MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

October 2020 – September 2022

MUI-START Report

Forschungsservice und Innovation
Medical University of Innsbruck
October 2020 – September 2022

Content

Disclosure

This annual report was prepared by the Department Forschungsservice und Innovation.

Dr. María Teresa Pérez Mediavilla is responsible for the editorial part concerning the MUI-START Programme. The PIs are responsible for the content of their final reports.

December 2022

1 Background and aim of the programme

MUI-START is the follow-up programme of the MFI (Medizinische Forschungsfonds Innsbruck) which ended in 2011.

The MUI-START programme is devised as a start-up fund for young scientists with the aim to offer them the opportunity of developing new project ideas, within the MUI research focuses, that could serve as basis for a successful subsequent application for external funding (e.g. FWF).

According to the present guidelines, eligible candidates must: 1) have a working contract with the Medical University of Innsbruck for the entire project duration, 2) have completed their doctoral studies, and 3) the applicant´s most recent degree (e.g. PhD/MD) must have been completed no longer than eight years ago. Fully justified career breaks can be taken into account (e.g. parental leave). Professors and PIs of third-party funded (FWF, OeNB, FFG and EU) projects are not eligible. Applicants' track record must be commensurate with their academic age. However, two peer-reviewed international publications as first author are compulsory**.**

The guidelines of the programme have been substantially modified over the years to adapt to the high standards applied by external funding agencies (e.g. FWF). Since 2016, proposals undergo a three-step evaluation procedure: 1) selection of proposals by the MUI-START jury, 2) international peer-review of the pre-selected proposals, and 3) hearing of the shortlisted applicants by the MUI-START jury. Final decisions are based on the reviewers' scores, as well as the outcome of the interviews.

Moreover, since the seventh call (2016) the submission of an external funding proposal before the end of the funding period has become compulsory for all MUI-START grantees. Failure to submit such an application results in the cancellation of the last quarter of the MUI-START grant budget.

2 Overview of MUI-START calls

The first MUI-START call was announced in the summer 2010 and supported 42% of the submitted proposals. Since then, the approval rates have been oscillating from year to year (Table 1) depending on both the available budget and the quality of the submitted proposals. The funded projects from the 13th call will start in December 2022.

Table 1. Overview of all MUI-START calls

Year	Call	Proposals submitted	Proposals granted (Male/Female)	Funding rate	Total funding requested	Total funding granted
2010	1st	31	13 (7M/6F)	42%	€ 2.074.365,7	€ 667.054,8
2011	2nd	11	5 (2M/3F)	45%	€ 629.968,9	€ 173.171,0

2012	3rd	29	9 (4M/5F)	31%	€ 742.808,2	€ 240.000,0
2013	4th	28	14(11M/3F)	50%	€ 713.652,9	€ 323.484,7
2014	5th	31	12(4M/8F)	39%	€ 771.750,5	€ 260.826,6
2015	6th	28	8 (4M/4F)	28%	€ 711.035,4	€ 176.726,0
2016	7th	9	3 (1M/2F)	33%	€ 248.945,0	€ 85.000,0
2017	8th	15	7 (5M/2F)	47%	€ 365.189,3	€ 162.208,8
2018	9th	8	4 (1M/3F)	50%	€ 192.576,2	€ 113.766,3
2019	10th	9	0 (0M/0F)	0%	€ 529.947,8	€ 00,00
2020	11th	16	3 (1M/2F)	19%	€ 559.657,5	€ 101.454,1
2021	12th	26	7 (6M/1F)	27%	€ 940.979,5	€ 263.885,9
2022	13th	10	3 (1M/2F)	30%	€ 321.140,45	€ 74.421,45

3 MUI-START jury members and reviewers

The MUI START jury members are professors and associate professors at the Medical University of Innsbruck working in both basic as well as in clinical research fields. The jury members are chosen according to their expertise in a specific field of research. The composition of the jury is not fixed, but changes as a result of the variety of topics covered by the proposals submitted to a particular call.

The following jury members helped in the selection of the projects in the last two calls. Their help and commitment is warmly acknowledged.

