Division of Surgical Research

Annual Report 2014

Department of Surgery
University Hospital Zurich
Switzerland

University of Zurich[UZH]

UniversityHospital Zurich

Content

Preface

Dear Colleagues

It is my privilege to present the Annual Report 2014 of the Division of Surgical Research at the University Hospital Zurich.

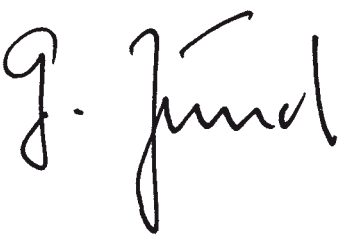
In 2014, the major investment of laboratory equipment was the purchase of a high-performing automatic immunohistochemistry staining system (Dako Autostainer Link 48) for our IHC-Laboratory.

For teaching activities several events were offered. The annual five day Advanced Course in Experimental Microsurgery (ACEM) was held in November. Our weekly research colloquium is a platform to present ongoing research projects for members of the nine surgical research divisions. In the bi-weekly Journal Club a research member presents an article of general interest published by an external research group. These activities were regularly attended by the members of our Division and other researchers. Furthermore, our monthly Newsletter is presenting an article published by one of the nine surgical research divisions.

It is my great pleasure to thank all members of our Division as well as our research partners from the University, University Hospital and the Swiss Federal Institute of Technology for last year's excellent contributions and fruitful collaborations.

Prof. Dr.
Gregor Zünd, MD
Head Division of
Surgical Research

Yours sincerely



Gregor Zünd, Prof. Dr. med
Head Division of Surgical Research

1. Organisation

1.1 Position of the Division of Surgical Research within the Department of Surgery

Prof. Dr.
Pierre-Alain Clavien,
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Trauma Surgery

Prof. Dr.
Walter Weder,
MD
Director Clinic of
Thoracic Surgery

Prof. Dr.
Volkmar Falk,
MD
Director Clinic of
Cardiovascular
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Prof. Dr.
Francesco Maisano,
MD
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Cardiovascular
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Prof. Dr.
Pietro Giovanoli,
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Plastic - Hand &
Reconstr. Surgery

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Tullio Sulser,
MD
Director Clinic of
Urology

Prof. Dr. Dr. dent.
Klaus W. Grätz,
MD
Director Clinic of
Cranio-Maxillo-
facial Surgery

