); influence of iron on the evaluation of liver fat (see Fig. 4).

b) Diffusionweighted MRI of peripherial nerves (with M. Reinhold, Orth. Surgery)
Value of diffusion-weighted magnetic resonance imaging for the diagnosis and treatment of patients with lumbar nerve root entrapment syndromes.

c) Diffusion tensor imaging of the median nerve in carpal tunnel syndrome.
PI: A. Klauser

d) Assessment of tumour microcirculation by dynamic magnetic resonance imaging (DMRI): Tumour microcirculation is an important biomarker for diagnosis, therapy outcome prediction and therapy monitoring. In our study group DMRI is applied for these purposes to prostate carcinoma, rectal carcinoma, glioblastomas, etc.

e) MR Molecular Imaging using Nanoparticles. Recent developments in nanotechnology provide a wide spectrum of nano sized material for various applications, including tumour targeting and molecular imaging. The main task of our work in this field is to implement MR measurement techniques to facilitate the preclinical characterization and testing of such materials from varying research groups. Main contact: C. Kremser

Imaging of Prostate Cancer
Image fusion and image guided biopsy of the prostate
Multimodal imaging of the GU-tract
Friedrich Aigner, Daniel Junker
PSA is commonly used in screening for prostatic cancer. Patients with high PSA levels frequently undergo systematic prostatic biopsies. However, PSA is not a reliable indicator for prostate cancer

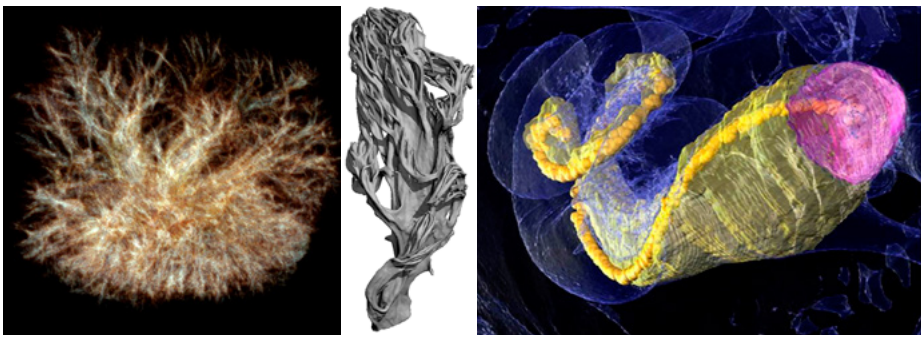

Fig. 3: Left: Application of micro-computed tomography to microstructure studies of the medicinal fungus Hericium coralloides. Pallua JD, Kuhn V, Pallua AF, Pfaller K, Pallua AK, Recheis W, Pöder R., Mycologia. 2015 Jan-Feb;107(1):227–38. arrow) and of measurement of the height of the bone (white line)
Right: 3D Visualization of the round window (pink), the scala tympani (light yellow) and the length (measuring points= yellowish brown) of a sheep cochlea from micro CT datasets, which were used for round window area, cochlea length and scala tympani measurement.

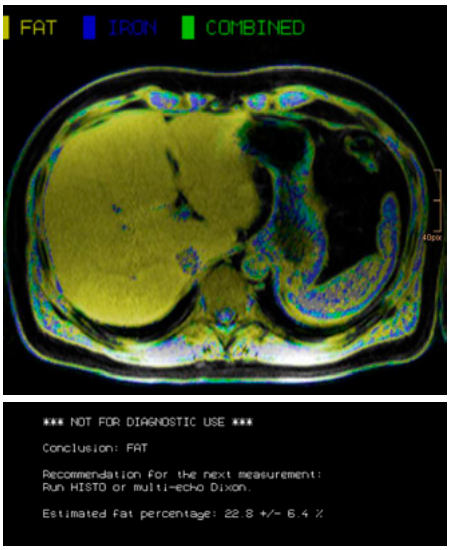

Fig. 4: Above: 43year old patient with suspected diffuse liver disease. The screening dixon sequence (work in progress package 718B, Siemens Healthcare) can provide a fast diagnosis of the predominant pathologic liver deposition – in this case it shows a fatty liver. Below: Automated two-point dixon screening for the evaluation of hepatic steatosis and siderosis: comparison with R2-relaxometry and chemical shift-based sequences.*

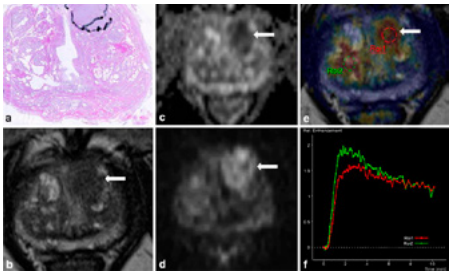

Fig. 5: A 67-year old patient with an anterior located Gleason score 7b prostate cancer in the transitional zone (PSA 5.69 ng/ml), encircled on the whole-mount step-section slide (a): The carcinoma (arrows) shows low signal on T2-weighted images with ill-defined margins (b), diffusion restriction on diffusion-weighted imaging (c, d), and hyperperfusion on dynamic contrast-enhanced MRI (e: red circle on perfusion map) with a focal plateau curve (f: red curve). An area with hyperplastic nodules appears unsuspicious in T2-weighted images (b), diffusion-weighted imaging (c, d), but shows hyperperfusion on dynamic contrast-enhanced MRI (e: green circle on perfusion map) with a focal washout curve (f: green curve), which is even more pathological (PI-RADS 5) than the perfusion of the carcinoma.

and systematic prostate biopsies are invasive and suffer from a rather high false negative rate. Thus, there exists the need for improving non invasive methods for detecting prostate cancer in its early stages. Our group has dealt with imaging of the prostate using ultrasound and multiparametric MRI for nearly 2 decades. Also, we used ultrasound since the early 90s for performing ultrasound guided biopsies. Recently, image fusion became available. We use ultrasound/MRI-fusion for guiding biopsies and avoiding "blind" systematic biospies of the prostate. This approach improves the detection of cancer in large prostates, in the anterior portion of the prostate and in the inner gland. Also, reporting imaging results using the PI-RADS classification helps to avoid unnecessary biopsies. A low PI-RADS classification is a very reliable indicator for the absence of prostate cancer. Our results indicate, that patients with a high PI-RADS classification should undergo an image guided biopsy which has a much higher true positive rate than "blind" biopsies (see Fig. 5).

Musculoskletal Imaging
Andrea S. Klauser *et al.*

- Sonography of Carpaltunnel: definition of cut off values
- Sonoelastography of epicondylitis: accuracy compared to histology
- Sonoelastography of plantar fasciitis: accuracy compared to histology
- Sonoelastography of achilles tendon: accuracy compared to histology
- US guided injections in CTS: Sonoelastographic appearance
- MR-Tractography (DTI, ADI) in median nerves in healty voluntees and CTS patients: comparison to so-nography
- US guided injection in Sacroiliac joints of children: to prove feasability
- DECT in gout: comparsion to US, findings in extraarticular regions
- Hip Traction MRI (FIG)

Ultrasound
Hannes Gruber; Alexander Loizides

Research Focus of the Research Unit:

- Peripheral nerve sonography
- Sonographic evaluation of soft tissue massesv
- Ultrasound guided injections in the spine
- Sonography of the musculoskeletal system
- Contrast enhanced sonography

The Section of surgical ultrasound is a leader in the development of ultrasound techniques for evaluation of peripheral nerves and ultrasound guided nerve root infiltration and pain therapy. One of the most recent publications illustrates our work:
The axillary nerve (AN) is frequently injured during shoulder trauma and imaging is required to define the site and extent of nerve injury. However, the AN has a rather complex course through several soft tissue compartments of the shoulder and axilla. Therefore, imaging of the nerve with MRI and sonography is troublesome. Thus detection and sonographic assessment requires a thorough knowledge of local topography.

Our investigation is aimed at defining reliable anatomical landmarks for AN-sonography in 5 volunteers and later validating the proposed sonographic examination protocol in 10 unselected patients. With strict adherence to the proposed examination algorithm, sonography of the AN was feasible in all volunteers and patients. Furthermore, sonographic findings correlated nicely with the gold standard "surgical exploration" concerning the severity and topography of neural impairment.

Based on our study results we propose our algorithm for AN-sonography as the first-line imaging tool for the assessment of axillary nerve trauma. (PIC)

Interventional Oncology
Reto Bale

- Image guided tumor ablation
- Stereotaxy
- Robotics
- Targeting
- Interventional Oncology

<u>Stereotactic Ablation of Liver Tumors:</u>
Radiofrequency ablation (RFA) allows for local curative tumour treatment by inducing coagulation necrosis with a high-frequency alternating current. The major limiting factor of percutaneous ablation methods is the tumour size, requiring multiple overlapping ablation zones. 3D-planning allowing for the simultaneous display of multiple trajectories and increased accuracy is required. In addition, the virtual 3D plan has to be precisely transferred into the patient. Our team has developed frameless stereotactic aiming devices and immobilization devices for precise punctures in different body regions. Stereotaxy enables highly accurate ablation probe positioning in liver tumors. In 2001 the worldwide first stereotactic radiofrequency ablation (SRFA) of a liver tumor was

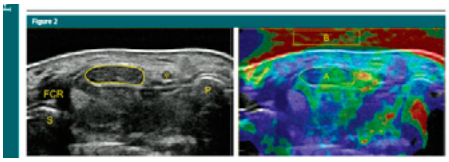

Fig. 6: Carpal tunnel syndrome: diagnosis by means of median nerve elasticity–improved diagnostic accuracy of US with sonoelastography (Miyamoto et al., 2014).

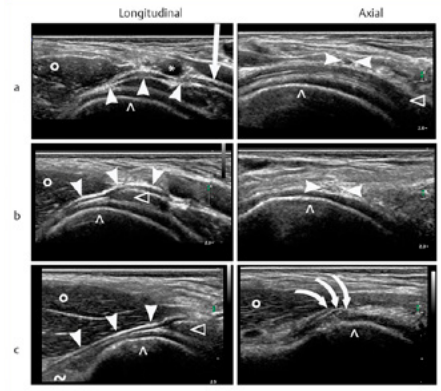

Fig. 7: The 2 US scans a (longitudinal and axial) show the sonographic situation at the "leaving" of the AN from the plexus. The 2 US scans b (longitudinal and axial) show the sonographic situation at the "middle segment" and the 2 US scans c (longitudinal and axial) show the sonographic situation at the "distal segment". The white arrowheads indicate the AN, the white arrow indicates the posterior fascicle of the plexus, (*) indicates the axillary artery, (^) indicate the cortex of the humeral head, (Δ) indicate the subscapular muscle, the rings (o) indicate the teres minor muscle, (~) indicates the long head of the triceps muscle and the 3 bowed, white arrows indicate the 3 terminal branches of the AN forming within the axillary gap.

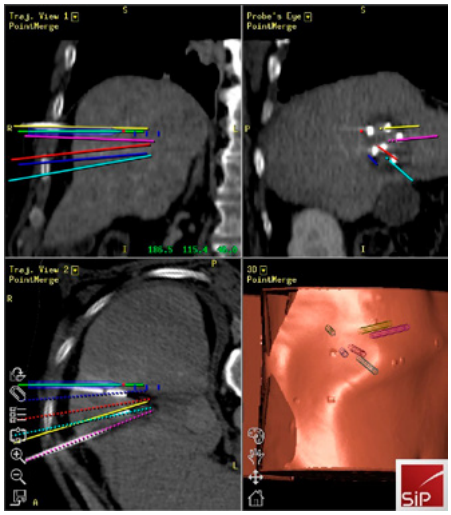

Fig. 8: Stereotactic Ablation of Liver Tumors.

performed in Innsbruck. In the meantime more than 600 patients were successfully treated at our department. Recently a database was established and connected to the hospital information system (HIS). All the relevant information about every patient, treatment and follow-up examinations is continuously collected. Local recurrence rate, complications, long-term survival etc. can now easily be calculated. Currently the efficacy and long-term survival after SRFA is evaluated for different tumor entities. In addition, a major topic of research is the implementation of robotic devices for interventional procedures.

Theragnostics/Image Guided Tumor Therapy (Mitigate Project)

MITIGATE stands for Closed-loop Molecular Environment for Minimally Invasive Treatment of Patients with Metastatic Gastrointestinal Stromal Tumours.

Gastrointestinal stromal tumour (GIST) is a rare disease and frequently affects young patients and often results in a short life expectancy of less than 3 years. Currently there is only one class of effective medications for systemic GIST therapy and often the tumours develop drug resistance after a few years. The MITIGATE consortium representing three European universities, three research organisations and four SMEs will pursue the ultimate goal of developing new protocols and guidelines to effectively diagnose and treat patients with metastatic GIST resistant to current treatment.

MITIGATE is co-funded by the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement no 602306 and will run from October 2013–2017 (Fig. 9).

Selected Publications

The association of chronic apical periodontitis and endodontic therapy with atherosclerosis. Petersen J, Glaßl EM, Nasseri P, Crismani A, Luger AK, Schoenherr E, Bertl K, Glodny B.
Clin Oral Investig. 2014 Sep;18(7):1813–23. doi: 10.1007/s00784-013-1156-3. Epub 2013 Dec 12.

Dual-energy contrast-enhanced spectral mammography (CESM). Daniaux M1, De Zordo T, Santner W, Amort B, Koppelstätter F, Jaschke W, Dromain C, Oberaigner W, Hubalek M, Marth C.
Arch Gynecol Obstet. 2015 Mar 27. [Epub ahead of print]

Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM). Cho I, Chang HJ, Ó Hartaigh B, Shin S, Sung JM, Lin FY, Achenbach S, Heo R, Berman DS, Budoff MJ, Callister TQ, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJ, Dunning AM, DeLago A, Villines TC, Hadamitzky M, Hausleiter J, Leipsic J, Shaw LJ, Kaufmann PA, Cury RC, Feuchtner G, Kim YJ, Maffei E, Raff G, Pontone G, Andreini D, Min JK.
Study.Eur Heart J. 2015 Feb 21;36(8):501–8. doi: 10.1093/eurheartj/ehu358. Epub 2014 Sep 8.

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Diffusion-weighted magnetic resonance imaging for the diagnosis of patients with lumbar nerve root entrapment syndromes: results from a pilot study. Reinhold M, Ederer C, Henninger B, Eberwein A, Kremser C. Eur Spine J. 2015 Feb;24(2):319–26. doi: 10.1007/s00586-014-3602-6

Pretreatment Evaluation of Microcirculation by Dynamic Contrast-Enhanced Magnetic Resonance Imaging Predicts Survival in Primary Rectal Cancer Patients. DeVries AF, Piringer G, Kremser C, Judmaier W, Saely CH, Lukas P, Ofner D. Int J Radiat Oncol Biol Phys. 2014 Dec 1;90(5):1161–7. doi: 10.1016/j.ijrobp.2014.07.042.

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Int J Nanomedicine. 2013;8:4659–71.

Comparison of real-time elas-tography and multiparametric MRI for prostate cancer detection: a whole-mount step-section analysis. Junker D, Schäfer G, Kobel C, Kremser C, Bektic J, Jaschke W, Aigner F. AJR Am J Roentgenol. 2014; 202: W263–9.

Achilles tendon assessed with sonoelastography: histologic agreement. Klauser AS, Miyamoto H, Tamegger M, Faschingbauer R, Moriggl B, Klima G, Feuchtner GM, Kastlunger M, Jaschke WR. Radiology. 2013 Jun;267(3):837–42.

Ultrasound-guided versus computed tomography-controlled periradicular injections in the middle and lower cervical spine: a prospective randomized clinical trial. Obernauer J, Galiano K, Gruber H, Bale R, Obwegeser AA, Schatzer R, Loizides A.
Eur Spine J. 2013 Nov;22(11):2532–7.

Laparoscopic liver packing to protect surrounding organs during thermal ablation. Schullian P, Weiss H, Klaus A, Widmann G, Kranewitter C, Mittermair C, Margreiter R, Bale R.
Minim Invasive Ther Allied Technol. 2014 Oct;23(5):294–301.

Selected Fundings

- K-REGIO Projekt Cardiospect, Land Tirol, Wirtschaftsförderung, ao. Univ.-Prof. Dr. Michael Schocke
- MITIGATE #602306, EU FP7, o. Univ.-Prof. Dr. Werner Jaschke
- RLS-Iron, Land Tirol, Translationales Research Programm, ao. Univ.-Prof. Dr. Michael Schocke
- DISCHARGE #603266; EU FP7; ao. Univ.-Prof. Dr. Gudrun Feuchtner
- Einsatz genetischer Algorithmen zur Erstellung realer, farbkodierter 3D-Modelle zur gleichzeitigen Darstellung von Hämodynamik und Morphologie in zerebralen arterio-venösen Malformationen; Autonome Provinz Bozen, PD Dr. Wolfgang Recheis
- Oralkarzinom WIF-273-01-00015/014-0034, Land Tirol, Translationales Research Programm, PD Dr. Wolfgang Recheis

Collaborations

- iSYS Medizintechnik GmbH
- Siemens Healthcare Österreich
- Ergospect GmbH

Core Facilites

- Micro CT
- Neuroimaging Research

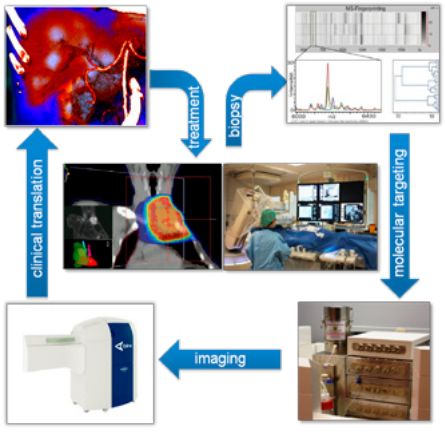

Fig. 9: Stromal Tumours.

Neuroradiology

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Keywords

High-field MRI, MR-spectroscopy, fMRI, DTI, VBM, multimodal imaging, dual-energy-CT, interventional neuroradiology

Research Focus

Neuroradiological research is to a large extent connected to and driven by its clinical partners (Neuro-Focus at the MUI, e.g. neurodegenerative and neuroimmunological disorders, epilepsy, sleep medicine, degenerative spine diseases, brain tumors, neurovascular diseases, psychiatric diseases…). Besides those main partners, Neuroradiology is also involved in the projects of many other departments (clinical and theoretical) at the MUI, MCI and LFU.

Projects generated within the Department of Neuroradiology itself mostly focus on technical developments (dose reduction/dual energy CT, MRI-sequence developments, fMRI/VBM, 1H and 31P MR-Spectroscopy); some projects arise in cooperation with the Department of Radiology, and yet others arise from research experiences in the cerebral processing of pain with emphasis on gender differences. Beside these more experimental projects, Neuroradiology also carries out clinical studies addressing neurovascular disease (Fig. 1), brain tumors and brain development. The Department of Neuroradiology administrates and leads the Core Facility Neuroimaging Research (CF-NIR).

General Facts

Structure of the Research Unit, Aims and Clinical Routine:
The Department of Neuroradiology was established in 2012 and is therefore still under development. Together with the Department of General Radiology, the Neuroradiology is involved in the radiographer and physician educational programs, but also in research and clinical routine activities. Furthermore, the two departments have a long-standing PhD program, and they also started a clinical PhD program in 2013.

Neuroradiology is a department with a large clinical workload, which includes diagnostic and interventional neuroradiology for all neuro-cases both of pediatric and of adult patients. One focus of research is clinically related imaging and intervention studies (including multicenter studies, e.g. SITS open, ACTS II). The senior physicians lead the younger colleagues with interest in neuroradiology and the PhD students of the Department in all aspects of clinical studies, and cooperate with clinical partners within the MUI (mainly Neurology, Neurosurgery, Psychiatry, Child and Youth Psychiatry, Neuropediatrics, Radiology, but also Gynecology, ENT, Nuclear Medicine, Cardiology, Neonatology, Radiation Therapy, Orthodontics and others).

The more experimental research is still developing. Up to now, Neuroradiology has 2 “Laufbahnstellen” (Tenure Track positions) with Ass. Profs. who lead their own research groups: “Diffusion Tensor Imaging (DTI) of spine and nerves” and “Multimodal imaging with focus on MR-Spectroscopy”. Within the latter group, one PhD student began studies in 2015 (ÖNB grant) with focus on 31P MR-Spectroscopy (MRS) in cerebral diseases; MRS and multimodal imaging represent a significant focus of the Department (Fig. 2).

One research focus of the Head of the department is the cerebral processing of pain. She was co-PI of two DFG-funded research projects dealing with visceral pain imaging: “Extinction learning” and “Placebo modulation of visceral pain processing”, and is now translating that experience to local research (Fig. 3, and project listed below). The extensive experience with high

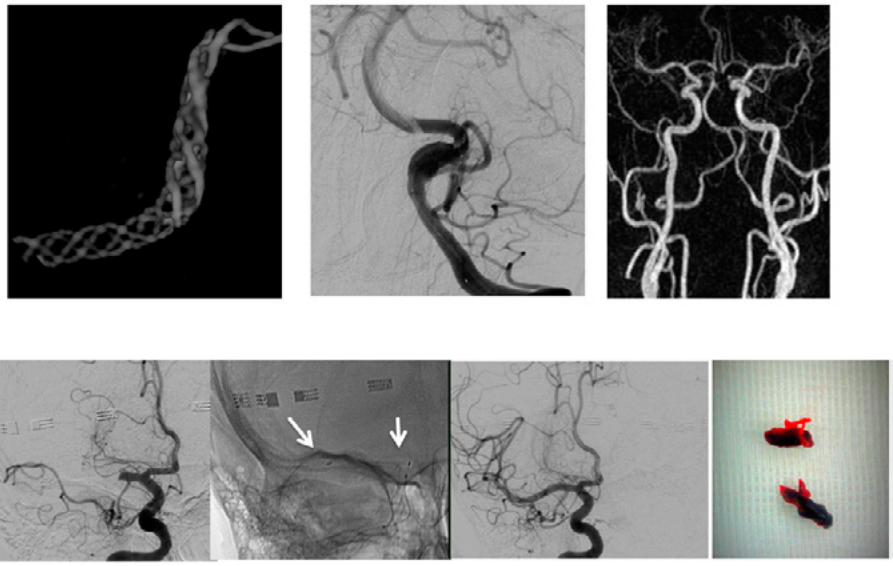

Fig. 1: Endovascular therapy of cerebral aneurysms is more and more important in clinical routine. The first row shows a recent development in stents which is here evaluated in clinical studies
The second row shows an example of endovascular stroke therapy with thrombektomy using one of the recently developed stent retrievers (arrows). Here, the Neuroradiology (in cooperation with Neurology) is part of a big mulicenter study.

field MRI (3T and 7T (now in cooperation with the Erwin L Hahn Institute in Essen, with the Excellence Centre of High Field MRI at the Medical University Vienna, and with the Imaging Unit of the DKFZ in Heidelberg)), both structural and fMRI (multimodal) also represent a further focus on brain processing related to cognitive and emotional processes, particularly with respect to possible gender differences. The fMRI group has a second focus on psychiatric research (resilience, affective disorders, eating disorders), and also on critical emotional situations arising in cardiology.

The Department of Neuroradiology has also a considerable number of collaborations outside the MUI.

Core Facility Neuroimaging Research (CF-NIR)

The main modality of this CF is the BMWF-funded 3 Tesla-MRI-system, which establishes a core facility for MR-based neuroimaging research at the MUI. The 3T MRI was installed in 2011 and started work exclusively for research use in 2012. The CF-NIR is centrally administered by the Head of the Department of Neuroradiology, who leads an interdisciplinary Steering Board. The technical equipment is supported by one physicist (since 2014) and an assistant radiographer. The Team "Neuroradiology" provides support to all associated scientists in technical and post-processing questions. Furthermore, the core facility develops and introduces new MR sequences and technical equipment, such as improved coils. Above all, the Neuroimaging platform offers opportunities to bring different groups together and to transfer knowledge, and it provides a setting for communication and cooperation.

One important recent development with the CF-NIR is the **Neuroimage WING,** which is a grant (Hochschulraumstrukturmittel) supporting an imaging platform at the Medical Universities Innsbruck, Graz and Vienna. Neuroimage WING (WienINnsbruckGraz) is led by MUI (Department of Neurology, Univ.-Prof. Dr. Christoph Scherfler: "Computational Neuroimaging", in cooperation with the Department of Neuroradiology) and was set up to collect and analyse data from different sites and from pooled patient populations. This will lead to higher efficiency and synergies in research projects and also to a know-how transfer. Multiple sclerosis, movement disorders and dementias were defined as the starting projects.

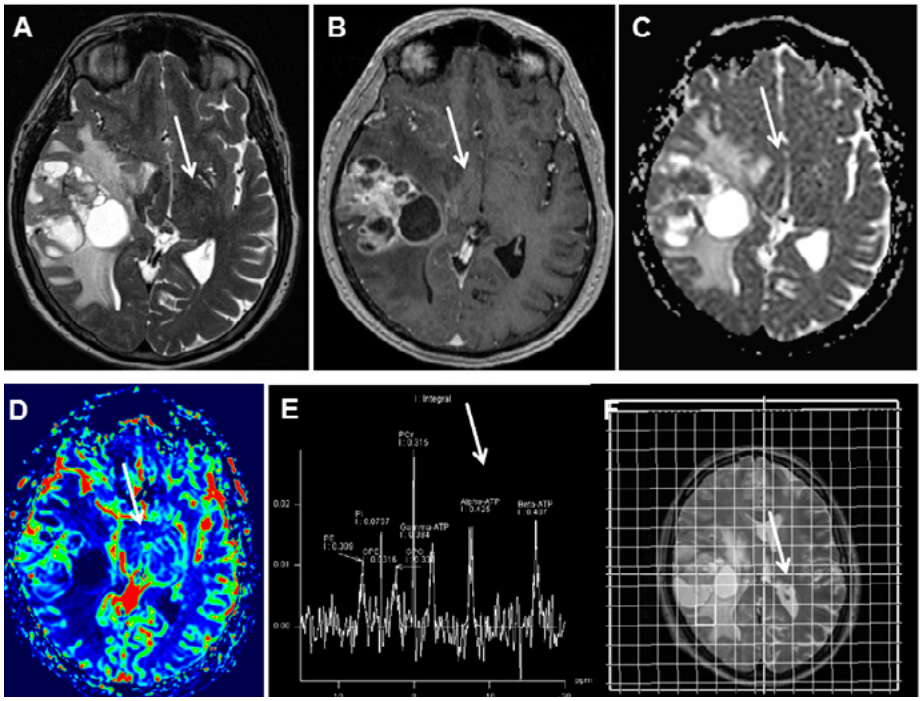

Fig. 2: Multimodal imaging in tumor patients. Multicystic WHO grade IV glioma on the right hemisphere with edema in T2 weighted images (A, arrow), contrast-enhancement (B, arrow), restricted diffusion (C, arrow) and increased perfusion (D, arrow) of the solid parts. 31P MRS spectrum, displaying the high energy metabolites phosphocreatine (PCr, arrow) and ATP (E), the arrow is pointing at the relevant voxel.

Research

This section lists only those research projects which are mainly led by Neuroradiology (NR). Further collaborations, mainly those involving the CF-NIR, have undertaken many additional projects, and yet other projects work with many further radiological techniques.

Attachment and Cerebral Processing
led by Prof. Dr. Buchheim and Prof. Dr. Gizewski, in cooperation with Dr. Labisch and Prof. Viviani

Attachment is a core function in healthy human life, but it is vulnerable in patients with psychiatric diseases. Well known tools such as the "Adult Attachment Projective Picture System" are available; however, this imaging system is not optimal for use in fMRI experiments. The goal of this study is to evaluate a new imaging suite we created, which is especially adapted for fMRI in healthy volunteers in a 3T MRI setting.