Univ.-Prof. Dr.rer.nat. Christine Bandtlow	*Neurobiochemistry*
Univ.-Prof. Dr.rer.nat. Georg Dechant	*Joint Institute for Neuroscience*
Univ.-Prof. Dr. Francesco Ferraguti	*Pharmacology*
Univ.-Prof. Dr.med. Elke Gizewski MHBA	*Neuroradiology*
Univ.-Prof. Dr.med.univ. Johannes Haybäck	*Pathology, Neuropathology and Molecular Pathology*
Univ.-Prof. Dr. Ludger Hengst	*Medical Biochemistry*
Univ.-Prof. Dr.med.univ. Johannes Holfeld	*Cardiac Surgery*

Univ.-Prof. Dr.med.univ. Lukas Huber	*Cell Biology*
Assoz. Prof. Priv.-Doz. Dr.rer.nat. Natascha Kleiter	*Cell Genetics*
Univ.-Prof. Dr. Markus Reindl	*Neurology*
Univ.-Prof. Dr.med.univ. Barbara Sperner-Unterweger	*Psychiatry II*
Univ.-Prof. Dr.rer.nat. Patrizia Stoitzner	*Dermatology, Venerology and Allergology*
Univ.-Prof. Dr.med.univ. Dominik Wolf	*Internal Medicine V*

The tasks of the jury members comprise:
1) internal review of the proposals,
2) nomination of the reviewers at the suggestion of the MUI Research Office (FSI), and
3) presentation of proposals during the decision meeting.

The reviewers of the MUI-START projects are international experts active in their field of research. Usually two reviews per proposal are necessary to support the jury members in their decision process.

4 External funding granted to MUI-START grant recipients

As stated in the first section of this report the aim of the programme is to help young scientists develop new project ideas that could serve as a basis for a subsequent application for third party funding.

So far, (status as of 30.09.2022) 76 MUI-START funded projects have closed. Twenty-three PIs quit the MUI either before the planned end or immediately after the end of the project. Approximately 75 % (40) of the remaining PIs applied for external funding. Given the competitiveness of the current funding landscape, not all applications generated funding.

Table 2. Funding acquired by former MUI-START grant holders in the period covered by the annual report.

Applicant	Project Title	Funding Agency	Duration (Months)	Funds Granted
Gamerith Gabriele	Soluble Checkpoints in Vasculitis	NIH	13	35.240 €

5 The MUI-START programme in numbers (status as of 30 September 2022)

★ **88 Proposals granted / 76 Projects completed**

★ **47 Male PIs / 41 Female PIs**

★ **108 Publications acknowledging the MUI-START programme**

★ **€ 2,6 Mio granted by the MUI START programme**

★ **€ 8,2 Mio funds acquired by former MUI-START grant holders**

Additionally, 56% of PIs of closed projects now have a permanent position at the MUI or at the Tirol Kliniken. Another 30% of PIs quit the MUI and got positions in other research institutions or at pharmaceutical or high-tech companies. The remaining scientists are still working at the MUI as project collaborators or hold non-permanent positions.

6 MUI-START final reports

The principal investigators of the MUI-START funded projects are responsible for the content of their respective final reports.

Soluble immune checkpoints in different NSCLC cohorts and their clinical relevance

Gabriele Gamerith MD
Department of Internal Medicine V
Anichstaße 35, 6020 Innsbruck

Project duration: 01.12.2018 – 31.05.2021

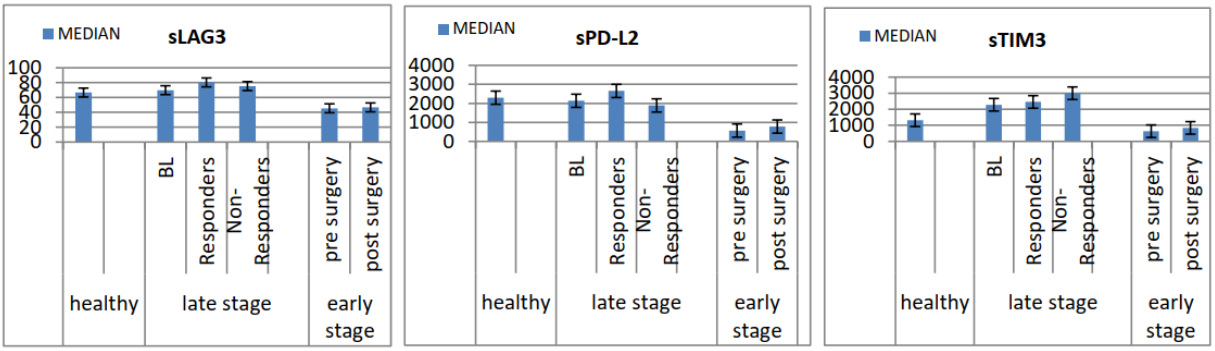
Project summary:

Background and objectives

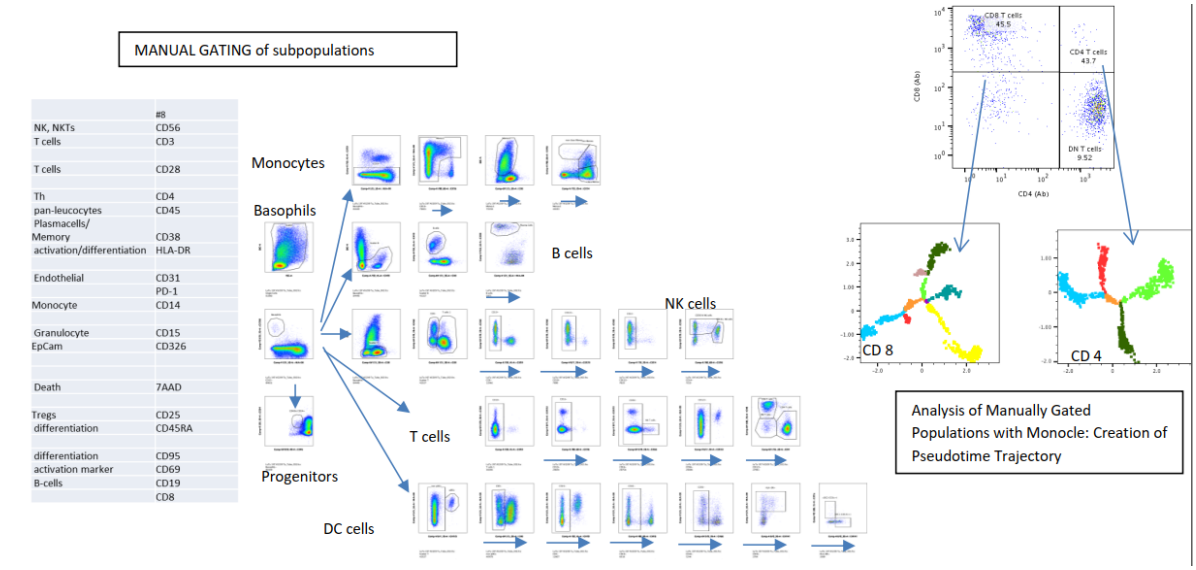
Cancer immune evasion is critical in non-small-cell lung cancer (NSCLC) and has been targeted by immunotherapy. High soluble (s)PD-L1 is associated with reduced survival and treatment failure in advanced stages. Hence, this study focused on the expression of soluble ICPs – also beyond sPD-L1 - and their differences between non-tumor cohorts and stages in lung cancer patients, as well as their prognostic role in combination with investigations of the peripheral blood and immunological local tumor microenvironment.
We measured the expression of various soluble ICPs (i.e. sPD-1, sPD-L1, sPD-L2, sLAG3, sTIM3) in different cohorts of lung cancer patients with a special focus on early stage, but also late stage prior treatment.
Compared results to a non-tumor cohort (age and gender matched patients) and assessed their correlation with the immunological tumor microenvironment (T-cell infiltration, ICP expression on primary tumor and TILs).
Clinical correlation analyses of these results (soluble ICPs, tumor-related microenvironment) with patient characteristics, such as gender, age, smoking habits, stage, histology and other molecular pathological characteristics in combinations and outcomes (progression free survival, overall survival) were done.