Prof. Dr. Dr. dent.
Martin Rücker,
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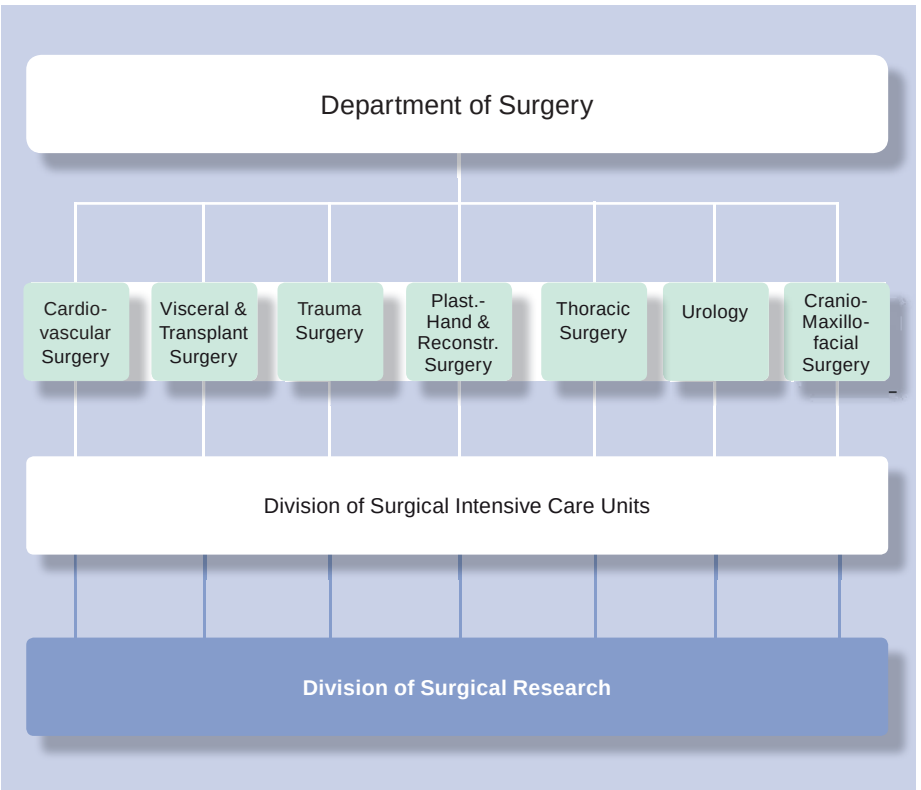
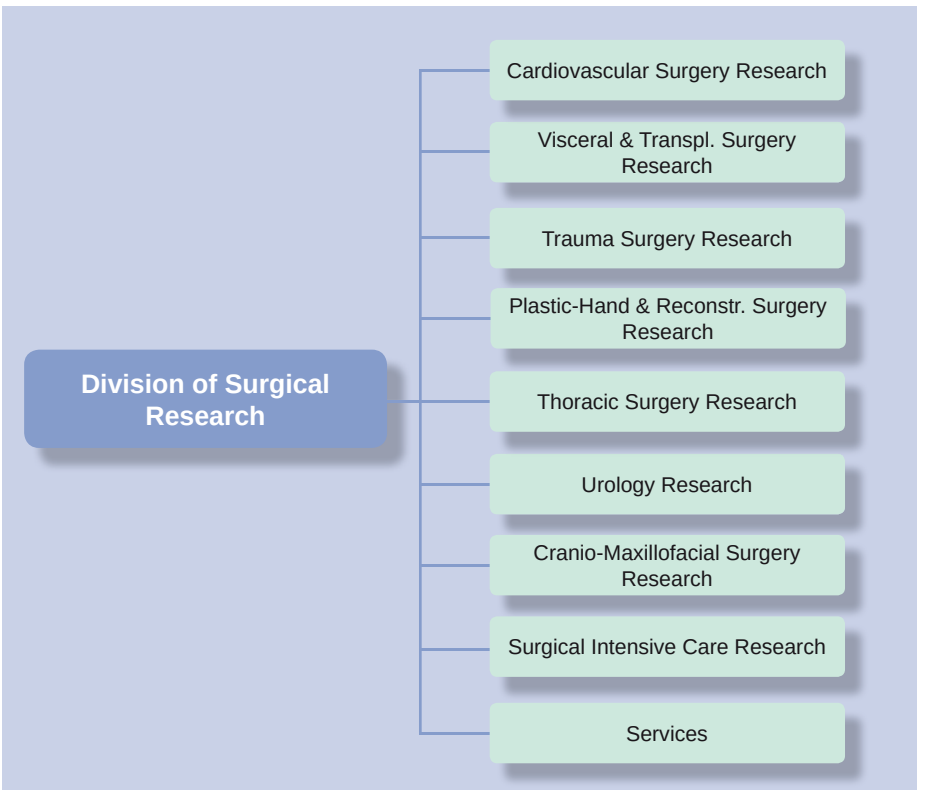
Dr.
Peter Steiger,
MD
Head of Intensive
Care Unit

Prof. Dr.
Gregor Zünd,
MD
Head Division of
Surgical Research



1.2 Structural Organisation of the Division of Surgical Research



Prof. Dr.
Gregor Zünd, MD
Head Division of
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Prof. Dr.
Rolf Graf, PhD
Co-Head Division of
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Susanne Frehner
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2. Research and Development

2.1 Cardiovascular Surgery Research


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MD, Director


Prof. Dr.
Francesco
Maisano,
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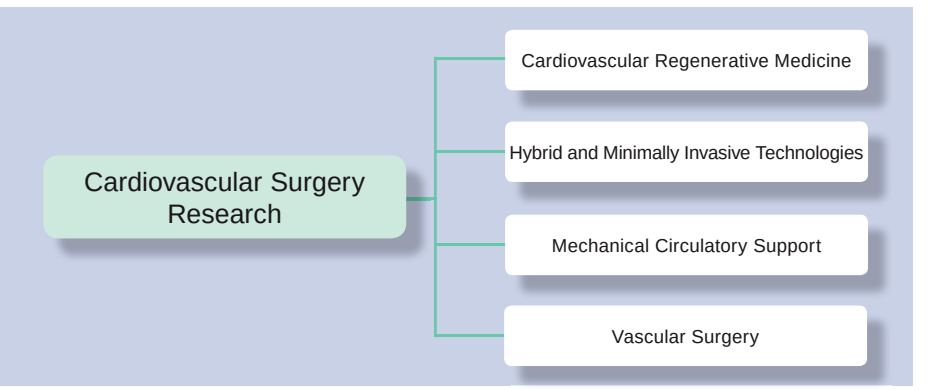