Cerebral Processes of Enteroceptive Pain in Patients with Dysmenorrhoea
led by Prof. Gizewski; NR: Dr. Siedentopf, Dr. Steiger in cooperation with Prof. Wildt, Dr. Böttcher, and Prof. Elsenbruch (Essen)

Pelvic pain is an important symptom having high impact in clinical care and therapy. There are several relevant pelvic pain types, including primary and secondary dysmenorrhea. To date, there is no study that addresses interoceptive pain thresholds, subjective perception of pain, and cerebral processing of such stimuli in patients with dysmenorrhea. The rectal barostat distension model, which is well established in the Essen laboratory and has now been transferred to Innsbruck, is a clinically relevant, valid and reliable interoceptive pain model. This paradigm is now being used in a pilot study on dysmenorrhea patients, with the first results showing typical activation in "pain matrix" areas (Fig. 3).

Cerebral Processing of Food Stimuli in Young Anorectic Patients in Respect to Personality Disorders and Gender
led by Prof. Gizewski, Prof. Sevecke, in cooperation with NR: Dr. Steiger, Child and Youth Psychiatry: Dr. Fuchs

Some earlier studies have revealed alterations in cerebral processing in adult anorectic patients. However, since they were based on longstanding disease, their results could not give clear answers on how those functional and structural differences developed in contrast to healthy

volunteers. We have therefore established the application of these stimuli to young patients and will correlate the measured brain parameters with psycho-social data.

Resilience: Neuroimaging of Gender Differences in Healthy Subjects
led by Prof. Hofer and Prof. Gizewski in cooperation with NR: Dr. Siedentopf
Resilience represents the capacity of some individuals to remain healthy or recover easily from adverse events, despite marked negative circumstances and risk factors, whereas others under comparable conditions are particularly vulnerable to disorders and illness. Few studies have examined the structural correlates of resilience, and they involved mostly subjects under risk circumstances or suffering post-traumatic stress disorder (PTSD). The Neuroradiology is involved in this study firstly by analyzing a cross-sectional survey to investigate resilience in healthy volunteers, with a primary focus on potential gender differences, and secondly by addressing the cerebral representation of resilience in the same individuals, with emphasis on gender specificities.

MRI and MRS Parameters in Cerebral Development of Preterm Infants
led by Dr. Djurdjevic in cooperation with Prof. Kiechl-Kohlendorf, Prof. Gizewski and Prof. Buchheim
Up to now, some studies have revealed structural parameters in preterm children that indicate an unfavourable clinical outcome (e.g. the Innsbruck NEOBRAIN study). These first results led to formulate further hypotheses and to develop a study addressing not only structure but also metabolism in preterm children, using MRS. Additionally, fMRI and psychological tests will be applied to obtain data from grown-up former preterm children.

31P MRS in Cerebral Gliomas and Metastases
led by Ass.-Prof. Grams;
NR: Dr. Walchhofer and Dr. Steiger in coop. with Prof. Thomé, Dr. Kerschbaumer, Dr. Freyschlag, Prof. Stockhammer and Dr. Nowosielski, Prof. Nevinny-Stickel
By using MR spectroscopy of phosphorus compounds (31P MRS) it is possible to detect various metabolites of energy metabolism and of membrane turnover. 31P MRS is being applied in patients with cerebral gliomas and metastases in order to investigate tumour heterogeneity and the effects of therapy not only on the tumorous area but on the healthy brain hemisphere as well. The resulting data will be correlated with results obtained from established methods such as 1H MR spectroscopy, MR perfusion and MR diffusion-weighted imaging, as well as with clinical, histological and PET parameters.

31P MRS in Stroke Patients
led by Ass.-Prof. Grams;
NR: Dr. Walchhofer and Dr. Steiger in cooperation with Prof. Willeit and Dr. Knoflach
31P MRS is being applied in patients with acute, subacute and chronic ischemic stroke to gain further insights into the energy metabolism and reorganization mechanisms of infarcted brain and surrounding areas during the acute stage, and to monitor subacute and chronic changes. The results will be correlated with those obtained from established imaging methods (see above) and with clinical data that are routinely collected in the Department of Neurology.

31P MRS in Healthy Volunteers and Brain Trauma Patients
led by Ass.-Prof. Grams;
NR: Dr. Walchhofer, Dr. Steiger in cooperation Prof. Thomé, Dr. Petr, and Dr. Pinggera
31P MRS is being performed in patients with severe traumatic brain injury during the acute, sub-acute and chronic stages. Trauma influence on energy metabolism and on reorganization processes will be investigated and the results correlated with established imaging parameters (see above) and with clinical parameters.

DTI of Spinal Cord
led by Ass.-Prof. Dr. Cartes-Zumelzu; Radiology: Dr. Kremser in cooperation with Prof. Thomé, Prof. Feuchner, Prof. Granata, PD Dr. Broessner and Siemens Medical Imaging
DTI is well established for analysis of white matter and brain structure. However, this method might also be helpful in spinal imaging, especially in degenerative diseases. However, it offers many challenges. The sequence used is influenced by many anatomical structures which cause artefacts, and it also has limited resolution. This project successfully optimized the sequence and then started the study of the first patients showing degenerative cervical changes with narrowing of the spinal canal (Fig. 4).

Dual Energy CT in Stroke Patients
led by Ass.-Prof. Grams; NR: Dr. Kurz in cooperation Prof. Poewe, Ass.-Prof. Glodny, Prof. Willeit, Dr. Knoflach, and Prof. Ortler
Dual energy computed tomography (DECT) can distinguish up to three different materials or tissues. Various projects are investigating the differentiation of blood-brain-barrier disruption, haemorrhage, thromboembolic material, and infarcted and healthy brain, and are correlating them with conventional CT.

Dual Energy CT for Artefact Reduction in Patients with Cranial and Spinal Implants
led by Ass.-Prof. Grams;
NR: Prof. Gizewski, Dr. Kurz, in cooperation with Ass.-Prof. Glodny, Prof. Ortler, Prof. Crismani
DECT also offers the opportunity to reduce beam-hardening artefacts from metal implants by extrapolation of monochromatic

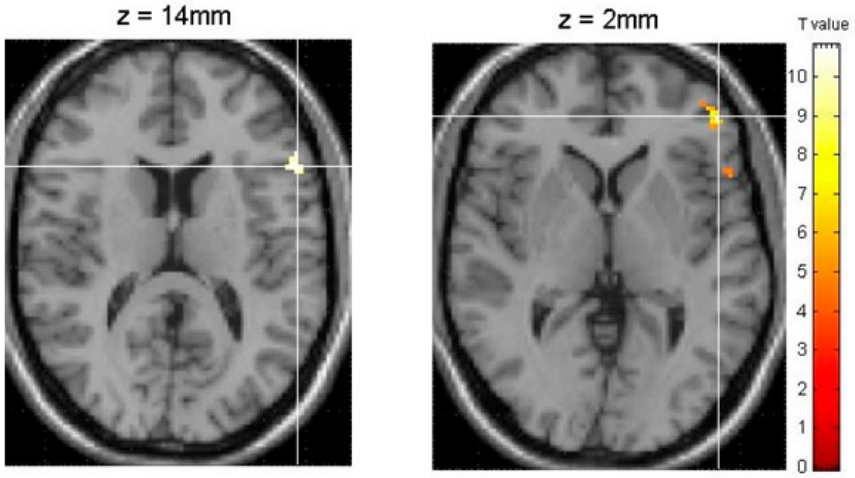

Fig. 3: Activation of insular and DLPFC in the contrast pain versus no-pain in patients with dysmenorrhea. These areas are understood today as main parts of pain processing and areas involved in altered signalling in patients with chronic pain syndromes.

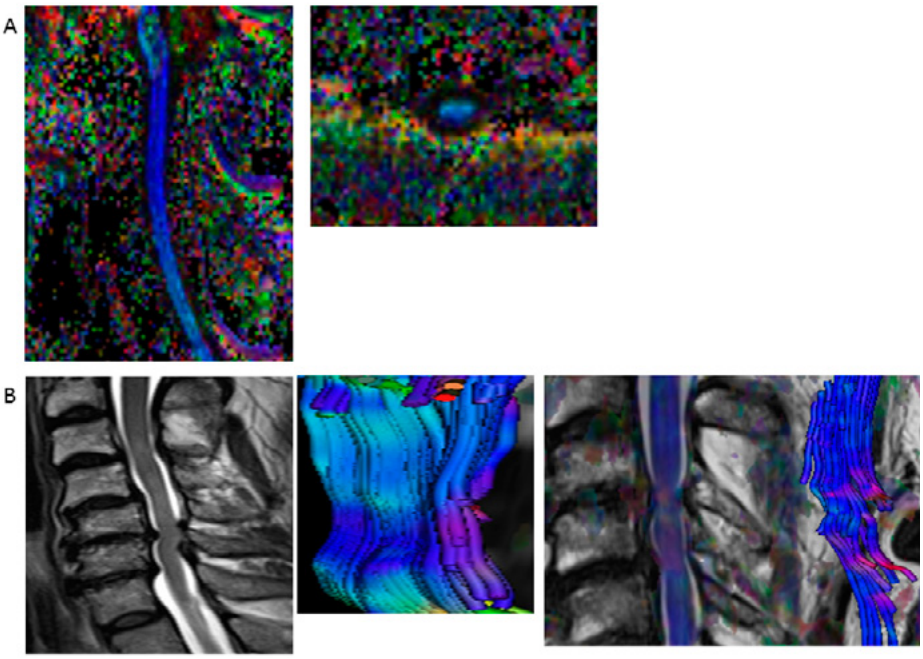

Fig. 4: A shows an optimized DTI sequence from a healthy volunteer. The anisotropy can be calculated without significant artefacts and the tracts can be visualized in both sagittal and transverse orientation with high resolution. 4B shows two patients with degenerative spine disease and visualizes tract disturbances.

(MC) series. This method is being applied in patients with cerebral clips, dentogenic and spinal implants. The aim of these studies is to evaluate the presence of artefacts and to assess the surrounding tissue, in comparison to conventional computed tomography.

Methods of Quantifying Supra-Aortal and Intracranial Artery Calcifications
led by Ass.-Prof. Grams;
NR: Dr. Steinkohl, in cooperation Ass.-Prof. PD Glodny, PD Dr. Beer, PD Dr. Helbok, Prof. Ortler and Dr. Julia Kerschbaum

A method developed in our department to quantify aortal calcification is being applied to examine the supra-aortal and intracranial arteries. The amount of calcification will be correlated with the incidence of intracranial aneurysms or cerebral vasospasm after a subarachnoid haemorrhage.

Selected Publications

Variability of clinical functional MR imaging results: a multicenter study. Wurnig MC, Rath J, Klinger N, Höllinger I, Geissler A, Fischmeister FP, Aichhorn M, Foki T, Kronbichler M, Nickel J, Siedentopf C, Staffen W, Verius M, Golaszewski S, Koppelstätter F, Knosp E, Auff E, Felber S, Seitz RJ, Beisteiner R. RADIOLOGY. 2013; 268(2): 521–531.

Cerebellar dysfunction in a family harboring the PSEN1 mutation co-segregating with a Cathepsin D variant p.A58V. Ehling R, Noskova L, Stranecky V, Hartmannova H, Pristoupilova A, Hodanova K, Benke T, Kovacs GG, Stroebel, T, Niedermueller U, Wagner M, Nachbauer W, Janecke A, Budka H, Boesch S, Kmoch S. NEUROL SCIENC. 2013; 326(1–2): 75–82.

Enhancement patterns in the fibro cellular tissue in different kinds of plaques of the internal carotid artery. Rantner B, Sojer M, Kremser C, Cartes-Zumelzu F, Fraedrich G, Jaschke W, Chemelli-Steingruber I. Eur J Radiol. 2013 Nov;82(11):1989–95.

Correlation of dopaminergic terminal dysfunction and microstructural abnormalities of the basal ganglia and the olfactory tract in Parkinson's disease. Scherfler C, Esterhammer R, Nocker M, Mahlknecht P, Stockner H, Warwitz B, Spielberger S, Pinter B, Donnemiller E, Decristoforo C, Virgolini I, Schocke M, Poewe W, Seppi K. BRAIN. 2013; 136(S): 3028–3037.

Experimental human endotoxemia enhances brain activity during social cognition. Kullmann JS, Grigoleit JS, Wolf OT, Engler H, Oberbeck R, Elsenbruch S, Forsting M, Schedlowski M, Gizewski ER.
SOC COGN AFFECT NEUROSCI. 2014; 9(6): 786–793.

Placebo analgesia in patients with functional and organic abdominal pain: a fMRI study in IBS, UC and healthy volunteers. Schmid J, Langhorst J, Gaß F, Theysohn N, Benson S, Engler H, Gizewski ER, Forsting M, Elsenbruch S. GUT. 2015; 64(3): 418–427.

Residual thrombembolic material in cerebral arteries after endovascular stroke therapy can be identified by dual-energy computed tomography. Astrid E. Grams, Michael Knoflach, Rafael Rehwald, Johann Willeit, Martin Sojer, Elke R Gizewski, Bernhard Glodny. AJNR. e-pub May 2015.

Selected Funding

- Characterization of brain metabolism in ischemic stroke with MR spectroscopy of phosphorous compounds, ÖNB, Dr. Grams
- As Co-investigator: Myocardial MRS correlates of cardiac sympathetic Denervation in PD, FWF, Prof. Wenning and: Clinical Neuroimaging / Neuroimage WING, BMWFS, Prof. Scherfler

Collaborations

- Austria: NEUROIMAGE WING (BMWFW grand: pooled MRI data collection and analysis Med. Universities Innsbruck, Graz, Wien (Neurology and Neuroradiology, 7T MRI), MCI Innsbruck
- Germany: University Hospital Essen (Medical Psychology & Behavioural Immunobiology, Forensic Psychiatry, Neurology, Neurosurgery, Radiology), Erwin L. Hahn Institut Essen, DKFZ Heidelberg/MR-Imaging, Justus-Liebig University Giessen (Neurology, Neuroradiology, Neuropediatrics), University Marburg (Neurology), LMU Munich and Technical University Dresden (Neuroradiology), University Hamburg (Neuroradiology), Goethe University Frankfurt (Neuroradiology), University Tübingen (Psychosomatic Medicine)
- Switzerland: Hirslanden Clinic Zürich, Neuroradiology

Core Facilities

Neuroimaging Research Core Facility (3T MRI)

Center of Dentistry and CMF-Surgery

Dental Prosthetics and Restorative Dentistry

Director:
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Keywords

all-ceramics, silicate-ceramic, CAD/CAM, dental implant, dental materials, dentures, periodontal diseases, rare diseases,

Research Focus

Traditionally, the research of the department addresses issues on dental material sciences, with a special focus on clinical and *in vitro* analyses of dental ceramics, as well as dentures.
The department further focuses on rare diseases with oral phenotypes, and especially on genetical and molecular basis of aggressive periodontal diseases.

General Facts

The Department of Prosthodontics and Operative Dentistry is part of the Department for Dental, Oral and Maxillo-facial Medicine. The Department of Prosthodontic and Operative Dentistry provides an important role in the University School of Dental Medicine by establishing foundational concepts of dentistry to the pre-doctoral dental students. Our primary responsibility lies in the education and training of pre-doctoral students in restorative aspects of damaged dentition to biologic health, function, aesthetics and comfort. This is accomplished by using operative, periodontal dentistry techniques, and prosthodontics, integrated biomaterials and occlusion. 80% of the curriculum is provided by staff members of our department, delivering information through lectures and clinical oversight of patient care 40 hours a week. We also serve a leading position in the preparation and analysis of the MEDAT-Z test for all public dental schools in Austria. Regarding the high competence in educational dentistry, our staff members are routinely consulted as external experts in international accreditations of dental curricula.

The department has access to well-equipped research laboratories for dental materials. These laboratories are routinely used by the faculty and the under-graduate students. Although the department has been involved in many areas of prosthetic and restorative dental materials research, they have been especially recognized for their leadership in the area of ceramics over the past twenty years. Early involvement with these materials and techniques has not only been beneficial in clinical experience and research studies, but also in many clinical publications.

Research

Longevity of Ceramic Restorations
Ulrike Beier, Herbert Dumfahrt

Silicate ceramic restorations are widely used for veneers, inlays, onlays and crowns in dentistry (Fig. 1a, 1b). Long-term data are of crucial importance to optimize clinical practice. Our present focus lies on the evaluation of clinical quality, success rate and estimated survival rate of silicate glass-ceramic restorations over a 20-year period. Aesthetic match, porcelain surface, marginal discoloration and integrity are evaluated following modified California Dental Association/Ryge criteria during clinical examination. Number of restoration failures and reasons for failures are recorded.

Our data show that the main reason for failure is predominantly due to ceramic fracture. Nonvital teeth significantly show higher risk of failure ($p<.0001$). There is a 2.3-times greater risk of failure associated with existing parafunction (bruxism, $p=.0045$).

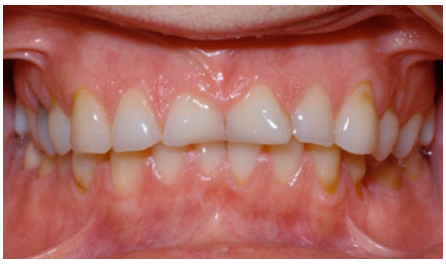
Major Achievements:
All-ceramic restorations offer a predictable and successful restoration with an estimated survival probability of 93.5% over 10 years and 78.5% at 20 years. Significantly increased failure rates are associated with bruxism and nonvital teeth.

Future Goals:
Clinical trials on long term survival and effects of ceramic materials in implant prosthodontics

Dental Material Sciences
René Steiner, Herbert Dumfahrt

Among the clinical researches, the *in vitro* evaluation of dental materials represents the main research focus of our faculty. Series of experiments are performed on the physical material properties like surface roughness, adhesion stability, abrasion resistance and thermostability. The present *in vitro* evaluation is focused on the ability of various ceramic polishing kits to mimic glazed dental ceramic surface. Clinically, chairside adjustments of ceramic restorations involve roughening of the ceramic surface by diamond polishing rotary instruments and subsequent layered to restore surface smoothness. The resulting surface roughness has been shown to decrease flexural strength, which may compromise the long-term prognosis of the restoration.

Rough surfaces may have an abrasive effect on antagonistic and adjacent teeth and lead to an increased adhesion of bacteria. Polishing ceramic restorations may be done by using polishing kits, disks, or diamond polishing paste materials. On the basis of the findings, none of the commercially available ceramic polishing kits could create an ini-



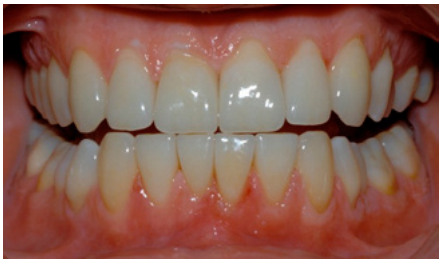


Fig. 1: ceramic restoration of an abraded dentition (A) before, and (B) after treatment

tially smoother surface than glazed ceramic. The addition of a polishing step with diamond polishing paste is recommended to achieve a significant improvement in ceramic surface smoothness. The cost of ceramic polishing kits should not be considered as an indicator of performance.

CAD-CAM-Fabricated Dentures
Patricia Steinmaßl, Ingrid Grunert

CAD/CAM manufacturing of dentures presents an innovative option for fabricating dentures with a reduced amount of dentist visits and promises to provide dentures with better surface properties, which could promote denture hygiene. Denture hygiene is crucial for maintenance not only of oral, but also of general health, as microorganisms colonising the denture surfaces have been shown to be correlated with severe complications such as pneumonia, a common cause of death among elderly people. An appropriate denture fit is important for denture retention. Only well stabilised dentures enable good nutritional intake and speech, and both these factors are very important for the patient's comfort and quality of life. Until now, hardly any preclinical and no clinical data are available on this topic.

To evaluate the material-scientific properties, we analyse conventionally manufactured as well as CAD/CAM manufactured dentures, comparing them *in vitro* with regard to surface roughness and porosity, measuring them both initially, and then again after thermocycling and brushing them; we also measure the release of PMMA-monomer from them. To estimate patient comfort, we measure denture fit, weight and thickness, as well as stress resistance. A clinical study assessing patient comfort, practicability and cost-effectiveness is planned.

The study design has been awarded the "ODV-Wissenschaftspreis des ZIV 2015" and is currently under review for funding by the Tiroler Wissenschaftsfonds and MUI start.

Implantology
Doris Burtscher, Ingrid Grunert

Not only partially but also fully edentulous patients benefit from the successful osseointegration of dental implants, which are a major advance in clinical dental treatment. Nowadays dental implants are available in different materials, such as titanium-based alloys or zirconia, each with various implant surface conditions. In all cases, maintenance of osseointegration and of a steady state in marginal bone level are imperative features for success in implantology. The aim of our present studies is the radiographical evaluation of marginal bone level changes around different titanium implant systems after several years in function. Machined-surface implants and rough-surface implants were early loaded with individual bar retained overdentures. Our data show that there is a significant difference ($p<0.003$) between the two implant systems at the baseline-measurements (0.36mm machined vs. 0.71mm rough-surface) and a highly significant difference for the annual bone loss (0.041mm machined and 0.12mm rough-surface $p<0.001$)).

Both of the implant systems are clinically satisfying. Nevertheless, the machined-surface-group shows a better radiological performance than the rough-surface one.

Future Goals:

- Clinical trials with different implant systems in single tooth gaps
- Clinical trials on patient satisfaction

Hereditary Dental and Periodontal Disorders
Ines Kapferer-Seebacher

Periodontitis is an inflammatory disease linked to complex polymicrobial infection. In susceptible individuals it leads to periodontal tissue destruction by the perturbing the homeostasis between the subgingival microbiota and the host defenses. Periodontal research of our department combines genetical, molecular and microbiological analyses of aggressive periodontitis. In collaboration with the Division of Human Genetics, a Tyrolian 4-generation family with Ehlers-Danlos syndrome type VIII (EDS VIII) is under investigation. EDS VIII is a clinically heterogeneous disorder associated primarily with aggressive periodontal disease, and variable connective tissue features. Only a few patients and pedigrees with this condition have been described. The members of the Tyrolian family have been characterized clinically and immunologically, and linkage analysis and exome sequencing have been performed. At present a candidate gene in the chromosomal region 12p13 is under functional investigation.

Furthermore, several families with rare diseases and oral phenotypes are currently also under investigation. For example:

1. Radicular dentine dysplasia is a rare inherited disorder characterized by abnormal dentine formation, which results in abnormal tooth roots and tooth loss at an early age; therefore, it is often misinterpreted as aggressive periodontitis.
2. (2) Kohlschütter-Tönz syndrome is a rare genetic disorder with epilepsy, psychomotor regression, and severe enamel defects (Fig. 2).
3. (3) In a turkish family with consanguinous parents, heterotaxy-syndrome with aberrant tooth shapes and root resorptions is inherited in an autosomal-recessive mode. In all these families, we perform genetical and medical analyses and characterize the dental defects clinically and histologically.

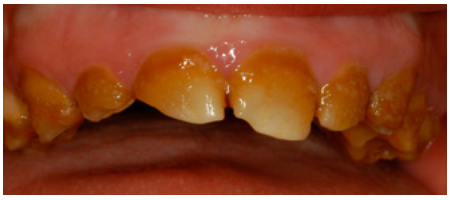


Fig. 2: Kohlschütter-Tönz syndrome is a rare genetic disorder with epilepsy, psychomotor regression, and a severe enamel defect with yellow or brownish discoloration of the teeth.

Selected Publications

Adjusting dental ceramics: An *in vitro* evaluation of the ability of various ceramic polishing kits to mimic glazed dental ceramic surface. Steiner René, Beier Ulrike S, Heiss-Kisielewsky Irene, Engelmeier Robert, Dumfahrt Herbert, Dhima Mathilda. JOURNAL OF PROSTHETIC DENTISTRY. 2015; doi: 10.1016/j.prosdent.2014.12.007. [Epub ahead of print]

A 7-year prospective radiographic evaluation of marginal bone level around two different implant systems: a randomized clinical trial. Burtscher Doris, Norer Burghard, Dalla Torre Daniel, Beier Ulrike S, Schubert K, Grunert Ingrid. CLINICAL ORAL IMPLANTS RESEARCH. 2014; doi: 10.1111/clr.12444. [Epub ahead of print]

Longevity of silicate ceramic restorations. Beier Ulrike S, Dumfahrt Herbert. QUINTESSENCE INTERNATIONAL. 2014;45(8):637–644.

Randomized controlled trial: lip piercing: the impact of material on microbiological findings. Kapferer Ines, Beier Ulrike S, Jank Siegfried, Persson Rutger. PEDIATRIC DENTISTRY. 2013;35(1):E23–28.

Instant dentin hypersensitivity relief of a single topical application of an in-office desensitizing paste containing 8% arginine and calcium carbonate: a split-mouth, randomized-controlled study. Kapferer Ines, Pflug Claudia, Kisielewsky Irene, Giesinger Johannes, Beier Ulrike S, Dumfahrt Herbert. ACTA ODONTOLOGICA SCANDINAVICA. 2013;71(3–4):994–999.

National and Selected Funding

- Genetic and Functional Studies to Identify the Molecular Basis of Aggressive Periodontitis, Jubilee Fund of the Austrian National Bank, Kapferer-Seebacher Ines

Collaborations

- Bernhard Gottlieb University Clinic of Dentistry, Vienna, Austria
- Division of Prosthodontics, Restorative Dentistry, Periodontology and Implantology, Medical University Graz, Austria
- International master for craniomandibular dysfunctions and musculoskeletal medicine, Fortbildungsinstitut ZÄT-INFO
- Mayo Clinic, Minnesota, USA

Orthodontics

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Keywords

3D low budget printer, malocclusion, angle class II, BioBiteCorrector®, miniscrew

Research Focus

Orthodontic mini-implants, 3D low budget printer, tooth surface texture after adhesive removal, class II appliance

General Facts

Orthodontics is a special field of dentistry that focuses on the prevention and correction of malocclusion of teeth and jaws. Orthodontics is performed using removable and fixed appliances.

Research

3-D Low Budget Printer

The aim of the study was to evaluate the benefits and drawbacks of 3D dental model printing compared to standard dental plaster casts. Two different 3D low budget printers were tested in the study. The advantages of 3D-printed casts compared to conventionally made plaster models are: lower weight and easier transport, high resistance to abrasion, low risk of fracture, ease of access: reprinting models at any time, no need for storage space.

12 plaster casts were scanned with the structured light scanner S600 ARTI (Zirkonzahn GmbH, Gais, Italy). The data obtained were used to recreate corresponding models with two low budget 3D-printers: Formlabs Form 1 (Formlabs Inc. Somerville, USA) and Makerbot Replicator 2 (MakerBot® Industries, Brooklyn, USA).

Formlabs Form 1 generates models with the stereolithography (SLA) technique, shaping build part's layer using an ultraviolet laser and light-curing resin. The Makerbot Replicator 2 prints models with the fused filament fabrication (FFF) technology, extruding thermoplastics from a nozzle, layer by layer. The printed copies were then rescanned with the structured light scanner.

The scans of plaster casts and corresponding printing copies were finally digitally compared using the GOMInspect software (GOM-Gesellschaft für Optische Messtechnik mbH, Braunschweig, Germany) and the data were evaluated.

3D-dental models can be a reliable alternative to conventional casts.

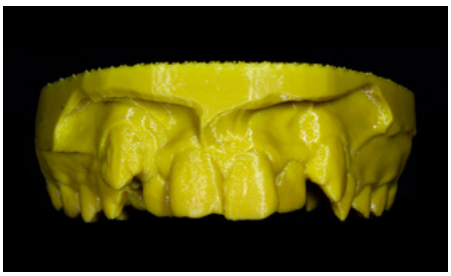


Fig. 1: Model printed by Makerbot Replicator 2

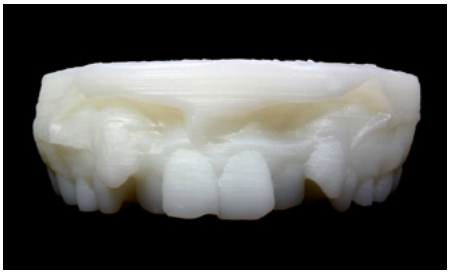


Fig. 2: Model printed by Formlabs Form 1

The Application of the BioBiteCorrector® in Orthodontics: Skeletal vs. Dentoalveolar Changes

The BioBiteCorrector® (BBC) is an orthodontic device that is fixed on the archwires of the multi-bracket appliance to treat class II malocclusions with no need of compliance. It is composed of two triple telescopes, whereas the protrusion of the lower jaw depends on the length of these telescopes.