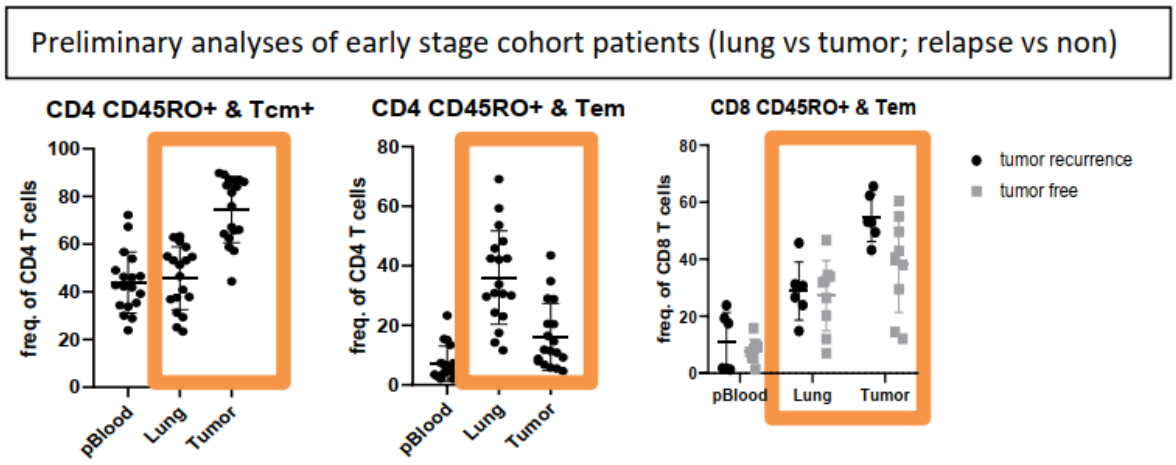
Results

MULTIPLEX ELISAs for sLAG3, sTim-3 and sPD-L2 in ng/ml



MAJOR Immune Cell Subpopulations in Lung Cancer Cohorts

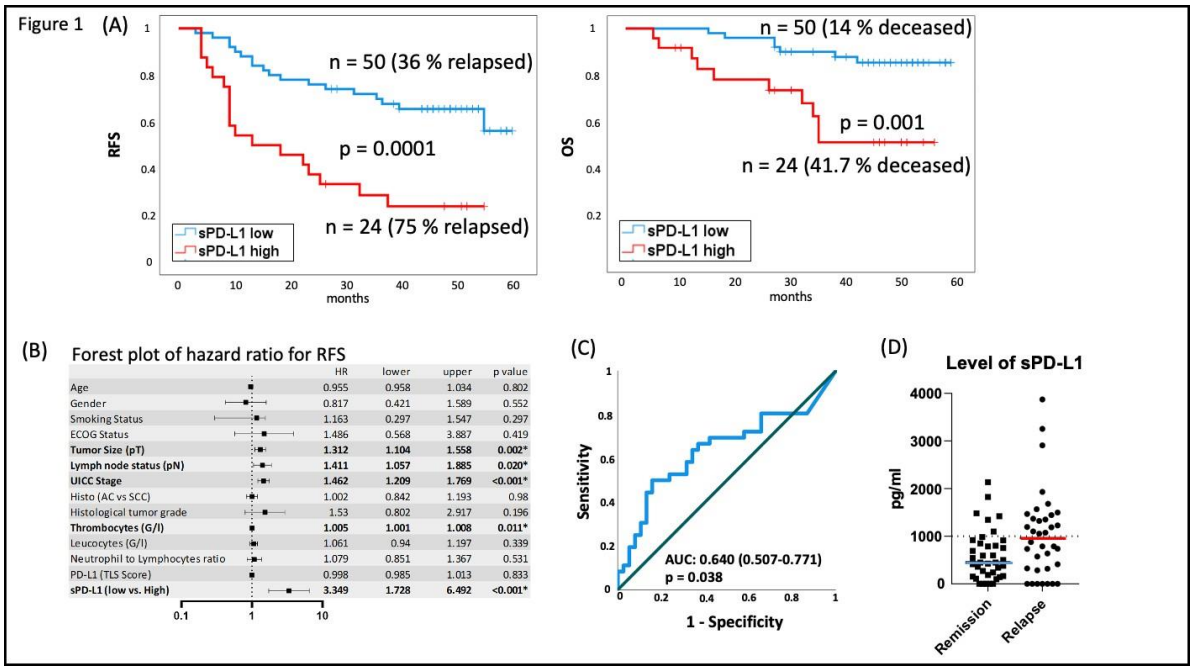




Results sPD-L1 immunosorbent assay in early stage NSCLC – main focus of the last project period based on clinical significant results