Prof. Dr.
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MD


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Michael Gessat


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MD


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Dr.
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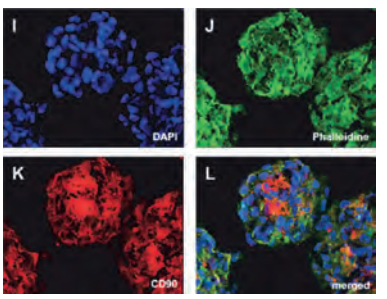
2.1.1 Cardiovascular Regenerative Medicine

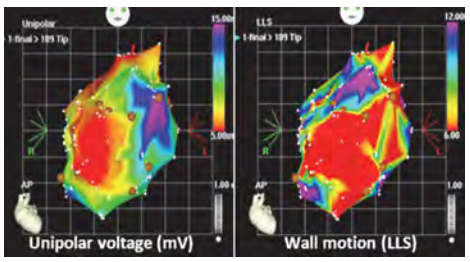
2.1.1.1 Stem Cell based 3D Microtissue Technology Platform for cardiac regeneration

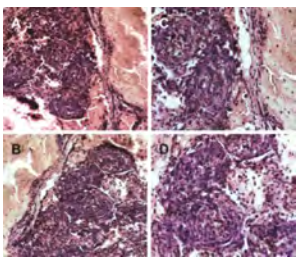
M. Emmert, S. P. Hoerstrup

Stem cells have been repeatedly suggested as a next generation therapeutic approach for the treatment of heart failure due to myocardial infarction or cardiomyopathy. Based on numerous pre-clinical animal trials, there are increasing numbers of early phase patient studies aiming to demonstrate the feasibility and potential efficacy of stem cell-based therapies in the clinical setting. However, although stem cells have shown great potential and have created substantial clinical hope, the anticipated beneficial effects (improvement of cardiac function) so far have been only marginal. The precise role of stem cells for myocardial regeneration is by far not understood. One major reason is certainly the too rapid translation from small animal studies or non-comparable large animal studies into clinical human studies, while key questions with regards to the so called “stem cell fate” which is crucial to explain a beneficial effect, have not been elucidated yet. The aim of this research is the development of translational, clinically relevant stem cell based 3D bio-engineering concepts for cardiac regeneration. In particular the focus is on the systematic assessment of clinically relevant stem cell sources and the evaluation of advanced, three dimensional stem cell delivery formats (3D microtissues). Based on the hanging drop method, the novel 3D microtissue technology allowing for a 3D cellular self-assembly was recently developed at the Swiss Center for Regenerative Medicine and is currently being tested in numerous animal disease models (mice, sheep and pigs) for cardiac regeneration. A further objective is to translate the concept of 3D microtissues in a GLP (Good Laboratory Practice) compliant manner preclinical setting (porcine myocardial infarction model) as an important step and preparation before entering the clinical setting. The state-of-the-art electromechanical mapping guided transcatheter NOGA technology has been recently established at our lab. The unique NOGA transcatheter technology will allow for the most accurate definition of the border zone of myocardial infarction (via endocardial electromechanical mapping of the ventricle) and to deliver the 3D microtissues.



Mesenchymal stem cell based 3D microtissues





Intramyocardial injection of human mesenchymal stem cell based 3D microtissues using the NOGA transcatheter based three dimensional mapping (left). Histological assessment of 3D-MTs post transplantation.