The aim of this study was to determine whether the effects of the BioBiteCorrector® are also skeletal or have to be attributed to a dentoalveolar compensation.

For the purpose of a pilot study, lateral cephalometric radiographs of 10 patients were analysed. The first radiograph was taken on the day that the BBC was fixed (T1), the second one was taken after the removal of the whole multi-bracket appliance (T2). The patients had an average age of 14.9 years and wore the BBC 6.5 months on average.

The results show a significant change in the position of the pogonion as well as the lower incisal edge.

The sagittal length of the mandible also increased significantly, which is indicative of the skeletal impact of the treatment, in addition to the dent alveolar effect.

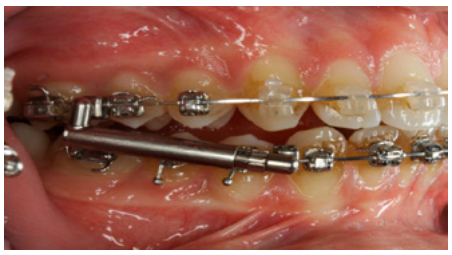


Fig. 3: BioBiteCorrector®

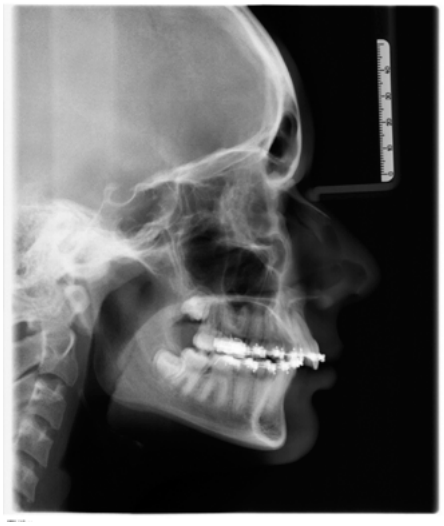


Fig. 4: cephalometric before inserting BioBiteCorrector®

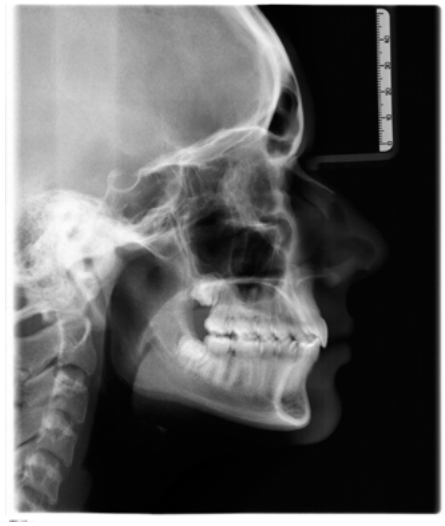


Fig. 5: cephalometric after inserting BioBiteCorrector®

BMP-2 Functionalization of Orthodontic Miniscrews Increases Stability and Cortical Level Bone-to-Implant Dontact: a Histomorphometric and Micro-CT Evaluation

Sufficient cortical bone thickness has been shown to critically effect miniscrew stability and low levels of cortical bone formation at the head of the miniscrew may be a reason for higher failure rates. Bone morphogenetic protein-2 (BMP-2) functionalized implant surfaces have previously been explored to enhance overall osseointegration and induce cortex-bearing bone formation at supraalveolar peri-implant defects. The aim of this study was to investigate the effect of a BMP-2 functionalized implant surface on the stability and cortical-level bone-to-implant contact ratio (BICR) of orthodontic miniscrews.

36 miniscrews (length: 6 mm; diameter: 1.5 mm) were placed in 3 swines. Half of the miniscrews were coated with nano-crystalline diamond (NCD) and functionalized with BMP-2. Upon insertion, stability was evaluated by measuring resonance frequency (RF) with an Osstell ISQ wireless probe. An animal was sacrificed after 2, 4 and 12 weeks and resonance frequency analysis (RFA) was performed again. Recovered miniscrews and surrounding bone were scanned by micro-CT before sectioning for bright field microscopy. BICR was then evaluated in 2D on histological samples and in 3D on micro-CT scans at both the cortical (head/neck) and trabecular (thread) level of the miniscrews. Stability, as expressed by an increase in RFA results, significantly increased for BMP-2 functionalized miniscrews after 4 and 12 weeks.

The neck/tread ratio of the 2D and 3D BICR showed significantly higher cortical level bone-to-implant contact of BMP-2 functionalized miniscrews at those time-points. There was a positive correlation between higher RFA results and cortical BICR. These results suggest an increase in stability of BMP-2 functionalized miniscrews as a result of higher BICR at the cortical bone level.

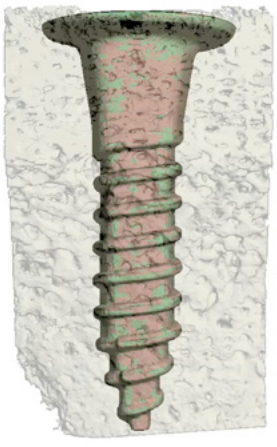


Fig. 6: Micro CT of miniscrew

Selected Publications

How Precise is the Production of Models by Low Budget 3D Printers? A Pilot Study. B Paal, M Bert, J Gröger, W Recheis, AG Crismani. Inf Orthod Kieferorthopädie. 2014; 46;261–266.

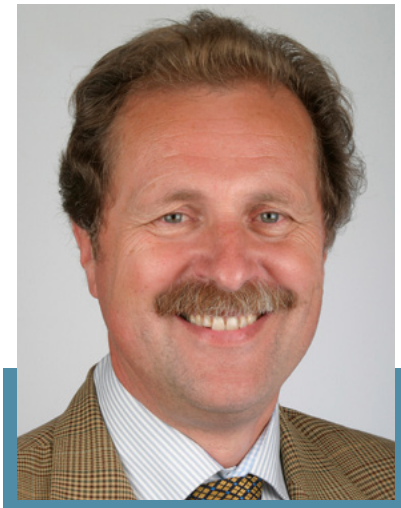
Is the Temperature Development During Debonding Identical for all Rotating Dental Instruments?. R Biedermann, K Winter, AG Crismani. Inf Orthod Kieferorthopädie. 2014; 46; 235–240.

The Application of the BioBiteCorrector® in Orthodontics: Skelettal vs. Dentoalveolar Changes. J Schmid, E Pasin, T Magg, AC Crismani. Inf Orthod Kieferorthopädie. 2014; 46;267–270.

Collaborations

- Wolfgang Recheis,Department of Radiology, Medical University Innsbruck, Austria
- Michael Rasse, Department of Oral and Maxillofacial Surgery, Medical University Innsbruck, Austria
- Volker Kuhn, Department of Traumatology, Medical University Innsbruck, Austria
- Michael Bertl, Department of Orthodontics, Medical University Vienna, Austria

Cranio-Maxillo-Facial and Oral Surgery



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Keywords

Cranio-maxillofacial and oral surgery, implants, biological surfaces, osseointegration, wound healing, tissue engineering, reconstructive medicine, nano technology

Research Focus

- Reversing impaired healing of irradiated bone through the use of immobilized growth factors on nanostructured osteosynthetic Material
- Smart Implants – Monitoring of osseous healing and bone remodelling *in vivo.*
- VascuBone – Development of a tool box for tailor-made angio-inductive or Vascularized Bone implants

General Facts

The consequences of Radiation Therapy in Head and Neck Tumour Patients is a major focus of the Department of Cranio-Maxillofacial and Oral Surgery since all aspects of wound healing including cellular behaviour, blood flow and stem cell activation are influenced by radiation.
Using smart implants as a new sensing technology allows us to gain an insight into bone healing based on serial analysis of impedance spectroscopic examinations before radiographic or histologic changes are detectable.

Reconstructive Medicine:
Reconstructive facial surgery is one focus

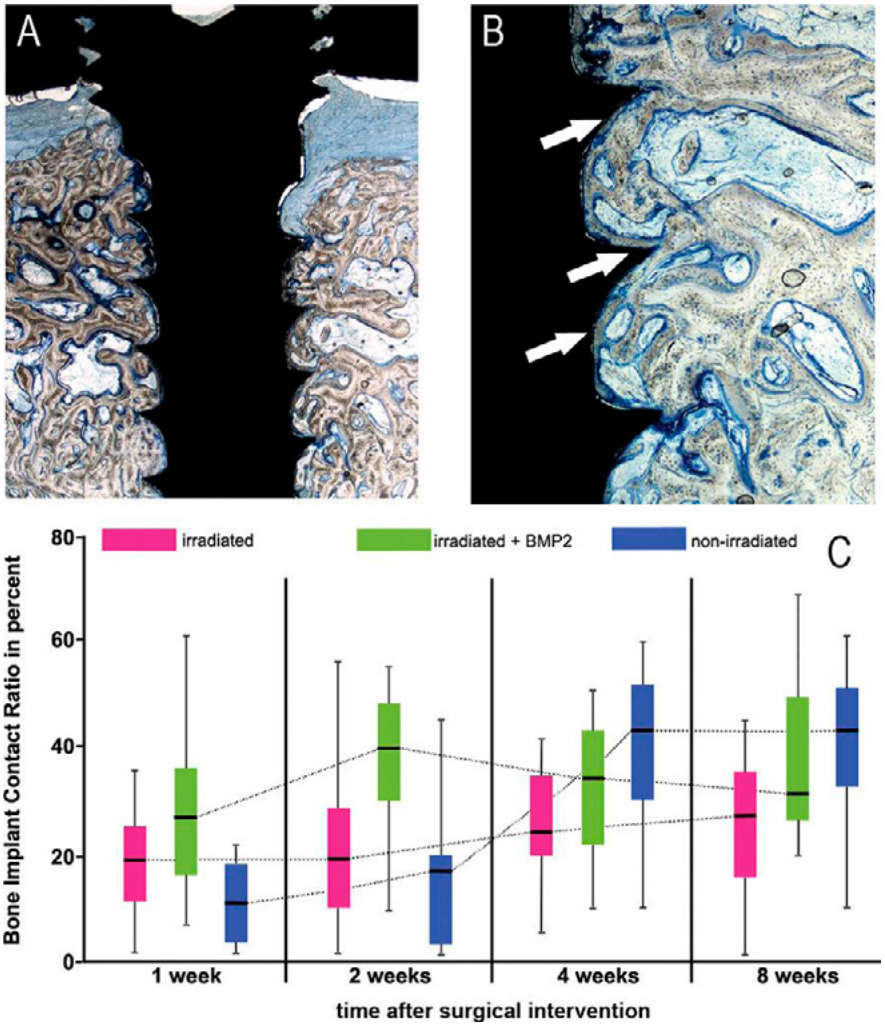

Fig. 1: Histological evaluation of the bone implant contact ratio (BICR) at the osteosynthesis screws. (A) Histological overview of the locking screw in bone subjected to toluidin blue O staining. (B) Detailed view of the osteosynthesis screw highlighting the bone contact areas (arrows). (C) BICR after 1, 2, 4, and 8 weeks of the 3 groups. BMP-2 immobilized on nano-crystalline diamond (green) resulted in an initial increase of BICR in the irradiated bone. Despite this initial increase the BICR after 8 weeks was lower compared with unirradiated bone (p ¼ .08) (blue).

of the Department of Cranio-Maxillofacial and Oral Surgery. After ablative tumour surgery or resection of osteonecrotic and infected bone, free tissue transplants are microvascularly anastomosed for facial rehabilitation. Research is focused on the development of minimally invasive or artificial transplants.

To achieve this goal the Department is part of the FP-7 framework project "Vascubone" together with a further 14 partners. The department is a leader in the field of preclinical trials, provides the technology for hard tissue histology and immohistochemistry and plans and conducts animal trials.

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W. Kapferer, G. Lepperdinger
Department of Biomedical Aging Research, University of Innsbruck, Innsbruck, Austria

Doris Steinmüller

Research

1. Bioactive Surfaces in Cranio-Maxillo-Facial and Oral Surgery

Implants have revolutionized patient care in all fields of medicine and dentistry. Titanium has evolved as the leading raw material when treatment of bone and cartilage diseases/degeneration as well as tooth loss necessitates osseointegration of individualized tissue replacement options.

This is mainly due to its bioinert properties. Titanium implants in particular provide excellent results in healthy young and adult patients. But the success rate of any implant is hampered if the implant site suffers from poor bone wound healing. Due to conditions affecting bone turnover and homeostasis such as osteoporosis, age, radiation therapy, bisphosphonate intake, infection, severe trauma or other pathology-related bone changes, osseous healing at the implant site is frequently limited. To

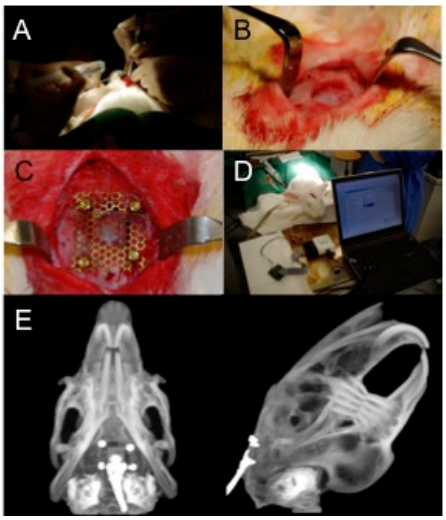

Fig. 2: Implantation of the biosensor and radiological control. (A, B) Creation of a full thickness calvarial defect; (C) Fixed biosensor; (D) Postoperative impedance measurement; (E) Radiological control of sensor position in two planes.

overcome shortcomings of bone healing and osseointegration we used bioactive BMP-2 on nano-crystalline DIAMOND (NCD) coated implants based on nanotechnology and physisorption which is an approach that has been patented (Steinmueller-Nethl D, Inventors: Steinmueller-Nethl D, Steinmueller D; Bonn G, Huck C, Najam-Ul-Haq M, Rainer M, Stecher G; Kloss F, Gassner R. Biological Surfaces. Patent Number: EP1824528 (Fig. 1).

2. Smart Implants: Sensors as Technology Asset

Radiology remains the gold standard to show bone wound healing and osseointegration of implants despite the fact that it provides only a snap shot of the dynamic bone growth and regeneration process. Even histology provides only a glimpse of the activity or inactivity of osteoblasts, osteoclasts and osteocytes in bone.

The goal of this research was to test a novel sensing technology that is based on bioimpedance and which in due course may allow the monitoring of the osseous healing processes in an uninterrupted manner. A sub-critical size defect with full thickness was created in a rabbit calvaria that was sufficiently large to accomodate the biosensor which was mounted on a titanium mesh and inserted into the defect. The mesh was then fixed to the adjacent bone with micro-screws. Measurements were performed every 3 or 4 days during a period of 6 weeks and spectroscopic analysis of the sensor signals were archived for later analyses. After 6 weeks the bone defects together with the biosensor was explanted and examined by means of micro-CT and histology. Serial analysis of the impedance spectroscopic examinations was performed by firstly fitting the data gathered during defect healing to a Cole-Cole equation. Thereafter the results were compiled, and the spectra thus obtained revealed gross changes in material densities during healing. Terminal analyses, by means of micro-CT as well as histology, demonstrated incomplete yet ongoing osseous healing as the defect was filled with both connective tissue as well as with newly formed bone. Furthermore, no obvious signs of inflammation were observed indicating that the implanted biosensor is biocompatible. Our results on dielectric spectroscopy may serve as a potential method for close continuous monitoring of bone wound healing in craniomaxillofacial and oral surgery in the future (Fig. 2).

3. VascuBone

The FP7 Project Vascubone deals with the development of an artificial vascularized bone transplant for the reconstruction of large facial defects. This is achieved through the use of a construct consisting of a vascular bed, modified bone replacement material and mesenchymal progenitor cells. The vascular bed is engineered by decellularicing a porcine gut segment with its supplying vascular bed and reseeding the vessels with endothelial progenitor cells from the future recipient.

Several animal experiments were performed in order to improve the common bone replacement material beta-tricalcium-

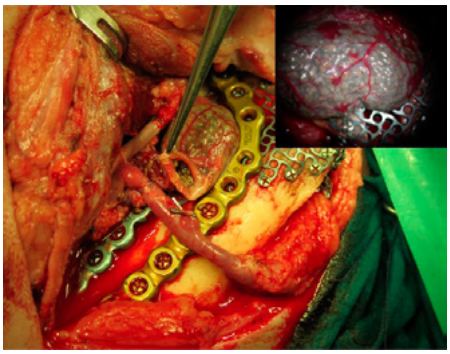

Fig. 3: Picture shows the mandibular continuity defect bridged with reconstruction plates and the microvascular anastomosed artificial transplant. The magnification shows the circulation of the transplant after anastomosis (DDr. Stigler).

phosphate. The functionality of the beta TCP surface with nanocrystalline diamonds was tested in animal models. The diamond particles by themselves modified the wettability and cell adhesion properties of the surface and were further shown to bind covalently or via physisorption different growth factors such as BMP-2 and Angiopoietin-1. The new knowledge thus acquired on functionalized biomaterials and cell behaviour led to the application of such an artificial transplant for reconstructing a mandibular continuity defect in sheep. The Horizon2020 Proposal "VascuReGenTis" has been submitted in order to test this technique in clinical trials (Fig. 3).

4. Bone Regenerating Effect of Strontium Functionalized Implant Surfaces

The functionalization of implant surfaces has gained increased attention in the last decade due to research into implant dentistry. A lot of different approaches directed towards enhanced bone healing have been investigated over the past couple of years and they always attempt to achieve rapid osseointegration of titanium implants. Since strontium (Sr) is known for its anabolic and anti-catabolic effects on bone, research has been focused on this alkaline earth metal and its potential impact on osseointegration.

The objective of our studies was to investigate the performance of Ti implants with a Sr functionalized titanium coating (Ti-Sr-O), which exhibits a continuous release of strontium, with respect to osseointegration.The examined Ti-Sr-O coatings, prepared from a magnetron co-sputtering process, differed from each other in coating thickness, Sr content and Sr release characteristics and the observed increase in new bone formation was found to correlate with the amount of Sr released *in vitro*. The results indicate that sputtered Ti-Sr-O coatings, showing sustained release of Sr, accelerate osseointegration in healthy and osteoporotic bone plus in comparison to established surfaces and may thus have an impact on practical applications for medical implants.

<u>Major Achievements Include:</u> The production of implant surfaces with predictable Sr release properties; Verification of beneficial effects of Sr functionalized surfaces *in vivo*

<u>Future Goals:</u> The evaluation of mechanical anchorage via push-out tests; Implementation of Sr functionalized implant surfaces in orthopedic and dental implantology

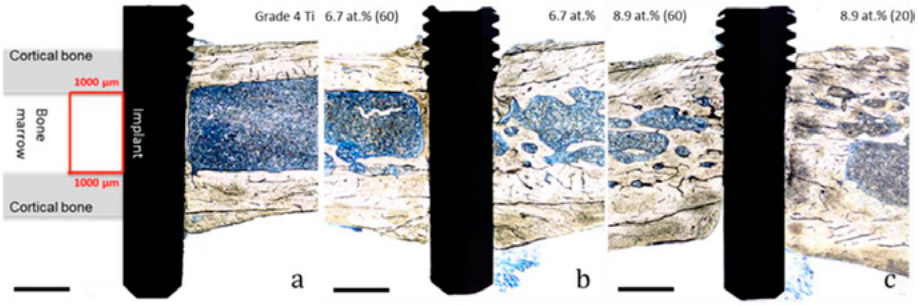

Fig. 4: Schematic illustration and histology (toluidine blue staining) of merged slides with representatives of each group. The 1500 x 1000 mm2 box marked scheme (a, left) indicates the standard area used to evaluate new bone formation. The area of new bone formation inside this box was measured for all samples and used to calculate the percentage of de novo bone synthesis with respect to the total reference area. The side of the reference box facing the implant surface was used to evaluate the percentage of direct bone-to-implant contact with respect to the total length of the reference. Minimal bone formation observed in the Grade 4 Ti (a, right). 6.7 at.% Ti-Sr-O with a 60 minute pre-wash (b, left) and no pre-wash (b right) showed increased bone formation. A higher amount of bone apposition could be observed for the 8.9 at.% Ti-Sr-O with a 60 minute pre-wash (c, left) and a 20 minute pre-wash (c, right). The implant bodies are not shown to scale as these had a diameter of 1100 µm. Scale bar is 1000 µm. Data and references cited in Offermanns et al. 2014.

Selected Publications

BMP-2 immobilized on nanocrystalline diamond-coated titanium screws; demonstration of osteoinductive properties in irradiated bone. Kloss F, Singh A, Hächl O, Rentenberger J, Auberger T, Kraft A, Klima G, Mitterlechner T, Steinmüller-Nethl D, Lethaus B, Rasse M, Lepperdinger G, Gassner R (2013).
Head Neck 35: 235–241, 2013. (Journal of the Sciences and Specialties of the) Head and Neck. doi: 10.1002/hed.22958.

Bone marrow T cells from the femur are similar to iliac crest derived cells in old age and represent a useful tool for studying the aged immune system. Pritz Theresa, Landgraf-Rauf Katja, Herndler-Brandstetter D, Rauf R, Lair J, Gassner R, Weinberger Birgit, Krismer M, Grubeck-Loebenstein Beatrix (2013).
Immunity & Ageing. 2013 10:17 doi:10.1186/1742-4933-10-17.

Systemic impact molds mesenchymal stromal/stem cell aging. Reitinger S, Schimke M, Klepsch S, de Sneeuw S, Yani SL, Gassner R, Ertl P, Lepperdinger G (2015, April 8).
Transfus Apher Sci / pii: S1473-0502(15)00072-5. doi:10.1016/j.transci.2015.04.008.

Accelerated bone ingrowth by local delivery of strontium from surface functionalized titanium implants. Andersen OZ, Offermanns V, Sillassen M, Almtoft KP, Andersen IH, Sorensen S, Jeppesen CS, Kraft DC, Bøttiger J, Rasse M, Kloss F, Foss M.
Biomaterials. 2013;34:5883-90.

Enhanced osseointegration of endosseous implants by predictable sustained release properties of strontium. Offermanns V, Andersen OZ, Falkensammer G, Andersen IH, Almtoft KP, Sorensen S, Sillassen M, Jeppesen CS, Rasse M, Foss M, Kloss F.
J Biomed Mater Res B Appl Biomater. 2014;25:33279.

Selected Funding

Jubilee Fund of the Austrian National Bank (# 12246) and Synthes, Salzburg, Austria (titanium reconstruction plates and screws):
Title: Reversing impaired healing of irradiated bone by immobilized growth factors on nanostructured osteosynthesis material
Function: Principal Investigator: Robert Gassner (70%); Co-Investigator: Frank Kloss und Günter Lepperdinger (30%)

Tyrolean Future Fund – Translational Research Project
Title: 'Smart Implants – Monitoring of osseous healing and bone remodelling *in vivo*'.
Function: Principal Investigator: Günter Lepperdinger / Biomedical Aging Research , University of Innsbruck (33%), Robert Gassner / CMF Surgery Innsbruck (33%) und Peter Ertl / Austrian Research Center Seibersdorf (33%)

EU project FP7-HEALTH project: VascuBone – Development of a tool box for tailor-made angio-inductive or Vascularized Bone implants

Medical University of Innsbruck / Robert Stigler (Frank Kloss), Robert Gassner, Michael Rasse
Consortium with 15 participating institutions / universities

"Strontium functionalized titanium implants", Danish National Advanced Technology Foundation, Frank Kloss/Vincent Offermanns

Collaborations

- Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Denmark
- Danish Technological Institute (DTI), Aarhus, Denmark
- Danish National Advanced Technology Foundation, Copenhagen, Denmark
- Elos Medtech Pinol A/S, Gørløse, Denmark
- Department of Engineering Sciences, Applied Materials Science, University of Uppsala, Sweden

Pediatrics I

Director:
Univ.-Prof. Dr. Gerhard Gaedicke

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Keywords

Molecular genetics of rare childhood diseases, cell biology, cancer biology, drug discovery, biomarkers, inherited metabolic disorders, metabolomics, breath gas analysis, paediatric gastroenterology and hepatology, inflammatory bowel disease, paediatric haematology and oncology, paediatric haemostaseology, diabetes in childhood, epidemiology, national diabetes registry and international registry comparison

Research Focus

- Genetics of rare diseases, metabolomics
- Genetic predisposition to chronic diarrhea, disruption of intestinal epithelial polarity
- Cell death and metabolism in childhood malignancies; FOXO transcription factors, XIAP, Survivin
- Biomarkers for autoimmune diseases
- Genetic and clinical characterization of inherited metabolic diseases
- Paediatric diabetes: epidemiology, national registry, long term complications, genetics of neonatal diabetes
- Paediatric endocrinology: clinical and genetic studies on thyroid, adrenal glands and bone disorders
- Haemolytic uraemic syndrome
- Role of ACE2 in ARDS
- mTOR inhibition in patients with neuroblastoma and acute lymphatic leukaemia
- Genetic characterization of rare channelopathies

General Facts

As part of the Medical University, the Children's Hospital has a unique position in providing the highest level of paediatric care in western Austria. Simultaneously, it represents an institution for scientific research as well as for the teaching of medical students. The training of physicians, as well as their scientific training which is a prerequisite for scientific careers, is a priority at our hospital. This also includes continued training of clinical specialists, physicians, as well as nursing staff and other medical professionals working with children and adolescents.

A great challenge will be the move into the second construction block of the new building in 2015. The Paediatric Intensive Care Unit (PICU) will be extended and will take over the existing emergency department, which will be completed by an admission and observation ward with eight beds. The general outpatient clinic, as well as the special outpatient clinic, will be extended by a day clinic with the same number of beds thereby avoiding hospitalization, especially of children with chronic diseases. Paediatric surgery as well as all of the departments of specialized surgery, which have been until now treating children in different paediatric surgical wards within their Departments, will in future have their beds in integrated into interdisciplinary wards at the Children's Centre. Interdisciplinary means that the surgeons will in future share the care of these children with the paediatricians. Close cooperation is already well established with our Departments of Pediatrics 2 (Neonatology) and 3 (Pediatric Cardiology, Pulmunology, Allergology and Cystic fibrosis).

It is our understanding that clinical psychology is an integral part of clincal paediatrics and therefore we closely cooperate with the Department of Paediatric and Adolescent Psychiatry. We will place a special emphasis on the participation of the Department of Human Genetics in the diagnosis and follow up of rare diseases. The same applies to imaging techniques in the field of diagnostics. Paediatric Radiology, ultrasound, CT scans and magnetic resonance tomography will be covered by the Department of Radiology in the Children's Hospital. Overall, the intention is that in the future the specialists will come to the child in order to avoid cumbersome transport of sick children within the entire campus.

Research

Molecular Genetics of Congenital Diarrhoea
Assoc. Prof. Dr. Andreas Janecke,
Assoc. Prof. Dr. Thomas Müller,
Assoc. PD Dr. Peter Heinz-Erian,
Dr. Georg Vogel,
Assoc. Prof. Dr. Michael W. Hess,
Univ.-Prof. Dr. Lukas Huber

In 2014, our Microvillus inclusion disease Research Group identified that loss of Syntaxin 3 causes a variant form of the congenital enteropathy microvillus inclusion

disease. Understanding the pathogenesis of these disorders can significantly advance our knowledge of intestinal epithelial cell polarity.