Plasma from 74 NSCLC patients (stage IA-IIIB; 78.4 % adenocarcinomas) was collected prior to curative surgery and sPD-L1 levels from an immunosorbent assay were correlated with RFS and OS. Immune infiltration in tissue was evaluated using immunohistochemistry. Data from The Cancer Genome Atlas was investigated for PD-L1 splice variants and enzymes involved in proteolytic cleavage *via* ADAM10. *In-vitro* T cell receptor (TCR) stimulation was performed in the presence of sPD-L1 to evaluate its immunomodulatory activity by flow cytometry.

sPD-L1 levels were significantly higher in NSCLC patients who experienced disease relapse (median: 966.44 vs. 448.24 pg/mL, p = 0.038). Multivariate analysis revealed high sPD-L1 (> 1000 pg/mL) as an independent predictor of RFS and OS. In sPD-L1 low patients, immune cell infiltration was associated with relapse. High ADAM10 protease expression was associated with reduced OS in the TCGA data. *In vitro*, sPD-L1 inhibited IFN-γ production, proliferation of T cells and induces a terminal effector CD4 T cell subtype expressing CD27.



High sPD-L1 is an independent prognostic factor for inferior survival and increased relapse risk in early stage NSCLC. Prospective validation of our findings in independent cohorts and standardization of sPD-L1 quantification assays are needed

Publications issued from this project:

External funding applications:

Collaboration with Personalis to sequence early-stage NSCLC samples based on above results and asses the immunological microenvironment – contract under legal finalization (estimated value in form of material costs & data analyses for MUI: 500.000 Euro)

ITN/NIH funding for sICP measurements in vasculitis patients under treatment (40.000 Euro) (preliminary data of this projects were used for the application)- accepted

Miscellaneous:

PhD Thesis of Finn Mildner, MD – ongoing (first author in submitted CCR publication – applicant corresponding author)

Posters at ÖGHO and ITOC-meetings, but conferences were canceled or online due to Covid-19

Detection of potential markers for liver function and regeneration during normothermic liver perfusion using the OrganOx metra®

Annemarie Weissenbacher
Department of Visceral, Transplant and Thoracic Surgery
Anichstaße 35, 6020 Innsbruck

Project duration: 18.04.2019 – 11.11.2020

Project summary:

Background and objectives

The normothermic liver transplant project could be performed and completed as planned and outlined in the MUI-start-project-proposal.
The first liver was included in the trial in April 2019, slightly delayed, and the last liver preserved normothermically and transplanted consecutively, was included in early March 2020.
The proposed research objectives have been met and we could deliver evidence for liver regeneration and parenchyma quality assessment (publication listed below). Also, the proposed glutathione measurements in bile, sampled during normothermic liver preservation, could be performed. The ELISA analyses were done successfully and revealed clearly differences between livers. The results of the analyses are currently under evaluation and correlation with measured perfusate parameters and the outcomes of recipients after liver transplantation (manuscript in preparation).
Another aspect of the proposed research objectives, reduction of ischaemia reperfusion injury, has also been addressed and a marker in the perfusate, interleukin 6, detected, measured and correlated with the occurrence of reperfusion syndrome in the recipient – a clinical marker for, potentially severe, ischaemia reperfusion injury. The data are currently under evaluation and a manuscript in preparation.
As a final aspect of the proposed trial, all results discovered in the normothermic liver preservation group will be compared to liver transplants after static cold storage (as mentioned in the proposal) to discover important, probably future-changing findings improving orthotopic liver transplantation.

Results

Normothermic machine perfusion (NMP) has become a clinically established tool to preserve livers in a near-physiological environment. However, little is known about the predictive value of perfusate parameters towards the outcomes after transplantation. Fifty-five consecutive NMP-livers between 2018-2019 were included. All of the livers were perfused on the OrganOx metra® device according to an institutional protocol. Transplant and perfusion data were collected prospectively. Forty-five livers were transplanted after NMP. Five livers stem from donors after circulatory death and 31 (68.9%) from extended criteria donors (ECD). Mean (SD) cold ischemia time (CIT) was 6.4 (2.3) hours; mean (SD) total preservation time 21.4 (7.1) hours. Early allograft dysfunction (EAD) occurred in 13/45 (28.9%) patients. Perfusate aspartate-aminotransferase (p=0.008), alanine-aminotransferase (p=0.006), lactate-dehydrogenase (p=0.007) and their development over time, alkaline phosphatase (p=0.013) and sodium (p=0.016) correlated with EAD. Number of perfusate platelets correlated with CIT-duration and were indicative for the occurrence of EAD. Moreover, vWF antigen was significantly higher in perfusates of EAD-livers (p<0.001) and ΔvWF antigen correlated with EAD. While perfusate lactate and glucose had no predictive value, EAD was more likely to occur in livers with lower perfusate pH (p=0.008). ΔPerfusate AP, Δperfusate AST, Δperfusate ALT and Δperfusate LDH correlated closely with MEAF but not L-GrAFT. Bile parameters correlated with ECD and donor risk index. To conclude, biomarker assessment during NMP may help to predict EAD after liver transplantation. The increase of transaminases and LDH over time as well as platelets and vWF antigen are important factors indicative for EAD.