2.1.1.2 Cardiovascular tissue engineering

M. Emmert, S. P. Hoerstrup

The strategy of cardiovascular tissue engineering

The main focus of cardiovascular tissue engineering is the development and *in vitro* generation of living tissues for cardiovascular surgery including tissue engineered blood vessels, heart valves as well as patches. Currently utilized heart valve and blood vessel prostheses carry disadvantages for the patients mainly because non-living, artificial devices are inserted into the human organism. Tissue engineering enables the *in vitro* production of autologous, living and functional replacements with the capacity of regeneration and growth - the latter being of particular importance for pediatric application as an alternative to state of the art artificial replacements to address the substantial limitations of state of the art artificial heart valve and vascular prostheses, the ultimate goal of tissue engineering is to construct living tissues, which combine most of the characteristics of the native original.

Pre-clinical trials in sheep

In recent years, research has demonstrated the principle feasibility of the autologous tissue engineering concept for cardiovascular applications in heart valves and blood vessels. Tissue-engineered large diameter vascular grafts have been successfully used in low and systemic pressure applications in sheep, and technology transfer to human cells has been shown. In a large animal study, we investigated the function and growth in tissue-engineered living main pulmonary arteries over a period of 100 weeks in a lamb model, covering the full growth of this animal model. Their investigation provides first evidence of functional growth in living pulmonary arteries engineered from vascular cells in a full growth animal model. These findings support the potential of the tissue-engineering concept for congenital applications and may provide a further experimental basis to justify the large-scale clinical implementation in the near future. A first in man trial based on this work is currently in preparation in collaboration with the regulatory authorities (SwissMedic). In numerous studies we have also tested tissue engineered heart valves in the adult sheep and non-human primates. We have shown the principal feasibility of combining the concept of Heart Valve Tissue Engineering (HVTE) and trans-apical delivery into the pulmonary position of adult sheep, before we further pursued this concept in the systemic circulation of adult ovine models using several implantation devices. In particular, just recently, we demonstrated the feasibility to merge a bone marrow cell based heart valve tissue engineering approach with the state-of-the-art, anatomically orienting, commercially available transapical delivery system. Next we have introduced the novel concept of off-the-shelf (decellularized) homologous TEHVs in an ovine model as a promising next step towards clinical application. In this study, functionality and importantly self-repair capacity of such off-the-shelf valves could be demonstrated in adult sheep for up to 6 months.

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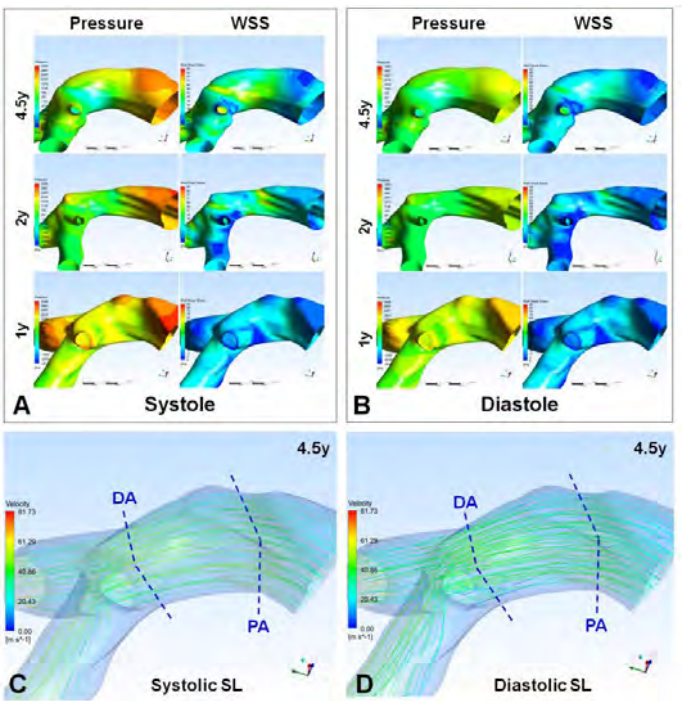


Calculated wall pressure (Pa), wall shear stress (WSS) (Pa) and velocity-coded streamlines (m/s) during systol and diastol of three different sheep, 50, 100 and 240 weeks after implantation of the tissue engineered graft. The flow pattern remains to be smooth with low wall shear stress during the systole especially after 240 weeks, although the pressure is slightly higher. The low shear stress and the absence of turbulences indicate that no significant wall irregularities, as e.g. atherosclerosis, aneurysms or scars, are present. (Kelm et al. Biomaterials 2012)