Paediatric Haematology/Oncology
Members: Assoc. Prof. Dr. Roman Crazzolara, Dr. Gabriele Kropshofer, Assoc.-Prof. Dr. Bernhard Meister, Univ.-Prof. Dr. Gerhard Gaedicke
The Paediatric Oncology Lab is focused on identifying transcription factors that regulate normal hematopoietic and leukemic cell biology. The strategy of targeting these protective growth-activating mechanisms holds significant promise with regard to the development of new therapeutic options. Our recent data suggest that disruption of the signalling molecules, mTOR and p38MAPK, will enhance the efficacy of current therapeutic agents. An ongoing clinical trial of the mTOR inhibitor Rapamycin in patients with relapsed neuroblastoma provides a source of patient samples which we will collect by our lab in order to further elucidate the biology of ALL and its response(s) to mTOR inhibition. Further studies into the signal transduction pathways inhibited by natural compounds are ongoing.

A clinical trial of gene modulation in ALL patients treated with glucorticoids has enabled us to obtain significant information on the details of leukemia biology and is currently directed towards the exploration of factors that affect chemo-sensitivity.

In addition we continue to explore disrupted signalling pathways in rare paediatric oncology and haematology patients. Recently, we identified deletion of KINDLIN-3 as an egress factor for osteoblasts, contributing to osteopetrosis in LAD-III patients. The characterization of IC1 deletion in a patient with Beckwith-Wiedemann syndrome has demonstrated its role in elevated IGF-2 expression and the origin of Wilms tumours in affected patients.

Cancer Biology
Assoc. Prof. Dr. Michael Ausserlechner
Our research team investigates how cell death and metabolism in childhood malignancies is controlled by FOXO transcription factors and by Inhibitor of Apoptosis proteins (XIAP and Survivin). In a translational approach, we develop strategies to target these death regulators with small compounds discovered by drug repositioning and in tight cooperations with pharmaceutical institutes and the pharmaceutical industry. Closely affiliated with both the division of Paediatric Oncology and Haematology at the Medical University of Innsbruck and the Tyrolean Cancer Research Institute, our research extends from the laboratory to the patient using the basic tools of molecular and cell biology, genomics, genetic epidemiology, human and cell imaging technology and cell therapy. Integrated in 5 local and 18 international clinical trials, the group's bench-to-bedside approach has enabled us to achieve greater translation of research from biomedical discovery into new prevention strategies, diagnostics, prognostics and therapies.

Inherited Metabolic Diseases/Rare Diseases
Assoc. Prof. Dr. Daniela Karall, PD Dr. Sabine Scholl-Bürgi
In recent years, our research has focused on identification of new disorders (e.g. CoQ4, mitochondrial fission and fusion, SPENCD, PIGQ) and characterization of known disorders (e.g. LCHAD deficiency, GLUT1-deficiency syndrome, PIGA, FBXL4, ALG8-CDG).

Neuropaediatric Diseases
PD Dr. Edda Haberlandt,
Dr. Matthias Baumann
We focussed our research on collaborations to describe rare channelopathies of neurological diseases (Ehlers Danlos, KCNQ2-, GABRG2-, GRIN2A-Mutation and Ring Chromosome 18).

Paediatric Diabetes Research Group
Assoc. Prof. Dr. Sabine Hofer,
Assoc. Prof. Dr. Elisabeth Steichen,
Assoc. Prof. Dr. Daniela Baumgartner
Sabine Hofer is a member of the scientific committee of the Austrian/German Diabetes registry DPV and is coordinating scientific research questions formed through the database. The main focus since 2013 is the international comparison between diabetes management in children and adolescents with the US. This group focused on the complications screening of children with diabetes in testing and establishing an early non-invasive method to measure aortic distensibility and stiffness – this work is ongoing. Another topic is devoted to rare neonatal forms of diabetes and hyperinsulinism.

Paediatric Endocrinology
Dr. Klaus Kapelari,
Assoc. Prof. Dr. Elisabeth Steichen,
Assoc. Prof. PD Dr. Sabine Hofer
The Paediatric Endocrinology group offers expertise in all areas of paediatric endocrinology including disorders of growth, puberty, sex differentiation, glucose metabolism, bone and mineral metabolism, the pituitary/hypothalamus, the thyroid gland, the adrenal gland, and the gonads. The group's main research focus encompasses clinical and genetic studies on the thyroid and adrenal glands and bone disorders.

Normal values of thyroid function were established by retrospective analysis of a big cohort of children and adolescents showing and it revealed that hormone levels change markedly during childhood. Molecular investigation of patients with association of congenital hypothyroidism, choreoathetosis, and pulmonary symptoms at the Institute of Experimental Pediatric Endocrinology (Charité Berlin) led to the identification of mutations in the transcription factor NKX2-1, which plays an important role in the development and function of thyroid, basal ganglia, and the lung. In collaboration with the German network "Netzwerk DSD" we are working towards a better understanding of the molecular basis of so-called ambiguous primary sexual characteristics. Furthermore, we evaluate treatment options for children, adolescents and adults who are born with this condition and perform an assessment of health-related quality of life issues. This study also encompasses individuals whose pattern of secondary sexual development at a later stage differs from common expectations. As a centre participating in the German "DPV-Hypothyreose" study group for quality assurance in paediatric endocrinology, longitudinal data of patients with congenital primary hypothyroidism are collected and analysed with regard to the long-term follow-up of patients and in order to assess treatment within the framework of current guidelines.

Paediatric Nephrology
Assoc. Prof. Dr. Siegfried Waldegger,
Dr. Magdalena Riedl, Dr. Thomas Giner,
Dr. Alejandra Rosales
Haemolytic-uraemic syndrome (HUS) is a severe disease, leading to transient or chronic renal insufficiency. A bacterial toxin produced by E. coli causes the classic form of the disease. These bacteria produce Shiga-toxin and cause a gastrointestinal tract infection. Atypical forms of HUS are induced by an overshooting activity of the complement system. The exact registration of the typical HUS as well as the investigation of the molecular mechanism causing the dysregulation of the complement system is a primary research focus of our paediatric nephrology group.

We are closely working together with the department of microbiology (Prof. Würzner) and the department of paediatric nephrology at the Hostpital for Sick Children at Toronto, Canada. With these collaborators we are developing new methods for analyzing the complement system. This helps to improve the diagnosis of this rare but important disease and helps to bridge the gap between bench and bedside. Our paediatric nephrology unit has become a European Reference Centre for HUS in childhood. Every 2 years we organize together with Prof. Würzner an international HUS meeting, which is very highly esteemed by the large, worldwide distributed HUS research family.

Paediatric Intensive Care Unit (PICU)
Dr. Uwe Klingkowski,
Assoc. Prof. Dr. Nikolaus Neu
Our group of investigators (N. Neu, Dept. of Pediatrics, B. Treml and A. Kleinsasser, Dept. of Anesthesiology) focuses on ACE2, a new principal enzyme in the renin-angiotensin-aldosterone system. This enzyme might play a crucial role in the development of acute respiratory distress syndrome (ARDS). We were able to demonstrate that ACE2 improves oxygenation and pulmonary blood flow in an experimental model system. Our findings provide the basis for clinical trials that are currently underway.

Rheumatology and Paediatric Infectious Diseases
PD Dr. MMag. Jürgen Brunner,
Dr. Manuela Zlamy PhD,
Assoc. Prof. Dr. Michaela Sailer-Höck,
Mag. Ulrike Binder PhD,
Dr. Thomas Giner
The main research area in paediatric rheumatology is the development of biomarkers for autoimmune diseases in infancy and adolescence. The complement system, representing a component of innate immunity, has been considered to be insignificant in the pathogenesis of autoimmune diseases. The first results of our work suggest an extremely high turnover of complement in some paediatric autoimmune pathologies and autoinflammatory diseases. The complement system might be a potential biomarker for monitoring autoimmune diseases and may herald subclinical inflammation.

Selected Publications

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**shared first authors; #shared senior and corresponding authors*

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Selected Funding

- Wirksamkeit neu identifizierter Krebsmedikamente *in vivo* PRIZE (Austrian Wirtschaftsservice) Project; Principal investigator: M.J. Ausserlechner
- Effect of GUCY2C mutations on NA^+/H^+ exchanger 3 (NHE3) regulation in classic congenital sodium diarrhea (cCSD). Else Kröner-Fresenius-Stiftung; 2013_A230; Principal investigator: T. Müller
- Translationale Forschung bei angeborenen Durchfallerkrankungen; OeNB Jubiläumsfonds Nr. 15627; Principal investigator: A.R. Janecke

Collaborations

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- Dr. Suse Benseler, Childhood Arthritis and Rheumatology Research Alliance (CARRA), Pediatric Rheumatology European Society: BRAIN WORKS; Toronto, Canada
- Prof. Dr. Hans Clevers, Hubrecht Institute, Utrecht, The Netherlands
- Prof. Dr. Wolfgang Sperl, Assoc. Prof. Dr. Johannes A. Mayr, Mitocenter, University Children's Hospital Salzburg
- Prof. Dr. Holger Prokisch, mitoNET (Network for diagnosis and therapy in mitochondrial diseases), Helmholtz Institute, München, Germany
- Prof. Dr. Stefan Kölker, EIMD (European Network for Intoxication Type Metabolic Disorders), Medical University of Heidelberg, Germany
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Keywords

Preterm infants, neonatal neuroscience, developmental outcome, cardiovascular risk, sudden infant death syndrome, neuroprotection, sigma-1 receptor ligands, mitochondrial metabolism, FOXO3, apoptosis

Research Focus

- Characterization of risk predictors for adverse outcome of preterm infants
- Monitoring of the preterm brain (aEEG, MRI)
- Investigation of effects of prematurity, neonatal growth and feeding practices (focus on human milk) on cardiovascular risk factors and neurodevelopmental outcome
- Development of substances for neuroprotection and treatment of perinatal brain injury
- Role of anti-apoptotic substances in mitochondrial metabolism
- Impact of FOXO3 gene expression on cell death and stress resistance in neuronal cells

General Facts

The Department of Neonatology at the Medical University of Innsbruck is a perinatal centre offering the highest level of care. It provides care for all very preterm and critically ill neonates in Tyrol and offers a standardized follow-up programme until these children reach school-age.

Researchers in the Department of Neonatology focus on both clinical and basic science (www.neonatal-research.at), with the aim of improving survival and long-term outcome of neonates.

Clinical research includes the characterization of neurodevelopmental and cardiovascular outcome of very preterm infants until school-age and the definition of risk predictors for adverse outcome. This encompasses multimodal monitoring of the neonatal brain (aEEG, MRI), and the evaluation of the role of nutrition/growth and research on the optimization of perinatal resuscitation. The department also focuses on risk factors for and prevention of sudden infant death syndrome (SIDS). The basic research programme is dedicated to identifying mechanisms of neuroprotection in perinatal brain injury models and aims at assessing new therapeutic strategies. In addition, the department participates in a world-wide quality improvement collaborative – the Vermont Oxford Network – with the aim of following key neonatal outcomes and thereby continuously improving patient care. There are close national and international collaborations with other perinatal centres and with the local neuroscience and cardiovascular science group.

Research

Neonatal Neuroscience – Clinical and Experimental Research Groups

Neonatal brain injury is a major cause of infant mortality and morbidity and thus a problem of great global and national concern. In industrialized Western countries, the most common cause of neonatal brain injury is prematurity. During the last years, improvements in neonatal intensive care medicine have decreased preterm infant mortality. However, infants born prematurely remain at high risk of neurodevelopmental delay and of lifelong handicap. To date, causal therapeutic strategies for neonatal brain injury are not available. Clinical management is based on an optimization of perinatal care and supportive measures and on identifying infants at high risk for adverse neonatal outcome.

Clinical Research Projects:
Elke Griesmaier-Falkner, Vera Neubauer, Anna Posod, Ulrike Pupp Peglow, Ursula Kiechl-Kohlendorfer

Neuromonitoring of Preterm Infants

The amplitude-integrated electroencephalogram (aEEG) constitutes a practicable and fast method to address specific neurological risks by continuously monitoring electrocortical activity during development. The research group is particularly interested in the potential use of aEEG in preterm infants

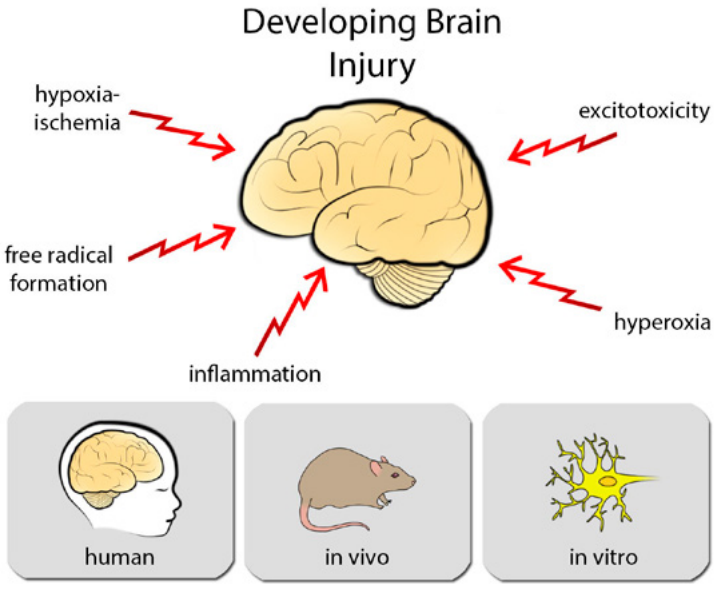

Fig. 1: Aspects of neonatal brain injury

for the evaluation of brain maturation and function, as well as its relation to long-term neurodevelopmental outcome. In addition, magnetic resonance imaging is performed in non-sedated very preterm infants at term age with the research focus on the evaluation of brain morphology, injury pattern and maturation.

Follow-up of Very Preterm Infants
Children born preterm are at risk for neurodevelopmental delay or disorder. Therefore, regular follow-up visits are important not only to provide support for these children and their parents but also for research purposes and for quality control of neonatal intensive care.

Experimental Research Projects:
Neuroprotection
Elke Griesmaier-Falkner, Karina Wegleiter, Anna Posod
The neonatal neuroscience research laboratory evaluates the potential of substances to protect the preterm brain. In the second and third trimester of pregnancy, as well as after birth, the brain rapidly increases in size, shape and complexity. During this period, the developing brain is particularly vulnerable to insults, such as hypoxia-ischemia, free radical formation, inflammation and excitotoxicity mediated by excess N-methyl-D-aspartate (NMDA) receptor activation. We are specially interested in substances that have already been tested and proven to show neuroprotective potential in animal models of adult brain injury. As both white and grey matter structures in the developing brain are known to be particularly susceptible, these substances are tested for their neuroprotective potential in pre-myelinating (pre- and immature) oligodendroglial and neuronal cell types. Furthermore three *in vivo* models have been established, mimicking key aspects of neonatal brain injury (excitotoxic, hyperoxic and hypoxic-ischemic brain injury models).
Using an established neonatal mouse model of excitotoxic brain damage, it could be shown that the substance dextrometorphan (DM) significantly reduced brain injury by reducing cell death. DM is a low-affinity NMDA receptor antagonist with anti-inflammatory properties and is widely and safely used as an antitussive in both adults and children. In the hyperoxia-mediated brain injury model DM also protected against cell death *in vivo* and *in vitro*. These were promising results and during the last years, NMDA antagonists have been favoured as therapeutic agents in neonatal and adult brain injury. However, they finally failed to live up to researchers' expectations in clinical trials of adult brain injury and showed unwanted side effects by triggering apoptotic neurodegeneration in the undamaged developing brain, calling for cautious use of these agents in the vulnerable preterm organism. Of interest, for DM it is well known that in addition to its NMDA antagonistic effect, it also is a sigma-1 receptor ligand. Therefore, in the last years, the role of the sigma-1 receptor and its ligands in perinatal brain injury were further investigated and exogenous sigma-1 receptor agonists (PRE-084 and PPBP) were shown to have protective potential in neonatal brain injury. The focus at present lies on the therapeutic potential of endogenous sigma-1 receptor ligands, such as dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS), which have been shown to be strong neuroprotectants in adult peripheral and central nervous system pathology.

Neuronal Metabolism
Judith Hagenbuchner
Mitochondria are at the centre of cellular pathways such as oxidative phosphorylation (ATP generation), the TCA cycle, glucose metabolism and oxidation of fatty acids. Alterations of mitochondrial metabolism can therefore contribute to cell death as well as to its prevention. The research group focusses on the role of the anti-apoptotic protein BIRC5/Survivin and its role in mitochondrial metabolism. Our recent data revealed that Survivin leads to recruitment of the main fission protein DNM1L/Drp1 and thus causes mitochondrial fragmentation, which shifts neuroblastoma cells from oxidative phosphorylation to aerobic glycolysis (Warburg effect) as main energy source (Sanofi Prize of the Medical University in 2014). This metabolic shift results in increased resistance to intrinsic cell death signalling, and also to dependency of Survivin-expressing cells on glycolysis. This allows us to kill Survivin expressing cells effectively by use of glycolysis-inhibitors *in vitro* and *in vivo*.

FOXO3 and its Target Genes on Cell Death and Stress Resistance in Neuronal Cells – Petra Obexer
The pathophysiology of preterm brain damage is multifactorial and phases of hypoxia and ischemia are known to play an important role. Since FOXO transcription factors are activated by different cellular stresses, our lab is primarily interested in the impact of the transcription factor FOXO3 on cell death regulation and stress resistance in neuronal cells. FOXO transcription factors are central regulators of cell death but also promote longevity, since they protect stem cells from oxidative stress. The research group has been focusing on the pro- and anti-apoptotic functions of the transcription factor FOXO3 in neuronal cells. FOXO3-triggered apoptosis induced by cellular stress involves a biphasic reactive oxygen species (ROS) accumulation at the mitochondria due to uncoupling of mitochondrial respiration through the BH3-only protein Bim. Recent studies in our lab identified C10orf10/DEPP as a direct transcriptional target of FOXO3 which localizes to peroxisomes and mitochondria. DEPP impairs cellular ROS detoxification and thereby sensitizes neuronal cells to ROS-induced cell death.
Future Goals: Identification and characterization of FOXO3-interacting drugs that inhibit the function of FOXO3 in neuronal cells.

Selected Publications

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Selected Funding

Early vascular ageing (EVA), part of the excellence initiative (Competence Centers for Excellent Technologies – COMET) of the Austrian Research Promotion Agency FFG: "Research Center of Excellence in Vascular Ageing – Tyrol, VASCage" (K-Project Nr. 843536) funded by the BMVIT, BMWFW, the Wirtschaftsagentur Wien and the Standortagentur Tirol; 1.1 Mio. Euro

Collaborations

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- Christiane Richter-Landsberg, Carl von Ossietzky University, Oldenburg, Germany
- Jan Lewerenz, Department of Neurology, University Hospital Ulm, Germany
- Martin Lee, Prolacta Bioscience, Monrovia, CA
- Mechthild Vennemann, Inst. of Legal Medicine, Univ. of Münster, Münster, Germany,
- Moon R, Goldberg Center for Community Pediatric Health, Children's National Medical Center, Washington, US, and Blair PS, University of Britstol, UK (International Society for the Prevention of Infant Death)

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Keywords

Peptide receptor radionuclide therapy, peptide ligand radionuclide therapy, radioiodine refractory thyroid cancer, hormone refractory prostate cancer, neuroendocrine tumours

Research Focus

The Department of Nuclear Medicine is best known for the work with radiolabelled peptides, both for diagnostic and therapeutic purposes, a theme that we have systematically explored over the last 2 decades. We identify and develop a variety of radiopharmaceuticals for different targets for clinical use. Our goal is to engineer more effective ligands/peptides/antibodies – "theranostics" – for individualized treatment.

General Facts

The Department of Nuclear Medicine accelerates translation of preclinical radiopharmaceutical research development (focus on radiolabelled peptides) into clinical applications towards imaging of biomarkers used for cancer treatment (70% of clinical routine), treatment of neurological impairment (20% of clinical routine) or cardiac disease (10% of clinical routine). The structure of the Department of Nuclear Medicine is based on a very creative, productive, well-funded and internationally respected preclinical Research & Development Unit of high quality. This group consists of several radiochemists/pharmacists, medical physicists and PhD-students. Their work results in the construction of radiotracers using different modal systems including a variety of radiolabelled peptide analogues such as for somatostatin, vasoactive intestinal peptide (VIP), CCK-2/gastrin, or prostata-specific membrane antigen (PSMA) ligand for specific tumour targeting. Other important developments are based on Arg-Gly-Asp (RGD) for imaging of angiogenesis in tumour lesions, or on hepatic binding protein imaging with galactosylated albumin for functional liver reserve estimation. Radiopharmaceuticals are produced at clinical grade in our dedicated laboratories for use in SPECT/CT or PET/CT studies.

About 20 whole body PET/CT studies are performed daily in our PET-center. Patients prior evaluated by dosimetry following SPECT/CT studies are treated at our Nuclear Medicine Therapy Unit with high dose theranostics.

Radioiodine ablation therapy of thyroid cancer remnants, peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumour patients and peptide ligand radionuclide therapy (PLRT) of prostate cancer patients are our most important therapy tools.

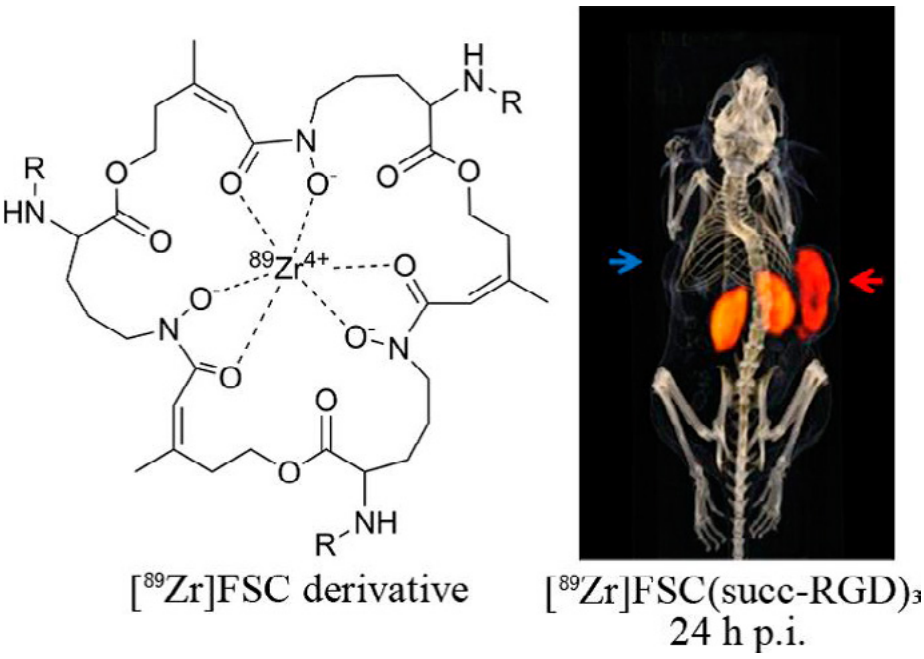

Fig. 1: Structure of the ^{89}Zr-fusarinine-C (FSC)-complex and ^{89}Zr-FSC-(RGD)3 in a mouse model targeting the receptor-positive tumour (red arrow), wheras the receptor-negative tumour shows no accumulation of the tracer (blue arrow)

Research

Preclinical Research Activities – Research & Development Unit

The research activities are focussed on preclinical research dedicated to the optimization and improvement of radiolabelling procedures for established radiopharmaceuticals, the in-house preparation of new radiopharmaceuticals for clinical studies, as well as the preclinical development of new radioligands for molecular imaging and therapeutic purposes.

Different research projects illustrate the activities in this field.

The FWF project P25899-B23 "Novel ^{68}Ga/^{89}Zr-chelators for targeted biomolecules in PET" (project leader: Prof. Clemens Decristoforo) explores novel opportunities to prepare highly specific radiolabelled biomolecules based on ^{68}Ga and ^{89}Zr, two radionuclides which have gained high attention for PET-application in the last years. By starting from a cyclic siderophore (fusarinine C, FSC) we have developed strategies to prepare new multimeric ligands for targeted molecular imaging for oncological applications. The trimers ^{68}Ga-FSC-(RGD)3 and [^{89}Zr]FSC-(RGD)3 with specific binding to alpha-v-beta3 integrin showed a more than 3-fold increased tumour uptake when compared to a monomeric form of the peptide. Also mono-, di- and trimeric FSC-minigastrin conjugates targeting CCK2 receptors labelled with ^{68}Ga and ^{89}Zr showed excellent tumour uptake in respective mouse models. (Fig. 1)

Within the co-ordinated research project (CRP) F22052 of the International Atomic Energy Agency (IAEA) "Development and Preclinical Evaluation of Therapeutic Radiopharmaceuticals Based on Lu-177 and Y-90 Labeled Monoclonal Antibodies and Peptides" (project leader: Priv.-Doz. Dr. Elisabeth von Guggenberg), in collaboration with other participants from Argentina, Brazil, Hungary, India, Iran, Italy, Macedonia, Poland, Saudi Arabia, Syria and Turkey we have preclinically evaluated two promising peptide derivatives for targeted radionuclide therapy. Specifically, a bombesin analogue was evaluated for targeting gastrin releasing peptide (GRP) receptors, a target molecule over-expressed on a variety of human cancer cells, including prostate, breast, lung, and pancreatic cancer. Furthermore, a radiolabelled cyclic minigastrin analogue developed by our group was evaluated for targeting CCK 2-receptors on different human tumours, including medullary thyroid carcinoma (MTC), small cell lung cancer, insulinomas, carcinoids, gastrointestinal stromal (GIST) tumours. Based on our initial studies on ^{68}Ga-labelled GSA-derivatives for non-invasive imaging of the functional liver reserve using PET we developed alternative compounds with improved metabolic stability and compared the new ^{68}Ga-NOTA-GSA in cooperation with the Department of Preclinical Imaging and Radiopharmacy of the University Hospital Tübingen with our lead structure ^{68}Ga-DTPA-GSA. Despite successful improvement of the metabolic stability imaging performance was comparable. Both compounds showed high uptake in the target organ and rapid elimination from the body in the corresponding rat model. Based on this promising data, at the moment, an initial clinical study with the ^{68}Ga-DTPA-GSA is being prepared.

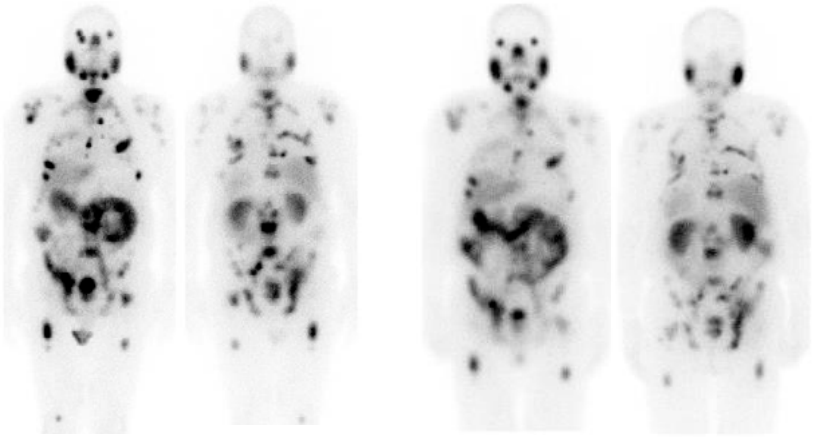

Fig. 2: Scintigraphy of a patient with metastasised prostate cancer before (A) and under (B) therapy with high-dose ^{177}Lu-PSMA ligand (2 x 6 GBq). The images demonstrate significant uptake of the radiopharmaceutical by disseminated bone metastases responding to therapy.