Publications issued from this project:

Perfusate Enzymes and Platelets Indicate Early Allograft Dysfunction after Transplantation of Normothermically Preserved Livers.

Weissenbacher A, Bogensperger C, Oberhuber R, Meszaros A, Gasteiger S, Ulmer H, Berchtold V, Krendl FJ, Fodor M, Messner F, Hautz T, Otarashvili G, Resch T, Margreiter C, Maglione M, Irsara C, Griesmacher A, Raynaud M, Breitkopf R, Troppmair J, Öfner D, Cardini B, Schneeberger S.Transplantation. 2021 Jun 17. doi: 10.1097/TP.0000000000003857. Online ahead of print. PMID: 34144552

External funding applications:

FWF 1000 ideas project (84. Sitzung des Kuratoriums am 21.06.2021 abgelehnt): Cholangioscopy for ex-situ bile duct assessment.

Miscellaneous:

Abstract submissions planned for glutathione and interleukin-6 and reperfusion syndrome results.

Material testing machine vs. shoulder test bench – a comparison of two test setups for biomechanical investigations of proximal humeral fractures

Dr. Susanne Strasser PhD
Department for Orthopedics and Traumatology
Anichstaße 35, 6020 Innsbruck

Project duration: 01.12.2018 – 31.05.2021

Project summary:

Background and objectives

The general life expectation in the population is continuously increasing. The risk of an osteoporotic fracture correlates with age. A proximal humeral fracture counts among the most common osteoporotic fractures [1]. Several operative treatments have been described like k-wires, intramedullary nails and plate fixation. The choice for the optimum treatment is still challenging for the trauma surgeon as there is not yet consensus for the standard of care.High complication rates of proximal humeral fractures are reported in the literature due to poor bone quality. The most common complications are secondary dislocation and the angular malposition of the fracture fragments. A resulting varus impaction of the humeral head leads to a worse clinical outcome. Prior to the clinical use of new implants biomechanical testing is essential. Various test set ups are described in the literature. So far the vast majority of biomechanical testing is performed using material testing machines. Various loading protocols are described in the literature. Commonly, a simplified test set up in a standard material testing machine is used. Bending and torsional stiffness of the used osteosynthesis material is tested by applying varying static loads. The loads are either expected to be within the elastic range of the construct [6, 11] or to lead to the failure of fixation. In different biomechanical test set ups several authors also applied cyclic loading (cycle amount ranges from 500-5000) with a static force vector to provoke loosening of the osteosynthesis. The aim of the presented project was to compare the biomechanical testing of the custom-made shoulder test bench with a material testing machine (MTS) using a standardized three part fracture model.

Materials & Methods

Specimen, Fracture, Implant
12 paired fresh frozen specimen were harvested from the Department for Anatomy, Embryology and Histology. The specimen were prepared in standardized way. A standardized 3-part fracture was created and treated with a locking compression plate (PHILOS - Proximal Humeral Internal Locking System). The specimen were randomly divided into two groups – 6 specimen shoulder test bench and 6 specimen MTS.

Biomechanical testing
Shoulder test bench: The test set-up is described in detail in a former publication [17] .6 different load sets of 20 cycles were conducted. Biomechanical testing began with a reduced arm weight. The load was increased after every 20th cycle to simulate the increasing range of motion during physiotherapy.
MTS: The test set-up is described in detail in a former publication [18]. The same load sets as in the shoulder test bench were used. The load magnitude was adapted to reflect the load magnitude of the shoulder test bench and compensate the different directions of the load vector of the two test setups.
Fracture gap movement: The gap movement of the fracture fragments during cyclic loading was measured using an ultrasound based 3-motion analysis system (Zebris, Isny, Germany). The failure of the implant was defined as a constant varus impaction ≥2 degrees.