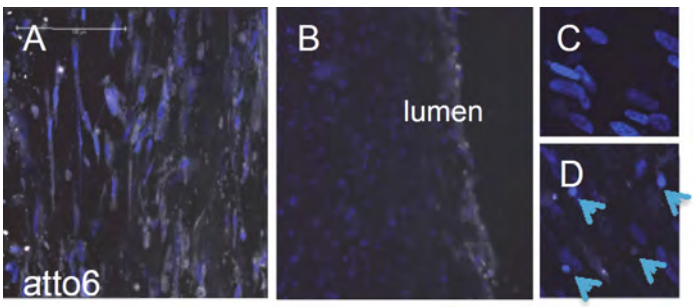
2.1.1.3 Disease modeling

B. Weber, S. P. Hoerstrup

Atherosclerosis builds up inflamed fatty plaques in the arterial wall. Over several decades, unstable atherosclerotic plaques may form in high-risk patients. To date, atherosclerosis mechanistic studies have been limited either to simple two dimensional *in-vitro* cell culture systems or animal models.

Tissue Engineered Atherosclerosis Modeling

Findings derived from such experimental settings suffer from large deviations from the human context. As a next generation approach, we employ a hybrid strategy to combine traditional cell culture assays with tissue engineered vascular systems. By investigating atherogenesis in biomimetic human based tissue engineered vessels complete with haemodynamics and threedimensional vascular histology, we observe unique bio-phenomena more congruent with human atherogenesis than conventional modeling. We now demonstrated the possibility to engineer functional artery equivalents as a model to study lipid transport under pathophysiological conditions, with key advantages of superior bio-mimetic conditions (i.e. flow and 3D histology) compared to current best-in-class vascular cell culture models. These experiments have set the stage for future lipid transport and monocyte studies using this model, with the aim of identifying next-generation therapeutic targets. (Figure A-D)



*Figures: **A**: localization of HDL in the engineered artery. Confocal image of the localization of HDL (white) in the engineering artery. HDL demonstrated a vesicular localization as well as a diffuse localization. **B**: localization of LDL (white) in the engineered artery. The LDL is localized in the endothelium and in subendothelial space of the engineered artery. **C&D**: monocyte adhesion in non-activated endothelium (C) or after activation of the endothelial cells with TNFα (D). After activation the number of adherent monocytes is enhanced (green arrows).Robert R., et al., PLOS One 2013*

2.1.1.4 Novel targets for infarction prevention strategies

C. Brokopp, C. Lohmann, M. Goeranson, S. P. Hoerstrup

The role of Fibroblast Activation Protein (FAP) in thrombosis

FAP is serine protease found at elevated levels in plasma and atherosclerotic plaques of patients suffering from acute coronary syndromes and myocardial infarction. Previous work indicates that FAP contributes to myocardial infarction by degrading collagen in thin-cap human coronary plaques, thereby rendering them more prone to rupture (Brokopp et al. European Heart Journal, 2011). Circulating FAP is also increased in obstructive coronary thrombi, and has been shown to accelerate thrombosis. In mice, genetic inhibition of FAP renders the animals resistant to arterial injury induced thrombosis. (PCT/EP2011/064807).

FAP diagnostics and therapeutic

An FAP blood test has been developed to accurately and reproducibly quantify FAP in human blood plasma with the aim of determining the diagnostic and predictive value of FAP in patients with coronary artery disease. (Figure 1A, PCT/EP2011/064807). A novel recombinant human monoclonal antibody that inhibits FAP activity (82C2) is also being developed. 82C2 has been shown to abrogate thrombosis in human plasma ex-vivo (Figure 1B). Ongoing work seeks to evaluate the efficacy of 82C2 in pre-clinical models, including efficacy and toxicology testing, as a prerequisite to clinical trials.