Clinical Research Activities

Within the ERA-NET Transcan call (FWF project I1224-B19, project leader: Prof. Clemens Decristoforo) "Phase I clinical trial using a novel CCK-2/gastrin receptor-localizing radiolabelled peptide probe for personalized diagnosis and therapy of patients with progressive or metastatic MTC" a new promising cholecystokinin-2-receptor targeting peptide CP04 (DOTA-DGlu-DGlu-DGlu-DGlu-DGlu-DGlu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH2) for the diagnosis of MTC is transferred from bench to bedside. So far, a GMP-conform kit formulation for radiolabelling with In-111 was developed and an Investigational Medicinal Product Dossier (IMPD) and all the documents for the clinical trial application were elaborated. The authorization by the national authorities as well as the EU is currently ongoing, suggesting a possible start of the clinical trial by mid-2015.

Prostate Cancer Theranostics

New receptorial radiotracers binding to PSMA with significantly increased expression on prostate cancer (PC) cells have been proposed for PET-imaging. The ^{68}Ga-PSMA ligand HBED-CC proved its feasibility to detect PC relapses and metastases with high sensitivity. Our clinical studies demonstrated the great potential of ^{68}Ga-PSMA PET/CT in patients with biochemical relapse. Furthermore, based on the high level expression of PSMA on PC cells we have started to treat patients with metastasised disease with high dose ^{177}Lu-PSMA ligand. Initial results demonstrate high tumour control ability of this radiopharmaceutical with significant implication on future PC therapy protocols (Fig. 2).

Thyroid Research Activities

Our recent thyroid research activities concentrated on the therapy options of

radioiodine-refractory thyroid cancer. Several potential kinase inhibitors have clinically been used with, however, a rather broad range of side effects. Radiolabelled somatostatin analogues have clinically been implemented for treatment by our group. The diagnosis and therapy of the MTC-subtype is addressed by the ERA-NET Transcan project as well as by the CRP F22052 of the IAEA (see above).

MITIGATE

In this concerted action several potential imaging diagnostics are currently evaluated. In WP7 the Department of Nuclear Medicine will perform the first diagnostic *in vivo* study in patients with GIST tumours, possibly starting this year.

^{68}Ga-NODAGA-RGD for Imaging Hepatocellular Cancer (HCC)

In an initial study, together with the Department of Internal Medicine II, we studied the feasibility of ^{68}Ga-NODAGA-RGD to image the hepatocellular carcinoma with PET. Additionally, tolerability, biodistribution and elimination from the body, *in vivo* stability, and radiation burden for the patient was studied in this Phase I/II study. Ten patients with HCC were included. The compound was well tolerated with no observed side effects observed. Further data collection and analysis is ongoing.

Quality of Life

Patients treated with radiopharmaceuticals are usually already at an advanced stage of disease and due to regulations of radiation safety they have to stay isolated for the period of radioactive treatment. This causes an additional level of anxiety for the patients. To support the wellbeing and well-feeling of the patients we have initiated translational projects integrating not only psychooncologists but also theologists, psychologists, nutritionists for the patients' supportive care.

Currently, the routine application of quality of life assessment is intensively investigated and fostered by respective institutions such as the EORTC Quality of Life Group or the ISOQOL. At the department a routine computer-based quality of life assessment program has been implemented in 2011 and is currently being evaluated. First results providing new "real-life" information on thyroid cancer patients' quality of life over the course of treatment and follow-up have already been published. The department is furthermore involved in the EORTC Quality of Life Group project on the development of a thyroid cancer-specific quality of life assessment tool, which currently is close to the finalizing phase III. Results will be published in 2016. The department was also part of the EORTC Quality of Life Group project on the development of a computer-adaptive test for role functioning – the manuscript has been submitted for publication.

In 2014, a study on the weekly web-based tele-monitoring of self-reported bone pain and quality of life in patients with metastasised prostate cancer has been initiated. Patients currently are consecutively included into the study. By the end of 2014 a study on the effect of music on the anxiety levels of patients during nuclear therapy has been finalised. The aim of the study was to offer music as a method of relaxation and distraction to cancer patients who have to be isolated for nuclear therapy and can only be offered limited support during that period. Data are currently being analysed.

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European Journal of Nuclear Medicine and Molecular Imaging. 2013 Apr; 40(4):514–523.

Somatostatin receptor PET in neuroendocrine tumours: (68) Ga-DOTA (0),Tyr (3)-octreotide versus (^{68})Ga-DOTA (0)-lanreotide. Putzer D, Kroiss A, Waitz D, Gabriel M, Traub-Weidinger T, Uprimny C, von Guggenberg E, Decristoforo C, Warwitz B, Widmann G, Virgolini IJ. European Journal of Nuclear Medicine and Molecular Imaging. 2013 Feb; 40(3):364–372.

[(68)Ga]NS(3)-RGD and [(68)Ga] Oxo-DO3A-RGD for imaging α(v) β(3) integrin expression: synthesis, evaluation, and comparison. Knetsch PA, Petrik M, Rangger C, Seidel G, Pietzsch HJ, Virgolini I, Decristoforo C, Haubner R.
Nuclear Medicine and Biology. 2013 Jan;40(1):65–72.

Selected Funding

- Phase I clinical trial using a novel CCK-2/gastrin receptor-localizing radiolabelled peptide probe for personalized diagnosis and therapy of patients with progressive or metastatic medullary thyroid carcinoma. Project leader: Prof. Clemens Decristoforo; ERA-NET: GRANT-T-MTC FWF Project I 1224-B19/€ 219,703.-
- Novel ^{68}Ga/^{89}Zr-chelators for targeted biomolecules in PET.
- Project leader: Prof. Clemens Decristoforo.
- FWF Project P 25899-B23 / € 238,011.-
- MITIGATE: Closed-loop Molecular Environment for Minimally Invasive Treatment of Patients with Metastatic Gastrointestinal Stromal Tumours.
- WP7 Leader: Prof. Clemens Decristoforo
- European Union FP7 under grant no 602306 / € 341,400.-

Collaborations

Clinical Cooperations:

- Prof. Dr. Richard Baum, Zentralklinik Bad Berka, Bad Berka, Germany
- Prof. Dr. John Buscombe, Cambridge University Hospitals, Cambridge, UK
- Prof. Pietro Muto, Ospedali dei Colli, Monaldi, Italia
- Prof. Annibale Versari, Az. Osp. Arcispedale S. Maria Nuova, Reggio Emilia, Italia
- Prof. Stefano Fanti, Policlinico S. Orsola-Malpighi, Bologna, Italia
- Dr. Lisa Bodei, IEO Istituto Europeo di Oncologia, Milano, Italia
- Dr. Chiara Maria Grana, IEO Istituto Europeo di Oncologia, Milano, Italia
- Prof. Helmut Maecke, University Hospital Freiburg, Freiburg, Germany
- Prof. Georgios S Limouris, Athens University Medical Faculty, Athens, Greece
- Prof. Dr. Hans-Jürgen Wester, Technical University Munich, Garching, Germany
- Prof. Dr. Thomas Beyer, Medical University Vienna, Vienna, Austria
- Prof. Dr. Marcus Hacker, Medical University Vienna, Vienna, Austria
- Prof. Jean-Noël Talbot, AP-HP & Université P&M Curie, Paris, France
- Prof. David R. Vera, University of California, San Diego, United States
- Prof. Stanley J. Goldsmith, Weill Cornell Medical College, New York, United States
- Prof. Ajit Shinto, Kovai Medical Centre and Hospital, Coimbatore, India
- Prof. Anthony Goh, Singapore General Hospital, Singapore
- Prof. Emerita Andres-Barrenechea, St. Luke's Medical Center, Quezon City, Philippines
- Prof. Harvey Turner, University of Western Australia, Murdoch, Australia
- Prof. Mike Sathekge, University of Pretoria, Pretoria, South Africa
- Prof. Alicja Hubalewska, Jagiellonian University, Kraków, Poland
- Prof. N. Ozlem Küçük, Ankara University, Ankara, Turkey
- Prof. Levent Kabasakal, Istanbul University, Istanbul, Turkey

Cooperations with Major Research Projects:

- Peter Laverman, University Medical Center Nijmegen, The Netherlands
- Milos Petrik, PhD., Palacky University Olomouc, Czech Republic
- Vladimir Tolmachev, Uppsala University, Sweden
- Jagiellonian University Medical College, Krakow, Poland
- Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
- IRRP, NCSR "Demokritos", Molecular Radiopharmacy, Athens, Greece
- National Centre For Nuclear Research, Radioisotope, Centre POLATOM, Otwock, Poland
- University Medical Centre Ljubljana, Ljubljana, Slovenia
- University Medical Center Mannheim, Germany
- Universita degli Studi di Torino Unito, Torino, Italy
- Advanced Accelerator Applications, Saint-Genis-Pouilly, France
- Universidad de la Republica Facultad de Ciencias, Montevideo, Uruguay
- National Institute for Physics and Nuclear Engineering, Bucharest-Magurele, Romania
- All India Institute of Medical Sciences, New Delhi, India
- Nuclear Medicine, S. Orsola Hospital, Bologna, Italy

Therapeutic Radiology & Oncology

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Keywords

Radiotherapy, oncology, radiosurgery, radiation biology, radiation protection, medical physics, medical biotechnology, medical molecular biology, cell biology, nanobiotechnology

Research Focus

Major research topics are:
- Radio-Sensitizing in Radiation Oncology: Many of the new systemic substances used in Oncology have a radiosensitizing (RSP) or radioprotective (RPP) potential. Often little is known about these properties before going into clinical use because investigation in this concern is not part of the EU guidelines for marketing authorisation. For Radiooncologists the knowledge of RSP or RPP is essential for the planning of any form of combined treatments.
- High Precision Radiotherapy: Our Institution is famous worldwide for the development of Patient Fixation Devices for high precision radiotherapy
- Radiobiology: Impact of low doses for the induction of secondary malignoma; cell culture modelling, nano-particle applications *in vitro*, modelling of micro-fluidics, electro-spinning of nano-fibrous cell culture substrates, developing cell-to-electrode interfaces at micron-scales

General Facts

Peter Lukas has headed the Department of Therapeutic Radiology and Oncology (ROI) at the Medical University of Innsbruck (MUI) since 1993. He has introduced several improved treatment techniques in radiotherapeutic routines, nowadays globally accepted as standard treatment protocols. Besides his clinical experience, Peter Lukas has strongly promoted basic and translational research in the field of radiobiology at his department

The Dept. of Therapeutic Radiology and Oncology (MUI) comprises eight units tasked with performing therapeutic as well as experimental irradiation (five linear accelerators to generate photon beams of energies up to 20 MeV; two Brachytherapy units, and a conventional x-ray-device up to 200 keV. Further Information: www3.i-med.ac.at/strahlentherapie/de/start.php

The first associated Laboratory of Radiobiology (headed by Thomas Seppi) utilizes experienced staff personnel (4 VPs) skilled in a broad spectrum of cell biology as well as in nano-technological methodologies. Equipment is available to perform flow cytometry analyses, long-term live-cell imaging (by light and fluorescence techniques), proteomics, metabolomics, intracellular ROS-quantification, advanced cell and tissue culturing (in-house fabrication of nano-fiber scaffolds, 2D- and 3D-perfusion culture models), impedance and TEER-methods to assess tissue integrity, cell-migration tracking, as well as up-take studies and subcellular localization of nano-particles by scanning and transmission electron microscopy. The second associated laboratory is the Laboratory for Experimental and Translational Research on Radiation Oncology (EXTRO-Lab), headed by Ira Skvortsova. This laboratory was established in 2006.

Research

Peter Lukas
The main Project in 2013/2014 was SEMPER: Secondary Malignoma – Prospective Evaluation of the Radiotherapeutic dose distribution as the cause for induction, funded by Oncotyrol.

Project partners are:
- University for Health Sciences,
- Medical Informatics and Technology (UMIT), Hall i. T. / Department of Biomedical Computer Science and Mechatronics;
- Tiroler Landeskrankenanstalten (TILAK);
- ELEKTA Oncology Systems.

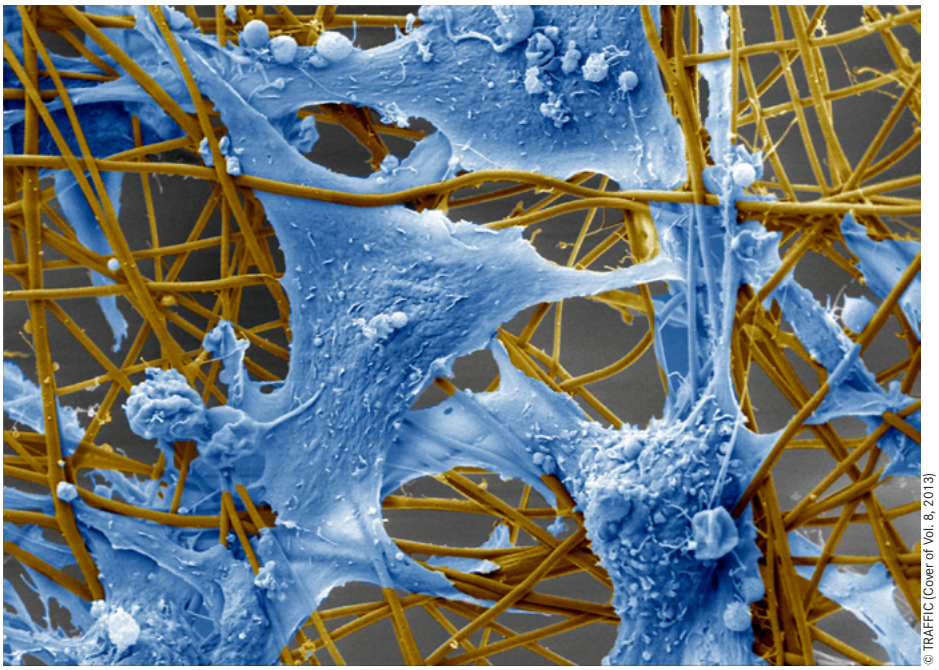


Fig. 1: Glioblastoma cells grown on functionalised electrospun gelatine-nanofibres (SEM-micrograph; 2000x).

Objectives: Based on the development of novel linear accelerator models, new radiation treatment techniques such as IMRT (Intensity Modulated Radiation Therapy), IGRT (Image Guided Radiation Therapy und VMAT (Volumetric Modulated Arc Therapy) have become applicable. According to the EU-directive 97/43, these techniques allow the theoretically best possible radiation dose distribution to preserve the normal tissue with the highest possible therapeutic effect on the underlying tumour. Note that these effects only hold for high doses. A negative site effect of using the aforementioned techniques is that considerably large volumes of the body of the patient will get "contaminated" through the use of small or minimal doses.

Well known radiobiologists such as Trott and Tubiana claim that radiation treatment with minimal doses is the reason for the induction of secondary malignancies which often occur several decades after the particular treatment. This and the steep dose gradient in conventionally used techniques might explain the observation that nowadays only a small fraction of patients treated by radiotherapy go on to develop secondary malignancies, despite the prediction of a higher incidence.

Appropriate data sets to prove or disprove this theory are currently lacking . From 2012 onwards radiation therapy techniques such as IMRT and VMAT will be available in the Department of Therapeutic Radiology and Oncology, at Medical University Innsbruck providing the best high dose conformity but simultaneously limiting the contaminating dose received by larger areas of healthy tissue within which the target volume is located. The objective of this project is to develop the platform and framework to perform a long term (range ~20 years) study based on the preconditions given by this new radiotherapy technology.

In order to tackle the problem, we plan to develop a technology for providing a platform to collect and archive data from patients who were treated by these special techniques and to perform temporary intermediate evaluations. Ongoing Projects are concerned with the membership of the permanent Quality Assurance Panel Radiooncology of the German Hodgkin Lymphoma Group and the membership in the Oncology Advisary Board of the Austrian Ministry of Health with the mission to create a national cancer programme

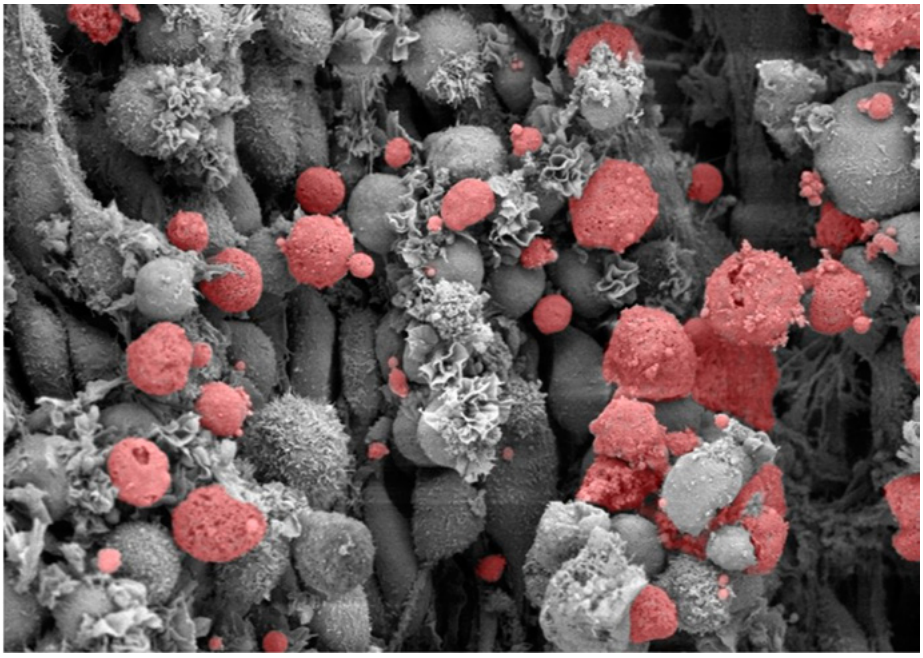


Fig. 2: Radiation-induced apoptosis in 3D-tissues of glioblastoma cells co-cultured with fibroblasts (SEM-micrograph; 1000x).

Thomas Seppi

The associated Laboratory of Radiobiology conducted several projects in the field of nano-technology and tissue engineering funded by the Austrian Nano-Initiative (FFG) or by other peer reviewed governmental grants. The team, headed by Thomas Seppi, is experienced in radiobiology, analytical chemistry, nano-coatings in biomedical applications, laser-optical cell analyses, electron-microscopy protocols, designing and prototyping of advanced cell culture models, as well as in molecular biology and toxicology of cancer cells.

Since 1998, 13 doctoral and 11 diploma theses have been supervised in the fields of analytical chemistry, radiobiology, molecular cell biology, and cancer research. Since then, scientific personnel and equipment has mainly been financed by granted fellowships. Currently, the research group is engaged in projects related to nano-particle applications *in vitro*, modelling of micro-fluidics, electro-spinning of nano-fibrous cell culture substrates, as well as in developing cell-to-electrode interfaces (impedance and TEER-analyses) at micron-scales.
A main objective of ongoing projects – performed in collaboration with several local and international partners – is to synthesize advanced nanoparticles (NPs) composed of a coated super-paramagnetic iron oxide core (SPIOs), to accommodate chemotherapeutics on the surface of NPs, and to investigate the potential of inducing drug release by gamma-ray/proton dilation as a trigger modality. NPs made of heavy metals, such as gold, may enhance the efficacy of cancer radiotherapy by increasing the local absorption of photon as well as proton radiation.

SPIOs can be detected by magnetic resonance imaging, and thus, could be coupled to gold to enable easily applicable cancer theranostics. In particular, the core magnetic properties of NPs will allow the identification of their bio-distribution in tumour tissues by MRT, whereas gold coating of NPs is used to increase photon energy deposition during radiotherapy of cancer. Investigations to study the effects of concomitant NP-treatment in comparison to conventional RT alone are performed *in vitro* by using in-house fabricated advanced cell culture models specifically developed to maintain 3D-tumour cell constructs. For this purpose, funded research is focussed on the micro-fluidic and extracellular requirements of three-dimensionally arranged tumour cell aggregates maintained *in vitro*.

Therefore, a special emphasis is placed by the research group on the study of the contribution of functionalised bio-surfaces in enhancing cell adhesion and in protracting culture protocols in order to enable long-term treatment investigations of fractionated radiotherapy *in vitro*.

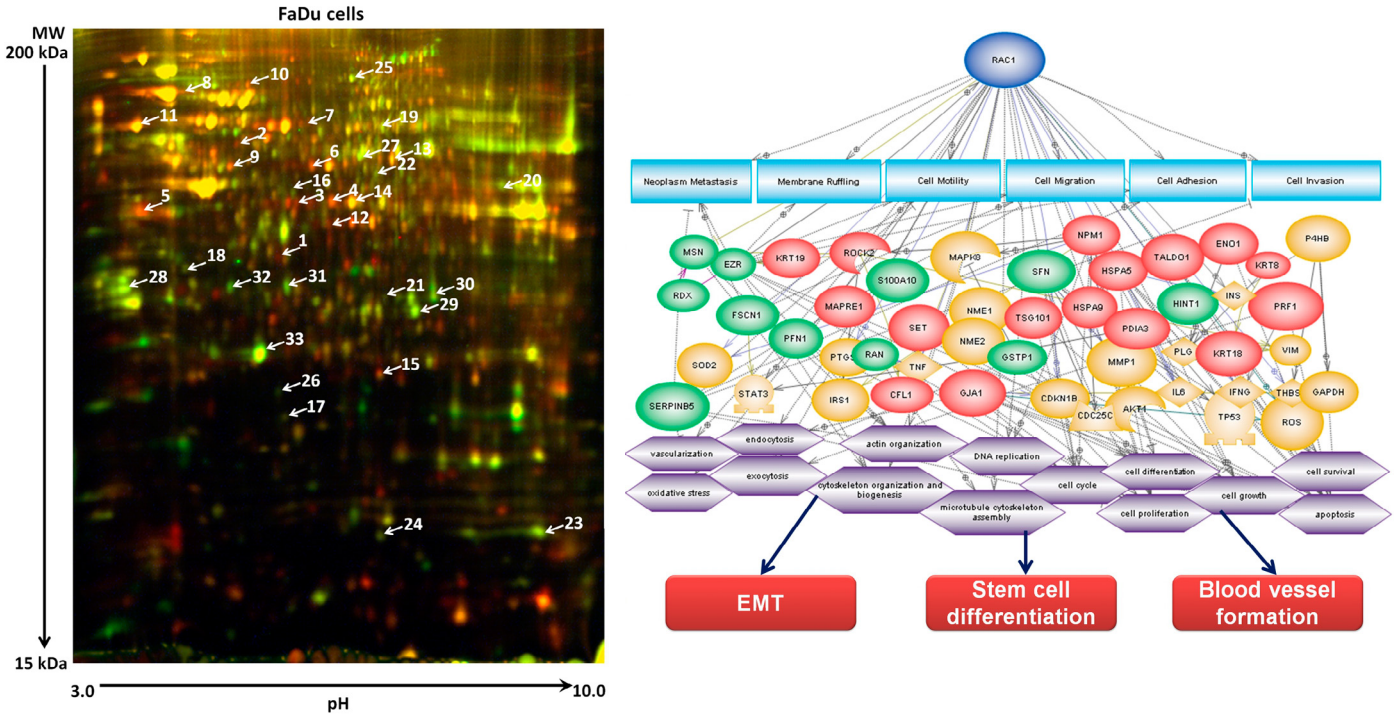


Fig. 3: Protein patterns in radioresistant FaDu-IRR cells

Ira-Ida Skvortsova

The research programme of the EXTRO-Lab is dedicated to the development of novel biomarkers and therapeutic targets to predict and improve radiation tumour response and individualize cancer therapy. In order to reach this endpoint of the programme, it is necessary to know more about the molecular background of primary and secondary (acquired) radiation resistance.

Therefore a proteomics based approach is widely used to identify the most commonly altered pathways in carcinoma cells exhibiting defined radiation responses. Proteome-related experiments are being conducted in our lab and also in collaboration with an OncoProteomics Laboratory in Amsterdam (The Netherlands). Additionally Dr. Skvortsova has developed a series of collaborations with t leading cancer translational researchers worldwide (USA, Spain, Germany, Netherlands, Belgium, Greece, Israel, Japan, Slovakia).

Since CSCs are refractory to conventional therapeutic approaches, it would be useful to establish a preclinical *in vitro* model of treatment resistance, in order to elucidate the intracellular molecular mechanisms of CSC insensitivity to anti-cancer therapy. Indeed, we have recently generated two radiation-resistant HNSCC cell lines (IRR cells): FaDu-IRR and SCC25-IRR, which survived after repeated exposure of the parental FaDu and SCC25 cells to ionizing radiation (10 Gy, 16 MV X-rays) in an Electa Precise Linear Accelerator (Elekta Oncology Systems, Crawley, UK). The cells received a total dose of 100 Gy. The newly obtained IRR cells retained their radiation resistance even after 3 years of passaging.

Additionally, the IRR cells possess not only radiation resistance, but are also insensitive to cisplatin, docetaxel, and EGFR blockers. These facts have a profound clinical impact: HNSCC relapsing after radiotherapy could also be resistant to chemo- and targeted therapeutics, hence the arsenal of agents available to treat HNSCC recurrences would be very restricted.

The software PathwayStudio 10.3 (Elsevier B.V., Amsterdam, The Netherlands) was used to analyze proteins showing differing expression in treatment-resistant IRR cells and in treatment-sensitive parental HNSCC cells, in order to determine their common targets (cell processes). In addition to our results reported in 2011, which illustrated involvement of proteins in cell motility, migration, invasion, adhesion and neoplasm metastasis, further cell processes were also identified: epithelial-to-mesenchymal transition (EMT), stem cell differentiation, and blood vessel development. All of the proteins identified using the proteomics approach had abundant relationships with Rac1 protein. Furthermore, Rac1 is closely linked to the intracellular pathways that are predicted to be activated in IRR HNSCC cells (Fig. 3).

Exponentially growing HNSCC carcinoma cells were analysed for expression of ErbB family members using RayBio® Human EGFR Phosphorylation Antibody Array 1 Kit (RayBiotech, Inc, Norcross, GA, USA). Integrated density values (IDVs) were normalized against the signal intensities of positive controls after background correction. Columns represent the mean value including standard deviation obtained from three independent experiments (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$) (Fig. 4)

Differences in the migration of parental and IRR HNSCC cells, and Rac1 inhibitor-treated cells (which induces a repression in cell migration), were determined using a QCMTM 24-well colorimetric cell migration assay (Merck Millipore, Darmstadt, Germany), following the manufacturer's instructions. HNSCC cells harvested in the appropriate serum-free quenching medium were placed in the upper insert with an 8-µm

pore size polycarbonate membrane. The lower chamber contained culture medium with a chemoattractant (10% FCS). Plates were incubated for 24 hours at 37°C in a 5% CO2 humidified atmosphere. HNSCC cells that migrated through the membrane were stained and then subsequently extracted using extraction buffer. The optical densities of dye extracts were read at 560nm using a microplate reader (Bio-Rad Microplate Reader 680, Bio-Rad Laboratories GmbH, Munich, Germany). **p < 0.01; ***p < 0.001. (Fig. 5)

Selected Publications

Nucleophilic cross-linked, dextran coated iron oxide nanoparticles as basis for molecular imaging: synthesis, characterization, visualization and comparison with previous product. Borny R, Lechleitner TW, Schmiedinger T, Hermann M, Tessadri R, Redhammer G, Neumüller J, Kerjaschki D, Berzaczy G, Erman G, Popovic M, Lammer J, Funovics M.
CONTRAST MEDIA MOL IMAGING. 2014; 10: S.18–27.

Cryo-immunoelectron microscopy of adherent cells improved by the use of electrospun cell culture substrates. Schmiedinger T, Vogel GF, Eiter O, Pfaller K, Kaufmann WA, Flörl A, Gutleben K, Schönherr S, Witting B, Lechleitner TW, Ebner HL, Seppi T, Hess MW.
TRAFFIC. 2013; 8: p. 886–93.

Proteomics of Cancer Stem Cells. Skvortsov S, Debbage P, Skvortsova I. Int J Radiat Biol.2014 Aug;90(8):653–8.