Results

All specimen had a failure in an early stage of biomechanical testing (shoulder test bench 12-22 cycle, MTS 1-25 cycle). The failure occurred in the first two loading increments. The load magnitude at failure showed a good correlation for the two test setups (r=0.93).

Conclusion & Outlook

The comparison of the number of load cycles for the two test methods, the shoulder test bench and the material testing machine, showed comparable results and a good correlation in the number of load cycles until failure. Therefore, the more physiological testing in the shoulder test bench is a well suited setup for testing of implant failure treatments for proximal humeral fractures.

In the future, it is planned to further enlarge the capabilities of the existing shoulder test bench by increasing the number of movement planes and simulated muscles. These modifications could enable the establishment of the shoulder test bench as valid Gold standard for biomechanical testing of proximal humeral fractures.

Publications issued from this project:

External funding applications:

AO Incubator – rejected
AO Strategy Fund – rejected

Miscellaneous:

Diploma students assisting the project:
Benedikt Hutzler
Luise Lange

Identification of intestinal epithelial inflammatory triggers in Crohn's disease

Lukas Niederreiter PhD MD
Department of Internal Medicine I
Anichstaße 35, 6020 Innsbruck

Project duration: 31.12.2020 - 30.06.2022

Project summary:

Background and objectives

We aimed at deciphering specific environmental triggers as an inflammatory trigger in human intestinal epithelial cells from Crohn's disease (CD) patients. To do so, we exposed organoids derived from inflamed ileal resection specimens of CD patients, as well as mildly inflamed mucosa obtained from ileal biopsies during colonoscopy from CD patients and stimulated these with polyunsaturated fatty acids for 24 hours. We characterized the inflammatory response at baseline and after a stimulation by qPCR and ELISA.

Results

We found that CD organoids that show impaired GPX4 activity (50%) responded with IL-8 and TNF expression upon exposure to polyunsaturated fatty acids. This was paralleled by lipid peroxidation and endoplasmic reticulum stress, both of which drive enteritis in susceptible mice that is induced by polyunsaturated fatty acid excess in a Western diet. Organoid studies were challenging because we noted strong inter-patient variability and inter-experimental variability, which required strong replicative effort to override potential bias.

Conclusion & Outlook

The study provides evidence that dietary polyunsaturated fatty acids trigger an inflammatory response from epithelium of CD patients. We published these findings in Gastroenterology (Impact factor 22,6) in January 2022, an article that will be in print in April. Further studies will be needed to identify whether other dietary factors control epithelial immune responses in CD. Moreover, we seek to translate these findings by designing a diet restricted in polyunsaturated fatty acids that could ameliorate the course of CD. To do so, we will need to define a CD patient population that possibly benefits from dietary PUFA restriction, and thus, we are currently trying to establish serum assays to predict response to PUFA restriction. This will be tested in a pilot nutritional and translational study at the Medical University of Innsbruck in the upcoming years.

Publications issued from this project:

PUFA-Induced Metabolic Enteritis as a Fuel for Crohn's Disease.

Schwärzler J, Mayr L, Vila AV, Grabherr F, **Niederreiter L**, Philipp M, Grander C, Meyer M, Jukic A, Tröger S, Enrich B, Przysiecki N, Tschurtschenthaler M, Sommer F, Kronberger I, Koch J, Hilbe R, Hess MW, Oberhuber G, Sprung S, Ran Q, Koch R, Effenberger M, Kaneider NC, Wieser V, Keller MA, Weersma RK, Aden K, Rosenstiel P, Blumberg RS, Kaser A, Tilg H, Adolph TE. Gastroenterology. 2022 Jan 12:S0016-5085(22)00012-9. doi: 10.1053/j.gastro.2022.01.004. Online ahead of print.

External funding applications:

None – all data was published in Gastroenterology above. The generation of unpublished preliminary data would require further financial support.

Miscellaneous:

The data was orally presented at a large national meeting (ÖGGH 2021) and at two large international meetings (UEGW 2021 and ECCO 2022)
Two Diploma Students, Miss Simone Tröger and Mr. Kai Kunz, performed studies on organoids.