Crosstalk between DNA repair and cancer stem cell (CSC) associated intracellular pathways. Sergej Skvortsov, Paul Debbage, Peter Lukas, Ira Skvortsova. Seminars in Cancer Biology 06/2014; 31. DOI:10.1016/j.semcancer.2014.06.002.

Rac1 as a multifunctional therapeutic target to prevent and combat cancer metastasis. Arnold CR, Abdelmoez A, Thurner G, Debbage P, Lukas P, Skvortsov S, Skvortsova I. Oncoscience. 2014, 1(8): 513–522.

Selected Funding

- SEMPER: SEcondary Malignoma – Prospective Evaluation of the Radiotherapeutic dose distribution as the cause for induction, Oncotyrol, Lukas P. (400,000 €)
- NanoDisc-Biomedical application of nano-surfaces on CD-formates, FFG-818050, Seppi T, Lechleitner T (588,700 €)
- i-Scaff – Intelligent scaffolds of electro-spun nano-fibres in advanced cell culture models, TZS-Translational Research Program, Seppi T, Schmiedinger T (294,000 €)
- Multiwell-Discs with reference microstructures, FFG-833467, Schmiedinger T (117,000 €)

Collaborations

- Fachhochschule Vorarlberg, Feldkirch, Austria
- Unit of Hydraulic Engineering, University of Innsbruckl; Innsbruck,
- Institute of Physics, Academy of Sciences Prague, Prague, Czech Republic
- Università del Sacro Cuore, Rome, Italy
- Department of Engineering, University of Trento, Trento, Italy
- OncoProteomics Laboratory in Amsterdam (The Netherlands)
- Anna Dubrovska, OncoRay – National Center for Radiation Research in Oncology
- Medical Faculty Dresden Carl Gustav Carus, TU Dresden Fetscherstr. 74 / PF4101307 Dresden, Germany
- Connie R. Jimenez, OncoProteomics Laboratory, Dept. Medical Oncology, VUmc-Cancer Center Amsterdam, Room CCA 1-60, De Boelelaan 1117, 1081HV Amsterdam, The Netherlands
- Emilie Varin, Translational Research Officer, EORTC, Avenue E. Mounier 83/11, Brussels, Belgium
- Takashi Imai, Advanced Radiation Biology Research Program, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage, Chiba 263-8555 Japan
- Silvia Pastorekova, Institute of Virology, Slovak Academy of Sciences, Dubravska cesta 9, 84505 Bratislava, Slovakia
- MedAustron, Wiener Neustadt, Austria
- University for Health Sciences, Medical Informatics and Technology (UMIT), Hall i.T. / Department of Biomedical Computer Science and Mechatronics

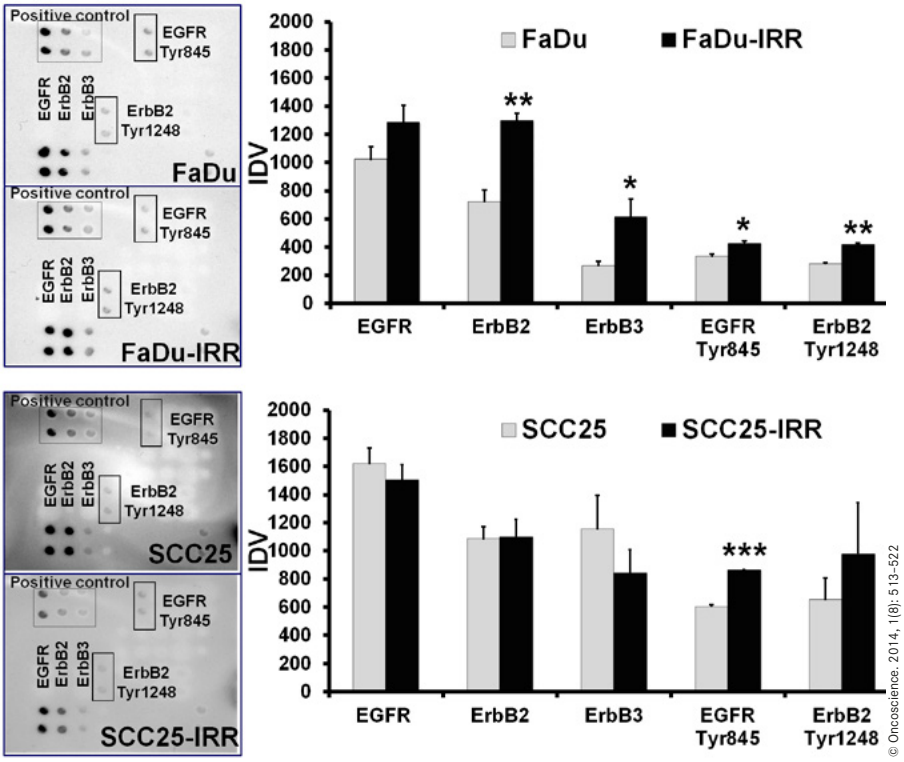


Fig. 4: Receptor status (EGFR and ErbB2, ErbB3) in radio-resistant HNSCC cells

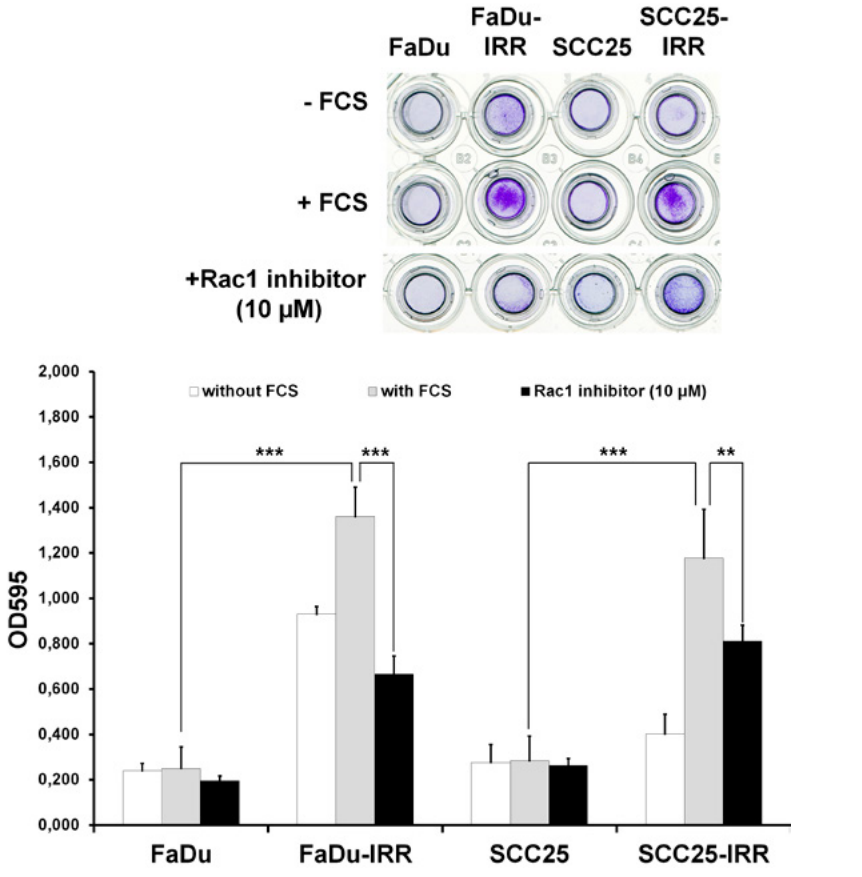
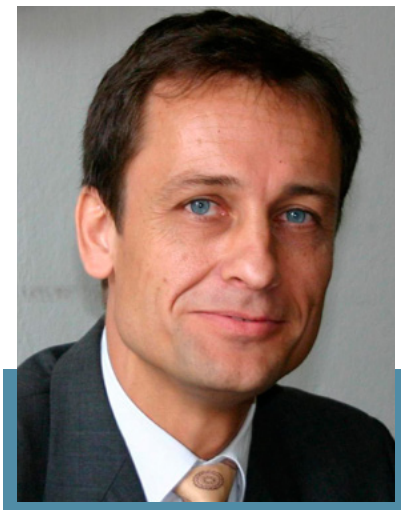


Fig. 5: Effects of Rac1 inhibitor on HNSCC cell migration

Dermatology, Venereology and Allergology & Experimental Dermatology Research Unit



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Keywords

Dendritic cells, genodermatoses, histiocytoses, HIV, immunity, lupus, melanoma, parasitoses, psoriasis, skin

Research Focus

- Dendritic cells
- Epidermal biology
- Cutaneous immune system, autoimmunity
- Infectious diseases of the skin, HIV/AIDS
- Photomedicine
- Dermatohistopathology
- Clinical trials

General Facts

In the dermatology department, basic research and patient care are intimately interconnected with each other. This is ultimately of advantage to our patients, who to benefit from new diagnostic and therapeutic approaches early in development.

Research

Differential Effects of Allergens and Non-Allergenic Antigens on Human Dendritic Cells

Christine Heufler-Tiefenthaler, Norbert Reider

Patients suffering from type I, IgE-mediated allergies constitute an important clientele of our department. Dendritic cells initiate and regulate virtually all immune reactions in the body, including the undesired allergic hypersensitivities. It is still unclear why chemically closely related molecules can be either allergenic or non-allergenic. We work on identifying the molecular basis for these differential responses in human dendritic cells exposed to non-allergenic and allergenic lipocalins, the most frequent group of animal derived respiratory allergens. Differential T cell responses and broad gene expression analyses of dendritic cells have been performed by microarray. Candidate molecules were identified, and their intracellular trafficking and processing by dendritic cells are now being studied in detail. The expected results will add to our knowledge of the fundamental biology of dendritic cells and may help to better understand the development of allergies to respiratory antigens.

Immunological Studies on Dendritic Cells of the Skin with Emphasis on Immunosurveillance against Cancer

Patrizia Stoitzner

The main topic of our research is the immunobiology of the different types of skin dendritic cells, with emphasis on epidermal Langerhans cells. The immunogenic function of Langerhans cells has been investigated in the context of skin cancer (melanoma and squamous cell / basal cell carcinoma). Hereby, several different mouse tumor models, including spontaneously arising melanoma, have been used to determine the phenotype of tumor infiltrating dendritic cells and effector cells, such as T cells and natural killer T cells. The occurrence and function of myeloid suppressor cells and their influence on the growth and metastasizing potential of tumors was studied. Importantly, mouse models, in which defined subsets of skin dendritic cells can be depleted, have been employed to clarify the importance of these cells for the development, surveillance and ultimately therapy of tumors. Based on these findings we currently attempt to develop novel alternative immunotherapies which can be tested for their efficacy in mouse tumor models and eventually translated into applications for human medicine.

Research with Special Emphasis on the Clinical Application of Dendritic Cells for Immunotherapy

Nikolaus Romani, Patrizia Stoitzner

Earlier research from our department has led to the development of a widely used method to generate large numbers of dendritic cells from monocytes of the human blood. These dendritic cells have been used as a powerful adjuvant to generate anti-tumor immune responses. In principle, dendritic cells from the blood of patients are grown *in vitro*, "loaded" with tumor antigens (peptides), and re-infused into the patients in order to elicit a potent cytotoxic anti-tumor T cell response. This approach has proven successful in several mouse models, and responses, though not curative, were

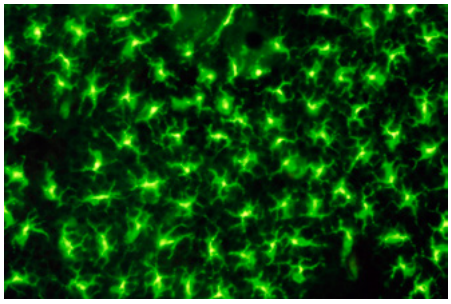

Fig. 1: Network of Langerhans cells in an epidermal sheet specimen. Approximately 700 Langerhans cells reside in one square millimeter of epidermis. These cells are directly targeted in situ by antibody-coupled vaccines.

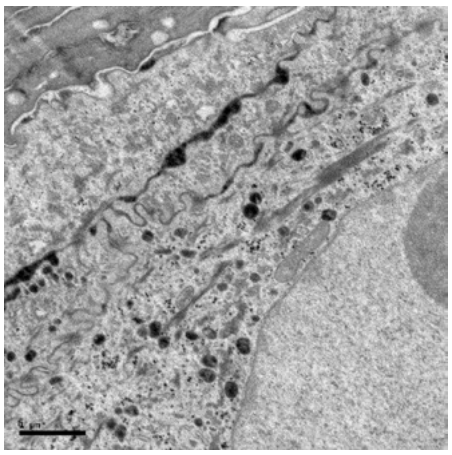

Fig. 2: Electron microscopic visualisation of lamellar bodies and secreted lipid contents in the intercellular space at the stratum granulosum – stratum corneum junction in the outer epidermis.

observed in clinical trials, including our own patients. We started investigating the direct targeting of dendritic cells in the skin with antibody-antigen conjugates (anti-DEC-205, anti-langerin), by intradermal and epicutaneous application in a human skin explant model. Different dendritic cell subsets were targeted differently. Based on these findings we are currently studying the T cell stimulatory functions of skin dendritic cells in this model. We are testing the hypothesis that antibody-conjugated antigen elicits massively augmented T cell responses. Such immunization, for instance against neoantigens in cancer, could prove highly useful in tandem with immune checkpoint therapies.

Epidermal Biology and Genodermatoses
Sandrine Dubrac, Robert Gruber, Verena Moosbrugger-Martinz, Matthias Schmuth

This research group focuses on the biological processes that regulate the interplay between skin barrier function and cutaneous inflammation. Ongoing projects address the genetic causes, as well as epidermal structure and function in genodermatoses; i.e. disorders of cornification and atopic dermatitis, as well as the role of nuclear hormone receptors (PPAR, LXR, PXR) in regulating inflammation and epidermal differentiation.

Cutaneous Immune System, Autoimmunity
Norbert Sepp, Barbara Böckle, Gudrun Ratzinger

This group has established registries of autoimmune skin disorders. Carefully recorded clinical and immune parameters are integrated with information about response to therapy and thus provide a rich scientific resource with which to address questions of both disease mechanisms and therapeutic strategies. Recent work has demonstrated serologic markers of malignancy in patients with autoimmune disease.

Infectious Diseases of the Skin
Robert Zangerle, Mario Sarcletti, Martin Gisinger, Maria Kitchen-Hosp, Reinhard Höpfl

This research program addresses questions of HIV epidemiology and response to therapy using the large national OEHIVKOS cohort that was initiated, and is led by researchers from the Innsbruck Department of Dermatology. The cohort is increasingly linked to European and international collaborative efforts, e.g. the Antiretroviral Therapy Cohort Collaboration (ART-CC), the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord, the CASCADE Collaboration in EuroCoord, and EuroSIDA in EuroCoord. Additional research addresses sexually transmitted infections (STI) and skin disorders caused by viruses (HPV), as well as by various parasites and fungi.

Photomedicine
Gudrun Ratzinger, Cornelia Gattringer

This research program addresses the effects of UV-irradiation as a causative factor of photodermatoses, as well as the therapeutic effects of UV-irradiation on common inflammatory skin diseases and skin cancer. Ongoing trials investigate the effects of phototherapy on the autoimmune skin disorder scleroderma and on cutaneous T-cell lymphoma.

Dermatohistopathology
Bernhard Zelger

Dermatohistopathology research in Innsbruck is renowned for innovative concepts describing a variety of morphologic discoveries in many skin disorders, with special emphasis on soft tissue tumors and cutaneous vasculitis. Current collaborative research projects include studies characterizing inflammation and rejection in limb transplantation.

Clinical Trials
Norbert Reider, Gudrun Ratzinger, Robert Zangerle, Van Anh Nguyen, Georg Weinlich, Matthias Schmuth

The department's clinical trial unit carries out numerous phase I-III clinical trials on chronic inflammatory skin disease (psoriasis), allergies, skin cancer, HIV and genetic skin diseases. Although most of our current trials are pharma-initiated, the Department also supports the planning and realization of investigator-initiated trials.
The unit works in close collaboration with the Coordination Center for Clinical Trials (KKS) and the Comprehensive Cancer Center.

Selected Publications

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Mycoses. 56:690–2, 2013.

Selected Funding

- The role of PXR in epidermal homeostasis and immunity relevance to non-melanoma skin cancer; FWF P21449; 2009–2014;Dubrac; € 308,414
- The role of the p14-MP1-MAP kinase scaffold complex in Langerhans cell biologyof skin dendritic cells in cancer and infection. FWF P23548 ;2011–2015; Romani; € 301,744
- Development of immunotherapeutic strategies against skin cancer; MCBO project part 15; 2011–2014; Stoitzner; € 63,800
- Einfluss von Lipocalinrezeptoren auf dendritischen Zellen auf die Entwicklung von Allergie; ÖNB 15069; 2012–2015; Heufler; € 100,000
- Dendritische Zellen: Brücke zwischen angeborener und erworbener Immunität bei Krebs; FWF P27001; 2014–2017; Stoitzner; € 332,876

Collaborations

- Universitäts Hautklinik, Wien (Profs. Georg Stingl, Adelheid Elbe-Bürger, Erwin Tschachler)
- Universitäts Hautklinik, Erlangen (Prof. Gerold Schuler)
- Laboratory of Cellular Physiology & Immunology, The Rockefeller University, NY (Prof. Michel Nussenzweig)
- Stanford University (Assoc. Prof. Juliana Idoyaga)
- The Malaghan Institute for Medical Research, Wellington, NZ (Prof. Franca Ronchese)
- Erasmus Universität, Rotterdam und Johannes Gutenberg Universität Mainz (Prof. Björn Clausen)
- Université de la Mediterranée, Marseille (Prof. Bernard Malissen)
- University of California at San Francisco (Profs. Peter Elias, Ken Feingold)
- Université de Strasbourg, Frankreich (Dr. Vincent Flacher)
- Universität Zürich, Schweiz (Prof. Christian Münz)

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Keywords

Neuropeptides, ophthalmooncology, anti-VEGF therapy

Research Focus

The research at the Department of Ophthalmology in Innsbruck is focused on three topics:
- Neuropeptide research in the eye
- Investigations on tumours in the eye
- Anti-VEGF therapy especially in wet ARMD and diabetic macular edema

General Facts

The main scientific aim at the Department of Ophthalmology in Innsbruck is to perform basic research on the topics listed above. For this purpose, a laboratory is available where most of the methods are established which are necessary to make investigations on the three topics, in particular cell culture with migration and proliferation assays, histochemistry (immunofluorescence), ELISAs, radioimmunoassays and RP-HPLC. There are two medical technicians and one Ph.D. candidate who has been employed by funding from the "Fonds zur Förderung der wissenschaftlichen Forschung" (FWF). Furthermore, there is cooperation with several other institutes at the Medical University Innsbruck, especially with Reiner Fischer-Colbrie from the Institute of Pharmacology, Christian Humpel from the Laboratory of Psychiatry, Heidi Fiegl from the Laboratory of Gynaecology and Rudolf Kirchmair from the Department of Internal Medicine. The laboratory at the Department of Ophthalmology is well equipped. The fact that there are standard methods well established in the laboratory and that cooperation exists with eminent scientists guarantees a very high quality of the research in this Department.

Research

Neuropeptides in the Eye
Josef Troger, Yvonne Nowosielski, Nikolaos Bechrakis

The aims of this topic are concentrated on three items: 1) it should be investigated whether certain neuropeptides contribute to pathologic neovascularisations in the eye. The peptides of interest are substance P (SP), neuropeptide Y (NPY), secretoneurin (SN) and catestatin because each of these molecules exert a very pronounced proangiogenic activity. The diseases of interest are wet age-related macular degeneration (ARMD), proliferative diabetic retinopathy, central retinal vein occlusion and retinopathy of prematurity since each of these diseases are characterized by the development of abnormal neovascularizations. 2) To find out whether certain neuropeptides act endogenously neuroprotectively on ganglion cells in the retina. Several neuropeptides are known to have a very strong neuroprotective potency. This is known from PACAP, VIP (and the VIP-related proteins ADNF and ADNP) but also from SN, SP, NKA and serpinin and since these peptides are present in the retina and are in close contact with ganglion cells, they might indeed act endogenously neuroprotectively. If this could be confirmed, this would have far-reaching consequences in the therapy of diseases such as glaucoma. The aim must be consequently to develop eye drops that maintain or accelerate the neuroprotective mechanisms in the retina, which represents a complete novel approach in the therapy of this disease. 3) To investigate the presence and distribution of chromogranin-derived neuropeptides. There are three main granins: chromogranin (Cg) A, CgB and secretogranin (Sg) II. These proteins are proteolytically processed which results in the generation of peptides, in particular of SN, secretolytin, PE-11, WE-14, GE-25, catestatin, pancreostatin, vasostatin and serpinin. The distribution of nerve fibres for these peptides will be explored including evaluation of the origin of the nerve fibres.

Ophthalmooncology
Nikolaos Bechrakis, Heidi Fiegl, Josef Troger

Several tumours are characterized by abnormal DNA-methylation. This might also be the case for intraocular tumours such as uveal melanoma or retinoblastoma. Therefore, the methylation pattern will be explored in these tumours and will be compared with "normal" choroidal tissues. Consequently, abnormal DNA methylation can indeed be found and as a next step it should be determined whether specific methylation patterns correlate with the prognosis of the tumours. This topic is currently being pursued.

Ocular Neovascularization and Effects of Therapeutic Angiogenesis Inhibition
Claus Zehetner, Nikolaos Bechrakis, Gerhard Kieselbach, Martina Kralinger

Neovascular age-related macular degeneration (AMD) is the leading cause of visual loss in ageing western populations. The current standard of care involves intravitreal administration of monoclonal antibody-based therapies directed against vascular endothelial growth factor (VEGF). VEGF is a multifunctional cytokine that regulates antiapoptotic pathways of endothelial cells in adult vasculature. Systemic VEGF acts as a vascular protective factor and is essential for maintaining the integrity and the anti-thrombogenic as well as anti-inflammatory properties of the endothelium. Our study group could demonstrate that intraocular application of VEGF inhibitors can induce a

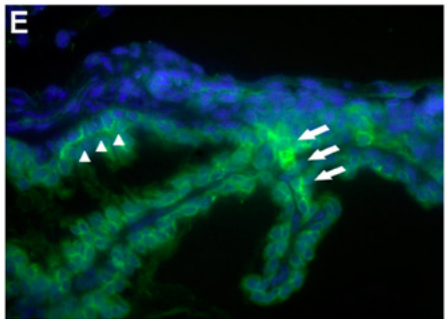

Fig. 1: Catestatin-immunoreactive nerve fibers in the stroma of the ciliary body (arrows) and in the stroma of the ciliary processes (arrowheads).

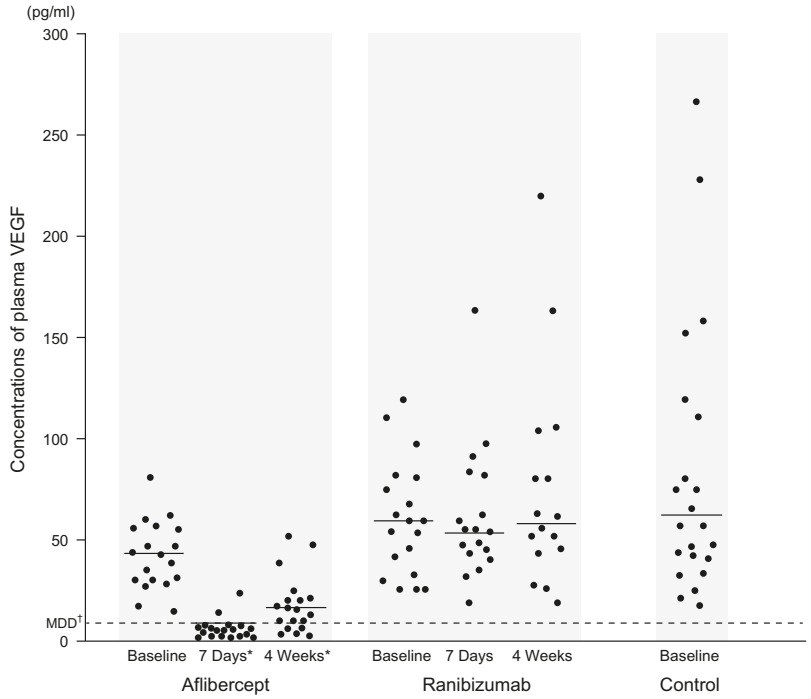

*Fig. 2: Plasma levels of vascular endothelial growth factor (VEGF) before and after intravitreal injection of anti-VEGF therapeutics in patients with exudative age-related macular degeneration. Systemic VEGF concentration was significantly decreased by aflibercept after 7 days and this reduction persisted throughout 4 weeks. No significant effects were seen with ranibizumab. *Statistically significant differences are indicated by an asterisk. †The minimum detectable dose (MDD) of VEGF defined by the manufacturer was 9 pg/ml. All measurement outliers are below the MDD.*

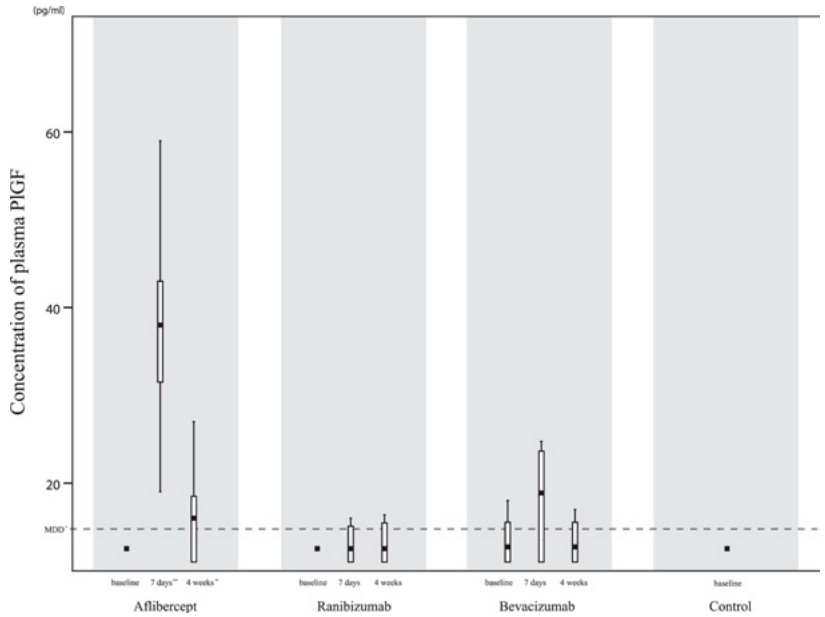

*Fig. 3: Plasma levels of PlGF before and after intravitreal injection of anti-VEGF therapeutics in patients with neovascular AMD. In those treated with aflibercept, PlGF levels significantly increased after 7 days, and this increase persisted throughout 4 weeks. No significant effects were seen in the ranibizumab and bevacizumab cohort. Statistically significant differences (***P < 0.001, **P < 0.01). †The MDD of PlGF defined by the manufacturer was 12 pg/mL. All measurement outliers are below the MDD*

significant reduction of systemic VEGF. Our study results are of translational relevance in regards to clinical safety. Sustained reduction of systemic VEGF in the general circulation is an inadvertent off-target effect that might increase the incidence of cardiovascular anti-VEGF class effects.

The selective therapeutic interference with factors of the proangiogenic signalling circuit for the treatment of pathologic neovascularization is likely to result in compensatory increases of other factors involved in this process. This could induce converse regulatory effects that might weaken the therapeutic efficacy of antiangiogenic drugs. Our study group found a significant systemic upregulation of the proangiogenic cytokine placental growth factor (PlGF) after intravitreal administration of VEGF inhibitors. Secondary alterations of proangiogenic factors could potentially promote an escape from angiogenesis inhibition and may be responsible for the decreased therapeutic efficacy or persistence of the neovascular tissue in patients undergoing antiangiogenic therapy. Identification of factors that confer antiangiogenic drug resistance would enable development of the next generation of drugs for more effective treatment of ocular vasculopathies.

Selected Publications

Catestatin-like immunoreactivity in the rat eye.
Gramlich Oliver W, Lorenz Katrin, Grus Franz H, Kriechbaum Maren, Ehrlich Daniela, Humpel Christian, Fischer-Colbrie Reiner, Bechrakis Nikolaos E, Troger Josef.
NEUROPEPTIDES. 2014; 48: p. 7–13.

Systemic Upregulation of PDGF-B in Patients With Neovascular AMD.
Zehetner Claus, Kirchmair Rudolf, Neururer Sabrina B, Kralinger Martina T, Bechrakis Nikolaos E, Kieselbach Gerhard F.
INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE. 2014; 55: p. 337–344.

Reduced-Fluence Photodynamic Therapy Combined with Ranibizumab for Nonproliferative Macular Telangiectasia Type 2.
Zehetner Claus, Haas Gertrud, Treiblmayr Bernhard, Kieselbach Gerhard F, Kralinger Martina T.
OPHTHALMOLOGICA. 2013; 229: p. 195–202.

Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema.
Zehetner Claus, Kirchmair Rudolf, Huber Stefan, Kralinger Martina T, Kieselbach Gerhard F.
BRITISH JOURNAL OF OPHTHALMOLOGY. 2013; 97: p. 454–459.

Correlation of vascular endothelial growth factor plasma levels and glycemic control in patients with diabetic retinopathy.
Zehetner Claus, Kirchmair Rudolf, Kralinger Martina, Kieselbach Gerhard.
ACTA OPHTHALMOLOGICA. 2013; 91: p. e470-e473.

Selected Funding

VEGF and neuropeptides in experimental choroidal neovascularization, FWF, Nikolaos Bechrakis

Collaborations

Oliver Gramlich, Katrin Lorenz, Franz Grus, Maren Kriechbaum: Experimental Ophthalmology, Department of Ophthalmology, University Medical Center, Johannes Gutenberg-University Mainz, Germany

Women's Health Center

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Keywords

Gender medicine, women's health, lifelong learning, prevention, affirmative action for women, work-life-balance

Research Focus

- How to get Gender Medicine into the Medical Curricula?
- How to get Gender Medicine into the Clinic?
- Gender Medicine and Prevention, Cardiology
- Women's Empowerment, Women's Careers, Work-Life-Balance
- Diversity, Migration
- How to deal with Sex and Violence in a Medical Setting

General Facts

The Gender Medicine Unit includes a Women's Health Clinic focusing on all aspects of Women's Health issues. It is a routing station within the University Clinics. There is a special focus on migrant women. The Women's Health Clinic consists of an ambulance and a ward, but there is also a lot of activity outside of the hospital, including outpatient clinics and talks for women's organisations. The other part of the Gender Medicine Unit is a research institute. One main topic is the implementation of Gender Medicine into the curricula of all health professions. At the Medical University of Innsbruck we provide courses in human medicine, dental medicine and molecular medicine. Gender Medicine is included in the compulsory curriculum and also in the compulsory examinations. Moreover it is compulsory in the PhD-programmes. The criteria for venia docendi also include a compulsory Gender Medicine course (SOS Lehre). The main aim of this course is to teach participants how they can implement Gender Medicine into all of their research programmes, not only in the case of clinical topics but also in basic research. We try to motivate our students to implement aspects of gender specific medicine into their PhD-theses and to encourage them to produce abstracts with a focus on gender issues for submission to national or international congresses as a minimum requirement. Thusfar we have had approximately 30 posters concerned with gender topics accepted for presentation at national or international conferences.

Gender Medicine is also a (key) component of the post-graduate training programmes of the doctor's association in Austria. The Gender Medicine ring lecture series is included in the programme. We have also taught Gender Medicine at the annual advanced training week for the past 10 years and this year we intend to implement an official diploma for Gender Medicine. We are currently developing the programme for the courses, which will start next year. The course will run for four terms:

We started with the Medical University, but our aim is to implement Gender Medicine in the curricula of all health professionals; for instance we also teach at the Fachhochschule Gesundheit (for midwives and all technical-medical professions) and the school of nurses (AZW). In this context we also conduct research on medical students' attitude towards gender and gender medicine. Medical students, but also students from allied health professions have been studied with regard to their gender sensitivity in medicine.

Our research work also focuses on migration. We perform a lot of surveys with our migrant medical students, predominantly those of Turkish origin and also with our Turkish patients.

Another focus of our research is on sex and violence. We developed a questionnaire for recording patient histories that has been approved by the Ethical Commission for our patients at the Women's Health Clinic and by the midwives. The aim is for our

Ring Lecture Series Gender Medicine

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paper/form/questionnaire to be utilized in everyday clinical practice.

Additionally we study women's careers in medicine. In this context several issues have been focused upon, such as work-life balance, social and gender inequality and also the challenge of working in a male-dominated environment. Women still face disadvantages when it comes to climbing the career ladder and acheiving higher ranks in academia. Currently, we are also focusing on these issues in other countries (Turkey, Israel) in order to study the differences and similarities in women's careers in medicine from an international perspective. We work on a lot of Women's issues and are very pleased to have incorporated Gender aspects into a wide range of research topics, encompassing both basic and clinically applied science.

Research

Implementation of Gender Medicine into the Curricula

Following the completion of the EuGiM project on Lifelong Learning, which developed Gender Medicine curricula for implementation into master studies and summer schools there is now a follow-up project called EuGenMed "Roadmap for a gender-sensitive approach to health care research and practice in Europe". The "Innsbruck Model" of integration of sex and gender in the different curricula was invited as example of best practice.

Migration

We started a lot of questionnaires with Austrian, German and Turkish medical students. The questionnaire seeks to ascertain their study situation, problems and barriers that they may encounter and also their perception of sex and gender. Furthermore, we analyse sex specific differences within these groups. There is also a PhD-student and a post-doc working on this topic.

Sex and Violence

We developed a questionnaire for patients on the topic of sex and violence, which we have already used at our Women's Health Clinic. Currently, we work with the midwives and their patients. The next cohort will be the male patients. Our aim is to develop a questionnaire for all of the patients at all of the clinics that is accepted not only by patients but also by the care providers, i.e. doctors. There is also a PhD-student and a post-doc working on this topic.

Medical Students' Attitude towards Gender Medicine

Medical students and students from allied health professions have been asked about their perceptions of the subjects of gender sensitivity and the gender role ideology of doctors and patients. This research has identified gaps in knowledge/understanding that need to be filled in order to improve students' gender sensitivity in medicine. There is also a PhD-student and a post-doc working on this topic.

Women's Careers in Medicine

Quantitative and qualitative data have been obtained in order to gather information on the challenges experienced by women wishing to progress in their respective careers. Additionally, a review of the Austrian literature about women's careers in medicine, pitfalls and positive aspects was performed in order to improve the working situation for women. Currently female and male doctors in other countries are studied with regard to their career aspirations. These studies will inform us about Austrian-specific and medicine-specific challenges in women's careers. There is also a PhD-student and a post-doc working on this topic.

Selected Publications

How Do We Get Gender Medicine Into Medical Education?
Hochleitner Margarethe, Nachtschatt, Ulrike, Siller, Heidi.
HEALTH CARE FOR WOMEN INTERNATIONAL. 2013; 34: 3–13.

Female and Male Physicians in Academic Medicine: Is Work-Life-Balance Still an Issue?
Siller Heidi, Bader Angelika, Waldenberger-Steidl Barbara, Hochleitner Margarethe
IN: Thege Britta, Popescu-Willigmann Silvester, Pioch Roswitha, Badri-Höher Sabah.
Paths to Career and Success for Women in Science. Springer Verlag: 2014.

RichterInnenstudie im OLG Sprengel Innsbruck
Siller Heidi, Voithofer Caroline, Hochleitner Margarethe
IN: Barta Heinz, Ganner Michael, Voithofer Caroline. Rechtstatsachenforschung heute: Tagungsband. 2013, Innsbruck university press: 2014.

Progress of Gender Medicine in Europe. Siller Heidi, Hochleitner Margarethe.
HEALTH CARE FOR WOMEN INTERNATIONAL (in press).

Collaborations

- Univ.-Prof.in Dr.in Vera Regitz-Zagrosek, Charité, GiM, Berlin/Germany
- Univ.-Prof.in Dr.in Karin Schenck-Gustafsson, Karolinska, Stockholm/Sweden
- Assoc.-Prof.in Dr.in Petra Verdonk, Amsterdam Medical Centre, Amsterdam/Netherlands
- Univ.-Prof.in Dr.in Ineke Klinge, Maastricht University, Maastricht/Netherlands
- Univ.-Prof.in Dr.in Alexandra Kautzky-Willer, MUW, Internal Medicine, Vienna/Austria
- Univ.-Ass.in Dr.in Caroline Voithofer, Leopold Franzens
- Universität, Zivilrecht, Innsbruck/Austria
- Priv.-Doz.in Dr.in Susanne Perkhofer, FH gesundheit, Innsbruck/Austria
- Dr.in Waltraud Buchberger MSc, AZW, Innsbruck/Austria
- ao. Univ.-Prof.in Dr.in Barbara Juen, Leopold Franzens University, Institute for Psychology, Innsbruck/Austria
- Prof.in Dr.in Patricia Davidson, Johns Hopkins University, Dean of the School of Nursing, Baltimore/USA

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Keywords

Neuronal plasticity, neurotrophic factors, cell signaling, transgenic animal models, induced pluripotent stem cells, neuronal differentiation, human models of neurological diseases

Research Focus

Our laboratory studies how nerve cells can be programmed and re-programmed depending on neural activity and neurotrophic growth factors. In transgenic mouse models we investigate activity-dependent mechanisms of learning and memory that depend on plastic chromatin reorganization in the cell nucleus. Another focus is to generate neurons from stem cells. We are developing protocols to differentiate human stem cells obtained with the "induced pluripotent stem cell" (iPSC) technology into specific neuronal populations. Based on these protocols we have established cellular models of human neurological diseases.

General Facts

The Institute for Neuroscience is located on the 3rd floor of the building at Innrain 66 in close proximity to the laboratories of Psychiatry, Neurology and Neurosurgery. Members of the Institute participate in the FWF-funded networks SFB-F44 and DK 106 SPIN. The Institute offers a modern infrastructure and state-of-the-art research equipment. Laboratories include a stem cell laboratory licensed for biosafety level 2 work dedicated to the generation and differentiation of human iPSCs. Procedures have been implemented to generate, steadily maintain and differentiate human iPSC-derived cell lines. Separate laboratory rooms are dedicated to work with nucleic acids and proteins. In addition, the institute supports a primary cell culture and animal transplantation laboratory. Rooms are fully equipped with stereomicroscopes, epifluorescence and confocal microscopes and a specialized room is dedicated to histology, sectioning and immunostaining.

Research

Neuronal Plasticity Group
Dr. Galina Apostolova

Modulation of Higher-Order Chromatin Architecture – Implications for Neuronal Plasticity

Complex behaviors such as learning and memory depend on changes in gene expression and subsequent long-lasting adaptations in synaptic strength and structure. Our current research interests are focused on the mechanisms of neuronal plasticity, with special emphasis on the role of chromatin conformation regulation in adaptive gene transcription.

A classical example of neuronal plasticity is the switch from noradrenergic to cholinergic neurotransmission, which occurs in differentiated postganglionic sympathetic neurons under the influence of target-derived signals. We identified the genome organizer Special AT-rich sequence binding protein 2 (Satb2) as an acutely up-regulated target gene of neurokine/p38 MAPK signaling in sympathetic neurons undergoing trans-differentiation.

Our gain-and loss-of-function studies revealed that Satb2 is both necessary and sufficient to trigger the sympathetic neurotransmitter switch. We reasoned that modulation of Satb2 and consequently chromatin architecture by neurotrophic factors might serve as a novel pathway involved in the long-term adaptive processes underlying higher brain functions.

In support of this hypothesis, recent results in our laboratory showed that Satb2 is induced by plasticity-mediating extracellular signals such as BDNF or Ca^{2+}-influx through L-type voltage-gated calcium channels in CNS neurons. The analysis of a conditional mutant lacking Satb2 in the adult forebrain (generated by our group), demonstrated that Satb2 is required for synaptic plasticity and long-term memory formation. In addition, we found that Satb2 interacts with genome organizing proteins of the inner nuclear membrane and regulates the geometry of neuronal nuclei in the hippocampus *in vivo*. Our findings give us grounds to hypothesize that a Satb2-containing DNA-protein complex determines both the nuclear shape and chromosomal conformations in neurons downstream of L-VGCC and BDNF signaling, thereby integrating plasticity-mediating extracellular signals into changes in the transcriptome.

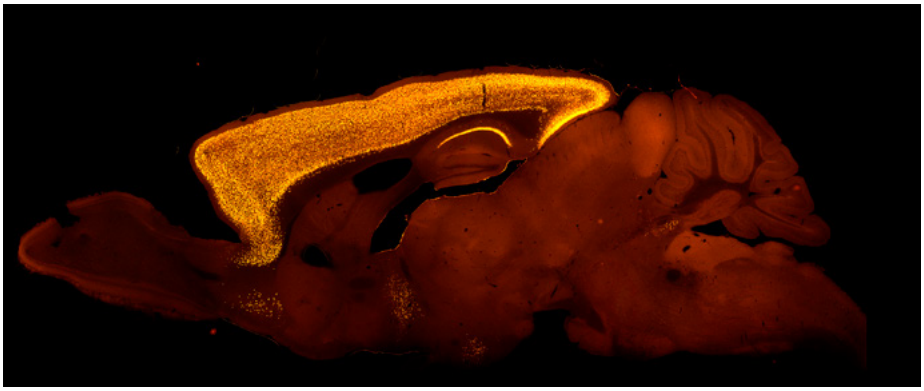

Fig. 1: Immunostaining for Satb2 in sagital mouse brain sections reveals strong Satb2 expression in the cortex and CA1 area of the hippocamus.

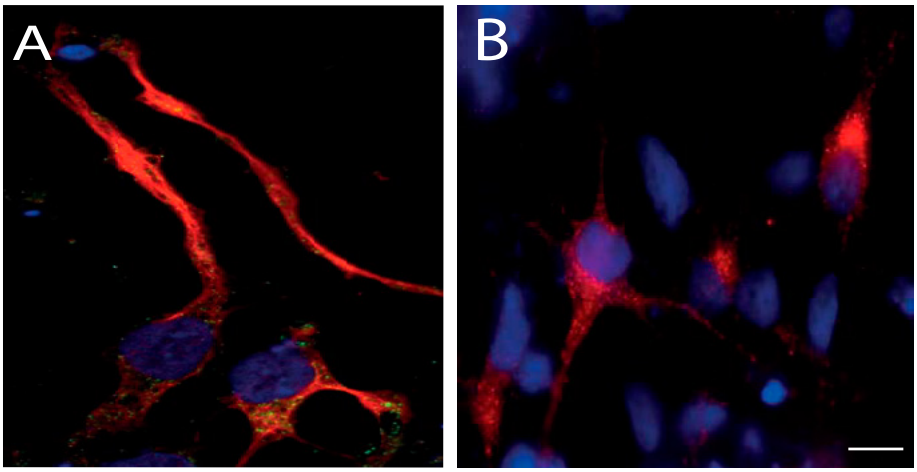

Fig. 2: Human neurons grown from pluripotent stem cells derived from a patient with Friedreich Ataxia (A) and from a patient with Spinocerebellar Ataxia type 6 (B). Stainings for Peripherin (A, red), Frataxin (A, green) and CAV2.1 (B, red), (scale bar 10um).

Our future goals are to provide evidence that Satb2-dependent rearrangements of the nuclear architecture and/or changes in the epigenetic profiles are necessary for higher cognitive functions and that dysfunction of these mechanisms leads to learning and memory deficits. We also aim to study whether cognitive deficits inherent to normal aging and neuropsychiatric diseases are caused by alterations in Satb2 expression or function.

Stem Cell Group

Priv. Doc. Dr. med. univ. Roxana Nat

The recent availability of the human pluripotent stem cells (PSC) reprogrammed from adult somatic cells provides a unique opportunity to investigate the mechanisms of human nervous system development and its disorders. There are currently 2 major areas of interest:

1. Explore the molecular mechanisms that regulate PSC conversion into specific neural progenitor populations, their neuronal subtype specification and functional maturation. We apply to mouse and human PSCs different neural induction, patterning and specification protocols, based on established models of nervous system development.

2. Modeling human neurological disorders with iPSC derivatives in order to understand the molecular mechanisms of diseases in pathologically-relevant phenotypes. We reprogram patient-derived somatic cells into iPSC lines, which are subjected to differentiation into neurons. The disease-relevant neurons are interrogated in order to disclose the molecular mechanisms causing and/or driving the particular disease, especially for the known monogenic diseases.

Ongoing Projects:

Project 1. Modeling Friedreich Ataxia with Patient-Derived iPSCs

Friedreich Ataxia (FRDA) is an autosomal recessive neurodegenerative disease caused by an elongated intronic GAA repeat in the gene encoding the mitochondrial protein frataxin. Peripheral sensory neurons are the most susceptible cells for FRDA pathophysiology. Animal models of FRDA reproduced GAA repeat expansion, frataxin deficiency, mitochondrial alterations and neurodegeneration observed in the human disease, but the central questions concerning FRDA pathophysiology remained elusive: why are specific neuronal populations particularly susceptible in FRDA and when during ontogeny does the pathology manifest itself in susceptible neurons? To address these questions, we have generated patient iPSC lines and differentiated them to peripheral sensory neurons (Eigentler *et al.*2013). Functional characteristics are compared during *in vitro* maturation of control and FRDA iPSC-derived sensory neurons. Furthermore, we analyse whether the frataxin deficit affects the development of peripheral sensory neurons and their circuitries after transplantation of human sensory precursors in chicken embryos.

Project 2. Modeling Spinocerebellar Ataxia Type 6 with Patient-Derived iPSCs

Spinocerebellar Ataxia type 6 (SCA6) is an autosomal dominant neurodegenerative disease associated with CACNA1A gene, coding for the alpha 1 A subunit of P/Q type voltage-gated calcium channel CaV2.1. SCA6 mutation consists of CAG repeats leading to a short expansion of a polyglutamine stretch located in the cytoplasmic C-terminal tail of the channel protein. Currently, the pathogenic mechanisms remain elusive, and no therapy is known.

We aim to investigate the effect of the SCA6 mutation on CaV2.1 channel protein functionality directly in human neurons. We generated iPSC lines from SCA6 patients and differentiated them in neurons. We are using confocal microscopy to investigate the subcellular localization of CaV2.1 channel protein and neuronal excitability, calcium currents and synaptic transmission in SCA6 neurons. Our further aims are to use our validated strategy to develop drug screening assays, and to extend it to the analysis of other monogenic diseases associated with mutations in the CACNA1A gene.

Selected Publications

Alternative generation of CNS neural stem cells and PNS derivatives from neural crest derived peripheral stem cells. Weber M, Apostolova G, Widera D, Mittelbronn M, Dechant G, Kaltschmidt B, Rohrer H. Stem Cells. 2015 Feb;33(2):574–88. doi: 10.1002/stem.1880.

Reacquisition of cocaine conditioned place preference and its inhibition by previous social interaction preferentially affect D1-medium spiny neurons in the accumbens corridor. Prast JM, Schardl A, Schwarzer C, Dechant G, Saria A, Zernig G. Front Behav Neurosci. 2014 Sep 24;8:317. doi: 10.3389/fnbeh.2014.00317. eCollection 2014.

Peripheral nerve regeneration and NGF-dependent neurite outgrowth of sensory neurons depends on STAT3 phosphorylation downstream of the neuropoietic cytokine receptor gp130. Quarta S, Baeumer BE, Scherbakov N, Andratsch M, Rose-John MS, Dechant G, Bandtlow CE, Kress M. J.Neurosci. Sep 24;34(39):13222–33. doi: 10.1523/JNEUROSCI.1209-13.2014.

Induced pluripotent stem cells from Friedriech ataxia patients fail to upregulate frataxin during *in vitro* differentiation to peripheral sensory neurons. Eigentler A, Boesch S, Schneider R, Dechant G, Nat R. Stem Cells Dev. 2013 15:3271–82.

Human pluripotent stem cells modeling neurodegenerative diseases. Nat R, Eigentler A, Dechant G. In "Pluripotent Stem Cells / Book 2", ISBN 980-953-307-463-9 Editors InTech.

Selected Funding

- 2013–2016: FWF DK W1206 "Signal Processong in Neurons" Dechant
- 2013–2016: FWF Stand-alone project P25014-B24 "Role of genome organizer Satb2 in adult brain function" Apostolova
- 2012–2015: FWF SFB-F44 "Cell Signaling in Chronik CNS Disorders"/MUI associated project, Nat, Dechant
- 2015–2019: FWF SFB-F44 "Cell Signaling in Chronik CNS Disorders" Apostolova, Dechant
- 2014–2016: FWF Standalone Project Nr P 26886-B19, "Modeling Friedreich Ataxia with patient iPSC-derived neurons", Nat

Collaborations

- Roland Foisner, Medical University Vienna; Vienna, Austria
- Marin Korte; TU Braunschweig, Braunschweig; Germany
- Nicolas Singewald; Innsbruck University, Innsbruck; Austria
- Jörg Striessnig,Innsbruck University, Innsbruck; Austria

FWF-funded Programmes

Doctoral Programmes (DK):

DK Molecular Cell Biology and Oncology – MCBO
DK Host Response in Opportunistic Infections – HOROS
DK Signal Processing in Neurons – SPIN

Special Research Programmes (SFB):

SFB-F44: Cell signaling in chronic CNS disorders

Molecular Cell Biology and Oncology – DK MCBO

Speaker:
ao. Univ.-Prof. Dr.
Bernhard E. Flucher

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Keywords

Doctoral research training, Molecular Cell Biology,
Austrian Science Fund (FWF) W1101

Focus – Research Training

- State-of-the-art PhD training in molecular cell biology and oncology
- Benchmark training standards: competitive recruitment, training opportunities, international exchange

Research Topics

- Cell Cycle
- Cell Death
- Cytoplasmic signaling
- Calcium channels
- Tumor-Immunology

FWF DK Program

The DK-Program by the Austrian Science Fund supports structured PhD programs at centers of excellence at Austrian universities. Programs are initiated by consortia of leading scientists and selected through a stringent international evaluation process. Programs are regularly reviewed and can be extended up to a total of 12 years.

General Facts

Molecular Cell Biology and Oncology (MCBO) is an excellence PhD program at the Medical University of Innsbruck funded by the FWF (Austrian Science Fund), with participation of the University of Innsbruck. The goal of the MCBO doctoral program is to equip young researchers with the knowledge, skills and attitudes necessary to excel in an independent scientific career in basic and applied bio-medical sciences.

Training

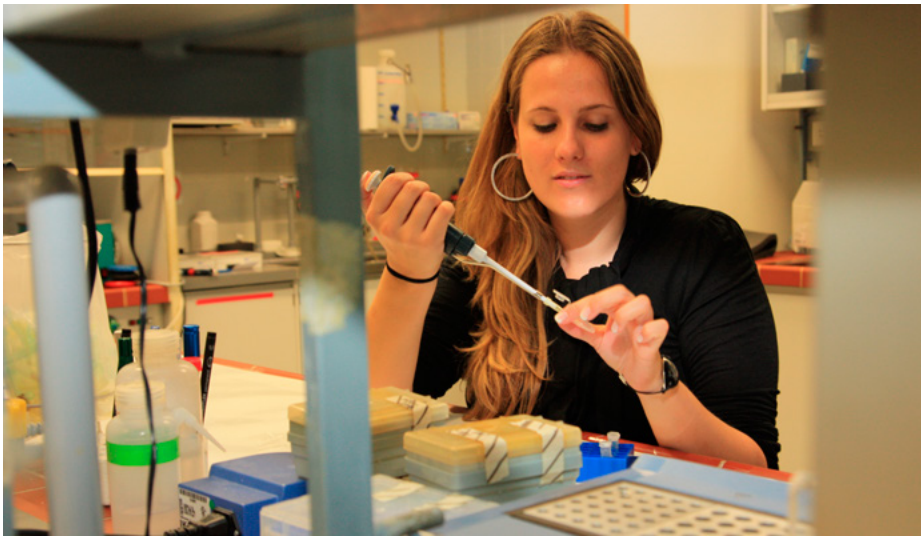
Research training within MCBO is designed to prepare students for solving basic research questions and to teach in-depth knowledge of cell biology with the ultimate goal of creating the basis for the development of novel treatments to fight prevalent human diseases. To achieve this goal, MCBO is dedicated to providing its students with a multitude of state-of-the-art methodological skills, important basic knowledge in the field of cancer cell biology and tumor immunology, as well as with a set of complementary and transferrable skills required to perform front-line research. It is the main goal of MCBO to teach its students strategies that allow them to efficiently and successfully study features of a particular molecule or a specific signalling process at the subcellular or single-cell level, as well as in the context of an entire organism.

MCBO offers a comprehensive system of lectures and laboratory courses. Peer-reviewed research projects, dedicated supervision by three-member thesis committees and a lively seminar program create a stimulating research environment, conducive to the successful completion of the PhD.

MCBO Facts

- Established in 2005
- 45 students enrolled
- 62 students graduated
- Students form 18 nations and 3 continents
- More than 180 publications
- Competitive recruitment
- Courses and lectures in English
- Three to four years thesis research
- International symposia and meetings
- 6 months stays abroad at prestigious Universities like the University of California (San Francisco), John Hopkins University (Baltimore), Karolinska-Institut (Stockholm), and many more.

Research Training



MCBO Team at mid-term retreat

MCBO Faculty

Baier Gottfried, Univ.-Prof. Dr. rer. nat.
Division of Translational Cell Genetics, MUI

Culig Zoran, ao. Univ.-Prof. Dr. med. univ.
Department of Urology, MUI

Flucher Bernhard, ao. Univ.-Prof. Dr. phil.
Division of Physiology, MUI

Geley Stephan, ao. Univ.-Prof. Dr. med. univ.
Division of Molecular Pathophysiology, MUI

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Division of Biochemical Pharmacology, MUI

Hengst Ludger, Univ.-Prof. Dr. rer. nat.
Division of Medical Biochemistry, MUI

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Division of Biological Chemistry, MUI

Stoitzner Patrizia, Assoz. Prof. Dr. rer. nat.
Department of Dermatology and Venereology, MUI

Striessnig Jörg, Univ.-Prof. Dr. med. univ.
Division of Pharmacology and Toxicology, LFU

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Division of Cell Biology, MUI

Trajanoski Zlatko, Univ.-Prof. Dipl.-Ing. Dr. techn.
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Villunger Andreas, Univ.-Prof. Mag. Dr. rer. nat.
Division of Developmental Immunology, MUI

Wilflingseder Doris, Priv.-Doz. Mag. Dr. rer. nat.
Division of Hygiene and Medical Microbiology, MUI

Former Members

Gastl, Günther, Univ.-Prof. Dr. med. univ.
Department of Internal Medicine, MUI

Klocker, Helmut, ao. Univ.-Prof. Dr. rer. nat.
Department of Urology, MUI

Kofler, Reinhard, Univ.-Prof. Dr. med. univ.
Division Molecular Pathophysiology, MUI

Troppmair Jakob, Univ.-Prof. Mag. Dr. rer. nat.
Department of Visceral-, Transplant-and Thoracic Surgery, MUI

Funding (2005 – 2017):

Austrian Science Fund (FWF):	€ 10,037,000
Medical University Innsbruck:	€ 3,365,000
University Innsbruck (LFU):	€ 250,000
Total:	€ 13,652,000

MCBO Students

Host Response in Opportunistic Infections – DK HOROS

Speaker:
ao. Univ.-Prof. DDr.
Reinhard Würzner

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Keywords

Host response, opportunistic infections
immunity, transplantation, biogerontology

Research Focus

Scientists and physicians of the Innsbruck campus, working in the related fields of Infection, Immunity, Transplantation and/or Biogerontology, have decided to join forces and have created a structured and multi-disciplinary research and training programme of excellence (DK). Their intention is to cooperatively and synergistically investigate genetic and environmental parameters, which destroy the immune homeostasis during host-pathogen interaction, thus leading to opportunistic infections, seldom developing in healthy, but quite often in immuno-compromised subjects. Six of the seven members of the consortium work at the Medical University of Innsbruck (MUI), one is heading the Institute of Biomedical Aging Research (IBA), now part of Leopold Franzens University (LFU) of Innsbruck. It is envisaged to strengthen the cooperation between both local universities in the coming periods. Four members of the consortium are medical doctors – one works at bedside and 3 mainly preclinically – three are natural scientists. All 7 contribute to various aspects of host-pathogen interaction, comprising inherited and acquired immunity. On the infection side fungal, bacteriological or virological models are in use.

From Basic Research to Clinical Implementation

HOROS is carried out by scientists and physicians working in clinical departments or "pre-clinical" research institutes of both universities, thus providing an important translational link between basic research and clinical application. MUI is very interested to have a broad and excellent DK on "Infection, Immunity & Transplantation", one of its major officially stated research topics. A strong liaison with industrial partners has been established for supplementary funding. HOROS fosters even closer collaborations between research groups and the strategic added values lie in an attractive educational curriculum, more coherent and practical than previously. HOROS provides perfect means to finance research stays of PhD students in collaborators' laboratories, a "HOROS annual retreat", and the possibility to offer a professorship to a distinguished researcher from abroad. Thus, HOROS strengthens the scientific environment of the research campus Innsbruck that attracts not only the best students, but also distinguished scientists to the campus.
In October 2014 six HOROS and two HOROS-associate students started their projects. Another four students started in March 2015.

Funding

FWF DK W1253-B24, € 2,200,000

Collaborations

- Peter Zipfel, Univ. Jena, Germany
- Peter Garred, Univ. Copenhagen, Denmark
- David Denning, Univ. Manchester, Great Britain
- Beate Kehrel, Univ. Münster, Germany
- Jürgen Löffler, Univ. Würzburg, Germany
- Axel Brakhage, Univ. Jena, Germany
- Ioav Cabantchik, Univ. Jerusalem, Israel
- Ferric Fang, Univ. Washington/ Seattle; USA
- Andreas Radbruch, DRFZ Berlin, Germany
- Guiseppe del Giudice, Novartis, Siena, Italy
- Stefan G. Tullius, Univ. Boston, USA
- Ondrej Viklicky, Univ. Prague, Czech Replublic
- Thomas Pietschmann, Univ. Hannover, Germany
- Alexandra Trkola, Univ. Zurich, Switzerland

Ao. Univ.-Prof. Dr. med. Reinhard Würzner, Ph.D (Speaker HOROS, right) and ao. Univ.-Prof. Mag. Dr. Markus Reindl (Clinical Department of Neurology, SPIN).

HOROS doctoral programme of excellence

HOROS Faculty Members and students

HOROS Principal Investigators

ao. Univ.-Prof. DDr. Reinhard Würzner

HOROS-Speaker

Identification of factor H binding complement evasion molecules in fungi

Reinhard Würzner is an expert in complement evasion strategies, in particular of bacteria and fungi, but also of complement related kidney diseases. He is the coordinating deputy head of all MUI doctoral programmes and also heading the related doctoral programme "Infectious Diseases".

Univ.-Prof. Dr. med. Beatrix Grubeck-Loebenstein

Deputy-Speaker

The role of the human bone marrow for the regulation of immune responses in old age

Beatrix Grubeck-Loebenstein is directing the Institute for Biomedical Aging Research (IBA) which is now part of LFU.
She is a leading scientist in biogerontology and in particular in immunology of old age and has inaugurated the related doctoral programme "Aging". Her contribution to HOROS will bridge medical and science faculties of both universities.

ao. Univ.-Prof. Mag. Dr. rer. nat. Hubertus Haas:

Siderophore-mediated diagnosis of fungal infections

Hubertus Haas is working at the Biocenter. He is a basic scientist involved in fungal diseases and in particular interested in the iron homeostasis of the fungus and the role of iron as virulence factor. One of his targets are siderophores which allow the fungus to acquire iron in hostile environments.

Univ.-Prof. Dr. med. Cornelia Lass-Flörl:

Establishment of a human lung tissue model to study fungal infections

Cornelia Lass-Flörl is directing the Division of Hygiene and Medical Microbiology.
Her research focuses on fungal infections with a special emphasis on the diagnosis, prevention and therapy of invasive infections and antifungal drug resistance.

Univ.-Prof. Dr. rer. nat. Katja Kotsch:

Influence of donor and recipient age on the outcome in SOT

Katja Kotsch is working at the Dept. of Visceral, Transplant and Thoracic Surgery and was recently appointed as Professor for Experimental Transplantation Immunology. Her research interests are related to the diagnosis and therapy of acute and chronic rejections in solid organ transplantation by defining risk factors of allograft survival including the increasing age of transplant donors and recipients. In addition she is interested in the impact of infections in this transplantation setting.

ao. Univ.-Prof. Dr. rer. nat. Heribert Stoiber:

Mechanisms for the specific acquisition of complement regulator proteins by HCV

Heribert Stoiber is specialized in medical microbiology and virology and deputy head of the Division for Virology.
His research focuses on the interplay of viruses with the complement system, in particular with evasion mechanisms viruses apply to circumvent the lytic action of the human complement system.

Univ.-Prof. Dr. med. Günter Weiss:

Role of NRAMP-1 in the control of host resistance against infection with intracellular bacteria

Günter Weiss is professor of clinical immunology and infectious diseases and is directing the Department of Internal Medicine VI. His research interest focuses on disorders of iron homeostasis and host-pathogen interaction with a special emphasis on regulatory interactions between iron homeostasis, natural resistance genes and immune function in various infections. He is the coordinator of CIIT at IMU.

Signal Processing in Neurons – DK SPIN

Speaker:
Univ.-Prof. Dr. Georg Dechant

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Research Focus

Neurological and psychiatric disorders are one of the greatest threats to public health. Research across a wide range of sectors and disciplines is needed to bring about the changes that people with such disorders need.
In precisely this spirit, we use an integrative, crossover approach. SPIN was set up to allow multidisciplinary interaction at the interface of molecular and clinical neuroscience. Our aim is to reach a new level of understanding of the fundamental integrative processes that govern the signaling within and between nerve cells under normal and pathological conditions.

The SPIN program has identified three broader areas of research:
- molecular/cellular neuroscience
- neuronal physiology and pathophysiology
- behavioral neuroscience

We have initiated a variety of integrated PhD projects that combine all three levels, which proves to be an ideal learning and training environment for our students.

What is SPIN?

The SPIN doctoral program is an initiative of the Medical University of Innsbruck (MUI) and the University of Innsbruck (LFUI). It was established in September 2007 with the support of the Austrian Science Fund (FWF) and offers interdisciplinary postgraduate training in translational Neuroscience for excellent Austrian and international students. It combines the expertise in Neurosciences across departments, making it currently the only doctoral college in Austria with an exclusive focus on Neuroscience.

TEACHING

The main goal of SPIN is to equip students with the practical and theoretical knowledge they need in order to actively contribute to future scientific advances. In order to obtain a PhD at our institution, students must carry out an experimental study and complete the courses in the PhD curriculum.

Monitoring and Mentoring

SPIN students work under the tutelage of a supervising professor and a board of advisors, the “Thesis Steering Committee”

Thesis Steering Committee (TSC)

A thesis steering committee is assembled for each student. The TSC consists, in addition to the supervisor, of two experienced researchers. During the process of preparing the thesis, the steering committee is to evaluate and supervise the progress of the PhD work in regular and structured meetings with the student.

Progress Report

Each week, one student in the SPIN network presents their progress with their research to other students and faculty members and thus marks the central communication platform for all SPIN members.

EXTRAS

Students also benefit from a number

SPIN
signal processing
in neurons

SPIN Faculty Members and students

of additional offers within the SPIN program. These include annual retreats in attractive locations in and around Austria, stays abroad to maintain old and make new contacts in their respective field, academic (soft) skills training workshops, as well as collaborations and joint events with our neighboring Graduate School of Systemic Neurosciences (GSN) LMU Munich.

SPIN in Numbers

- PIs: 10
- Departments: 8
- Current students: 22
  (14 female, 8 male)
- Alumni: 25
  (15 female, 10 male)
- Nationalities: 15

FUNDING

FWF: € 4,899,980.50 (until the end of 2016)
MUI: € 2,448,773.50 (until the end of 2015)

SPIN Principal Investigators | Members on Campus

Univ.-Prof. Dr. Christine Bandtlow
Division of Neurobiochemisty

Univ.-Prof. Dr. Georg Dechant
Institute for Neuroscience

Univ.-Prof. Dr. Francesco Ferraguti
Department of Pharmacology

Univ.-Prof. Dr. Lars Klimaschewski
Division of Neuroanatomy

Univ.-Prof. Dr. med. Michaela Kress
Department of Physiology and Biomedical Physics

ao. Univ.-Prof. Dr. Markus Reindl
Clinical Department of Neurology

ao. Univ.-Prof. Dr. Christoph Schwarzer
Department of Pharmacology

ao. Univ.-Prof. Dr. Nicolas Singewald
Department of Pharmacology and Toxicology (LFUI)

ao. Univ.-Prof. Dr. Nadia Stefanova
Department of Neurology, Division of Neurobiology

ao. Univ.-Prof. Dr. med. Gerald Zernig
Experimental Psychiatry Unit

SFB-F44 – Cell Signaling in Chronic CNS Disorders

Coordinator :
Univ.-Prof. Dr. Jörg Striessnig (LFU)

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General Facts

Chronic diseases of the central nervous system (CNS), such as fear/anxiety disorders and neurodegenerative diseases occur with high and increasing prevalence. Since molecular disease mechanisms are not fully understood, current drug therapies are often unsatisfactory. The development of novel and improved therapeutic strategies requires the identification of innovative targets for therapeutic intervention. Therefore competent laboratories at the two Innsbruck universities joined their complementary expertise to comprehensively study signaling pathways that bear such potential. The major research focus is on L-type calcium channels (LTCCs) and epigenetic modulators, in particular histone deacetylases (HDACs). These pathways appear to participate in the etiology of several neurological and neuropsychiatric disorders. Moreover, recent preliminary findings from our consortium suggest that they can be (patho-) physiologically linked.
Strong local expertise is bundled to study Ca^{2+}-mediated, epigenetic and non-coding RNA (ncRNA)-mediated regulatory mechanisms to disclose the role of these pathways for the pathophysiology of Parkinsonian disorders (Parkinson's disease, Multiple System Atrophy), Alzheimer's disease and abnormal fear and anxiety.

Members and Projects MUI

Importance of Intra- and Extracellular Cav1.3 Modulators for Synapse Stability in Normal and Diseased Striatal Medium Spiny Neurons

Gerald Obermair, Bernhard E. Flucher
Division of Physiology

In brain dendritic spines are small postsynaptic membrane protrusions on neuronal dendrites involved in excitatory synaptic transmission and synaptic plasticity. Neuronal L-type calcium channels are located in dendritic spines and contribute to the local concentration of the ubiquitous second messenger calcium. Thereby calcium channels integrate synaptic signals, effect changes in spine morphology and the synaptic structure and contribute to basic neuronal functions including learning and memory formation. Neurological diseases are often accompanied by synaptic adaptations including altered form and function of dendritic spines. For example, a specific loss of dendritic spines of striatal neurons has previously been shown to be involved in the pathology of Parkinson's disease (PD). Interestingly a loss of dendritic spines in the striatum may also underlie the development of L-DOPA-induced dyskinesia, the major debilitating side effect of the common treatment for PD. In our project of the first SFB funding period we have identified a specific role of a specific L-type calcium channel and its interaction with postsynaptic proteins in regulating the stability of dendritic spines. Building on this important result, we now test in the ongoing project whether and how this proposed mechanism contributes to the etiology of PD and other neuronal diseases. To this end we are employing high- and super-resolution fluorescence microscopy and state-of-the-art electrophysiology. Our results will contribute to the understanding of synaptic adaptations during neurological disorders and probe the therapeutic potential of targeting the identified synaptic mechanisms.

Alpha-synuclein – a Pathogenic Trigger and Interventional Target in Multiple System Atrophy

N. Stefanova, G. Wenning
Department of Neurology

Multiple system atrophy (MSA) is a distinctive neurodegenerative disorder characterized by oligodendroglial cytoplasmic inclusions of fibrillar α-synuclein (α-syn) and associated with progressive multisystem neurodegeneration. Our group will provide detailed characterization of the functional phenotype of a transgenic mouse model with targeted overexpression of α-syn in oligodendrocytes as an important readout for preclinical drug screening for MSA. To identify underlying pathogenic mechanisms and candidate targets for future therapies we will focus on the putative bilateral interactions between epigenetic factors, and α-syn aggregation and propagation in MSA models. The outcomes are likely to critically enhance our insights into the pathogenesis and progression of MSA. The results will have immediate relevance for interventional target discovery which in turn will promote future clinical trial activities in MSA patients.

Identification of Regulatory ncRNAs in Chronic CNS Disorders

Alexander Hüttenhofer
Division for Genomics and RNomics

This project aims to identify regulatory ncRNAs involved in neuronal development and chronic CNS disorders. Using special probes and techniques recently developed in this lab ncRNAs that are regulated in disease and may therefore contribute to signaling pathways involved in neurodegeneration will be identified and characterized. Existing expertise will also be used to probe for regulatory ncRNAs participating in L-type Ca^{2+} channel-mediated plasticity and nuclear signaling in various neurons.

Function of Special AT-rich Sequence-Binding Protein 2 (SatB2) in Aging and Neuronal Pathophysiology

Georg Dechant, Galina Apostolova
Institute for Neuroscience

Complex behaviors such as learning and memory depend on changes in gene expression and subsequent long-lasting adaptations in synaptic strength and structure. Current research interests of this group are focused on the mechanisms of neuronal plasticity, with special emphasis on the role of chromatin conformation regulation in adaptive gene transcription.
A classic example of neuronal plasticity is the switch from noradrenergic to cholinergic neurotransmission, which occurs in differentiated postganglionic sympathetic neurons under the influence of target-derived signals. We identified the genome organizer Special AT-rich sequence binding protein 2 (Satb2) as an acutely up-regulated target gene of neurokine/p38 MAPK signaling in sympathetic neurons undergoing trans-differentiation. Gain-and loss-of-function studies of this group revealed that Satb2 is both

necessary and sufficient to trigger the sympathetic neurotransmitter switch. Therefore modulation of Satb2 and consequently chromatin architecture by neurotrophic factors might serve as a novel pathway involved in the long-term adaptive processes underlying higher brain functions.
In support of this hypothesis, recent results in our laboratory showed that Satb2 is induced by plasticity-mediating extracellular signals such as BDNF or Ca^{2+}-influx through L-type voltage-gated calcium channels in CNS neurons. The analysis of a conditional mutant lacking Satb2 in the adult forebrain (generated by our group), demonstrated that Satb2 is required for synaptic plasticity and long-term memory formation. In addition, we found that Satb2 interacts with genome organizing proteins of the inner nuclear membrane and regulates the geometry of neuronal nuclei in the hippocampus *in vivo*. Therefore Satb2-containing DNA-protein complex may determine both the nuclear shape and chromosomal conformations in neurons downstream of L-VGCC and BDNF signaling, thereby integrating plasticity-mediating extracellular signals into changes in the transcriptome.
Future goals are to provide evidence that Satb2-dependent rearrangements of the nuclear architecture and/or changes in the epigenetic profiles are necessary for higher cognitive functions and that dysfunction of these mechanisms leads to learning and memory deficits. Another aim is to study whether cognitive deficits inherent to normal aging and neuropsychiatric diseases are caused by alterations in Satb2 expression or function.

Dopamine Regulation of Amygdala Inhibitory Circuits: Relevance for Pathological Fear Structures
Francesco Ferraguti
Institute or Pharmacology
Parkinson's disease (PD) is classically considered as a movement disorder resulting from the loss of dopaminergic (DAergic) neurons. However, a number of non-motor symptoms, including pathological fear and anxiety, predate the emergence of motor impairment. PD could then be seen as a multidimensional disease. Dopamine exerts a pivotal role in the regulation of fear responses most likely by affecting GABAergic transmission within the amygdaloid complex. We postulate that pathological fear in early PD results from altered associative plasticity in the basolateral amygdala (BLA) mostly dependent on the reduced function of DA on specific local interneurons. In addition, enhanced phasic DAergic transmission during fear extinction training may facilitate extinction learning and the concurrent plasticity. These hypotheses will be experimentally addressed by means of a multidisciplinary approach combining optogenetics, viral monotransynaptic tracing and novel ultrastructural techniques. A mouse model for non-motor symptoms of early PD, lacking motor impairments, will also be established and characterized. Therefore, this project will complement other investigations within this SFB on aberrant signaling mechanisms leading to selective neurodegeneration (e.g. PD), altered neural plasticity and abnormal fear memory processing.

Members University of Innsbruck (LFU)

Epigenetic Mechanisms in Aberrant Memory Regulation
Nicolas Singewald
Department of Pharmacology and Toxicology, University of Innsbruck
Effective long-term treatment for fear and anxiety-related disorders is a continuing challenge. One emerging treatment strategy is combining exposure-based cognitive behavioural therapy (CBT) with cognitive enhancers. Key results from the first SFB funding period (FP) support the utility of this approach for long-term fear inhibition. Specifically, we provide evidence that histone deacetylase (HDAC) inhibitors and facilitating dopaminergic signaling act as cognitive enhancing strategies to rescue aberrant fear extinction consolidation in S1 (129S1/SvImJ) mice. Additional findings indicate that non-coding RNAs, including – microRNAs (miRNAs), and Cav1.3 channel-mediated signaling – may be additional promising targets to exploit for novel pro-cognitive properties supporting extinction memory formation. Building on results obtained in the 1st FP, we now aim to elucidate the how and where in the brain HDAC inhibition, enhancement of dopaminergic signaling, interference with non-coding RNAs- or Cav1.3 mediated-signalling can augment fear extinction to form a persistent and context-independent fear inhibitory memory. In addition, we aim to improve the tolerability of exposure based therapy by combining the therapeutic actions of non-sedative anxiolytic drugs which do not impair extinction learning and appropriate cognitive enhancers. Finally, this project started to identify potential epigenetic biomarkers in blood cells that can be associated with the sensitivity to and the extent of the therapeutic effect of exposure therapy in anxiety disorder patients. Revealing mechanisms via which rescue of impaired fear extinction can be achieved in a better tolerated, persistent and context-independent manner is expected to foster the rational development of novel cognitive enhancers which may be used as augmenting CBT adjuncts to treat anxiety disorders more effectively.

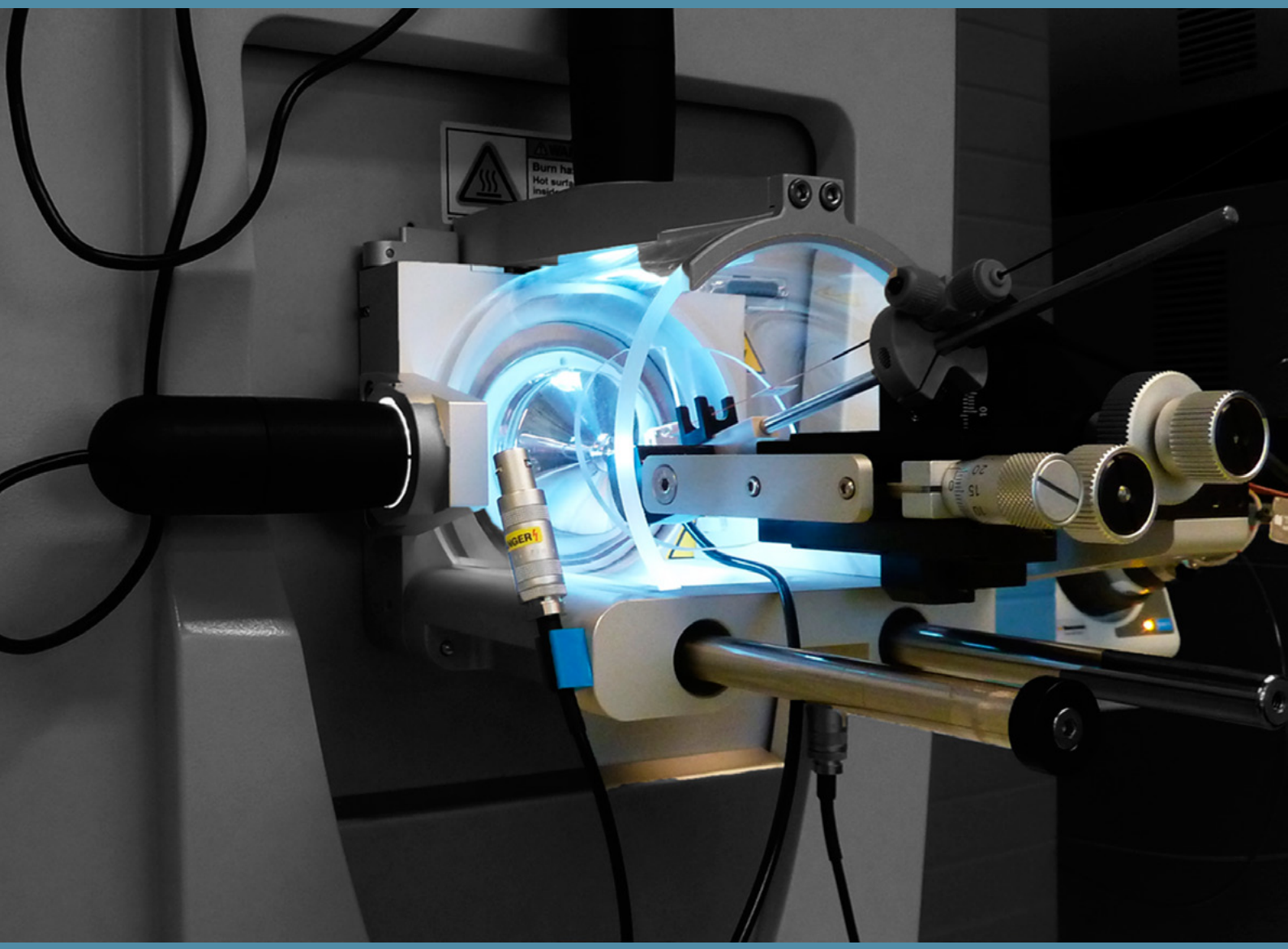
Role of Cav1.2 and Cav1.3 Calcium-Channels for Parkinson's Disease and Neuropsychiatrc Disorders
Jörg Striessnig
Department of Pharmacology and Toxicology, University of Innsbruck
L-type Ca^{2+} channels (LTCCs) have recently emerged as novel drug targets for the treatment of Parkinson's disease (PD) with already licensed or new channel blockers. The concentrations of available drugs required for effective block, the LTCC channel isoforms in involved in PD pathophysiology and the mechanisms of neuroprotection are still not known. This group recently identified human mutations that strongly point to a crucial role of brain LTTC gain of function (including the so-called Cav1.3 subtype) for the pathophysiology of psychiatric diseases (particularly autism spectrum disorders, ASD). This suggests a pathogenic and thus also potentially therapeutic role of brain LTCCs beyond PD. New tools and assays will be developed to determine if LTCCs in the brain are blocked as effectively as Cav1.2 channels in the cardiovascular system. This will allow predictions if already licensed drugs can be used for neuroprotection in PD or the therapy of selected ASD patients with Cav1.3 mutations. Moreover, suitable mouse models will be established that will allow us to study the functional consequences of human ASD mutations in different tissues, in particular the brain. Finally we ask the question if knockout of Cav1.3 channels or chronic inhibition of these channels leads to compensatory upregulation of other ion channels that could counteract their pharmacological action. These highly translational questions will be addressed in collaboration with other members of the consortium. Our work has immediate relevance for better understanding of Ca^{2+}-dependent human disease mechanisms and ongoing drug discovery in industry.

Members from other Universities

Birgit Liss, University of Ulm
Ludwig Aigner, Paracelcus Medizinische Privatuniversität, see homepage

Former Members (1st Funding Period)

Christian Humpel, Josef Marksteiner
Dept. for General and Social Psychiatry, MUI
Alexandra Lusser
Division of Molecular Biology, MUI

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Core Facility Net

www.corefacilitynet.org

What is the Core Facility Net?

The inter-university core facility network has produced Austria's largest platform for the exchange of life science technology services and expertise.

The three Medical Universities of Graz, Innsbruck and Vienna, as well as the Austrian Institute of Technology (AIT) and the University of Veterinary Medicine Vienna are participating in the setup of this "shared technology space". They are linking up existing technologies worth approximately 30 million € and the expert know-how of 80 specialists from the four core areas of OMICS-technologies, imaging techniques, biocomputing and functional biomodels.

In addition to the research infrastructure network, pan-university, post-graduate further education and training will be provided, especially to young researchers, in order to initiate and encourage networking. In the future, additional partner institutions will be integrated into the network. The technical realisation of the project was carried out in cooperation with the FAW GmbH; the research infrastructure platform is open to the public since July 2014.
The total cost of the project is more than 520,000 € and has been approved for 152,000 € of financing as a part of a federal fund for infrastructure in higher education by the former Federal Ministry of Science and Research.

Benefits

Work togehther with experts

Many experts, who are willing to cooperate, have given their commitment to the network. They provide a short summary about their expertise – try searching for a special expertise and get a list of experts!

Know about high-end infrastructure

Available infrastructure is represented and described on the web portal, including information like User Manuals, experts related to this special device and other information. With help of the integrated search functionality it's possible to find it quickly.

Geo Information

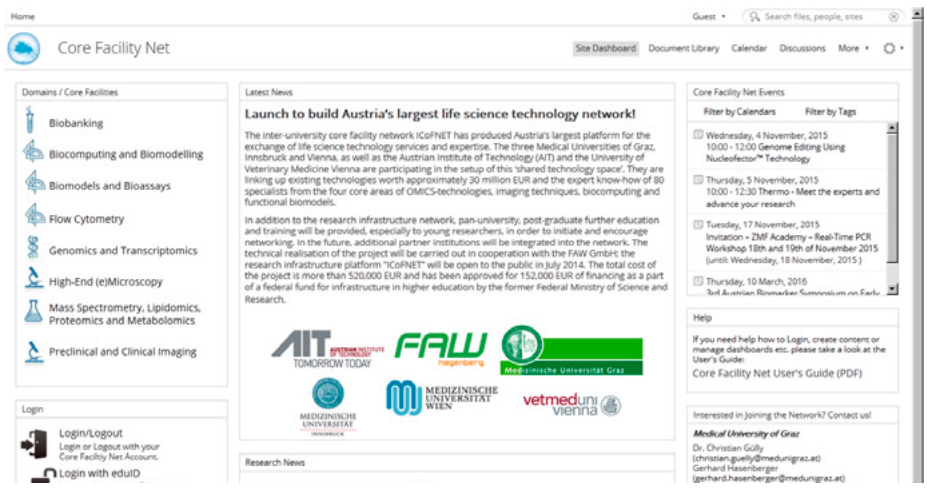
Look out for experts by searching the map – a full Google Map Integration is available therefore. Every content, like experts, devices or even documents/publications can be Geo-tagged.

Calendar

At the portal all events provided by the members could be found in one place. To help finding the relevant events for you, use the integrated filter functionality – filter by site or by tags, or just search for it.

Document Management

Take advantage from the built-in document management system, including history and versioning, working together on the same document and more.



Core Facilities at Medical University of Innsbruck

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