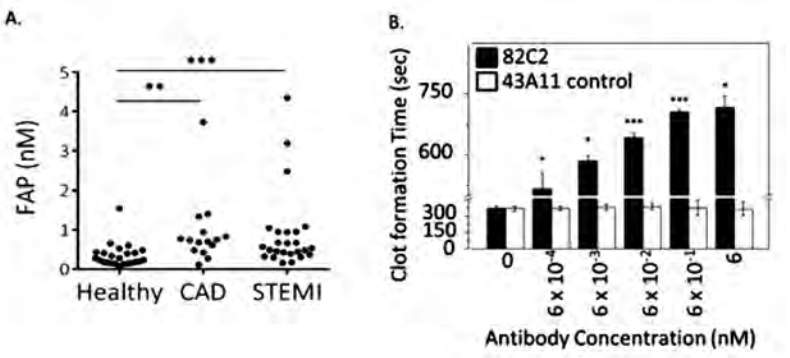


Figure 1: A. The FAP blood test shows increased levels of FAP in patients with coronary artery disease (CAD) and ST Segment Elevation Myocardial Infarction (STEMI)
B. FAP-inhibiting antibody 82C2 prolongs clot formation time in human plasma (ex-vivo) in a dose dependent manner compared to a biologically inactive isotype-matched control antibody (43A11).

Collaborations:

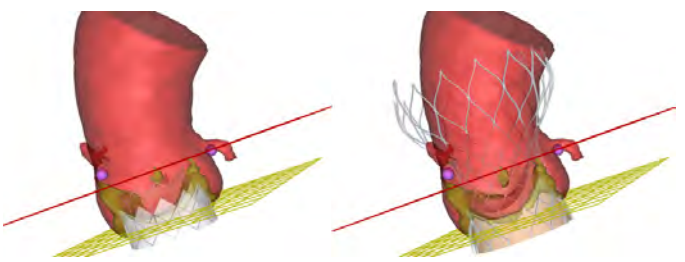
- Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, USA
- Department of Biomedical Engineering, Technical University Eindhoven, The Netherlands
- Center for Integrative Human Physiology, University of Zurich, Switzerland
- Department of Materials, Federal Institute of Technology, Zurich, Switzerland
- Department of Biochemistry, University of Zurich, Switzerland
- Department of Mathematics, Federal Institute of Technology, Zurich, Switzerland
- Department of Computational Science, Federal Institute of Technology, Zurich, Switzerland
- Department of Veterinary Surgery, MSRU Vetclinics, University of Zurich, Switzerland
- Department of Cardiac Surgery, Children's Hospital, Harvard Medical School, Boston, MA, USA
- Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
- Massachusetts Institute of Technology (MIT), Cambridge, MA, USA
- Laboratory for Tissue Engineering, German Heart Centre, Berlin, Germany
- Department of Cardiology, Medical University of Vienna, Austria
- Institute of Nuclear Medicine, University of Debrecen, Hungary
- Institute of Chemistry and Applied Biosciences, Federal Institute of Technology Zurich, Switzerland
- Institute of Anatomy, University of Bern, Switzerland
- Human Genetics Laboratory, Genetica AG, Zurich, Switzerland
- Departments of Pathology, Neurosurgery, Cardiology, and Laboratory for Transplantation Immunology, UniversityHospital, Zurich, Switzerland
- Randall Division of Cell and Molecular Biophysics, King's College London, UK
- Embryonic Stem Cell Laboratory, Fraunhofer Institute for Biomedical Engineering IBMT, St. Ingbert, Germany
- Department of Pathology and Immunology, Geneva University, Switzerland
- Experimental Cardiology Unit, Department of Medicine, University of Lausanne Medical School, Switzerland

2.1.2 Hybrid and Minimally Invasive Technologies

2.1.2.1 The advanced role of imaging in transcatheter cardiac valve treatment

S. Born

Interventional, catheter based treatment of heart valve disease has become a widely accepted alternative option for the treatment of aortic and mitral valve pathologies in patients at high risk for surgery. Pre-, intra-, and postoperative imaging is crucial because -unlike to open surgery- no direct visual assessment of the pathology or the treatment result is possible.
Preoperatively, computer-tomography (CT), magnet resonance imaging (MRI) and transthoracic as well as transesophageal echocardiography are routinely used to assess cardiac function and valvular pathologies. Accurate treatment planning requires various quantitative analyses to be performed on these images which are necessery to decide which surgical or interventional treatment option offers the optimal trade-off between outcome quality and perioperative risk. Our interdisciplinary team of cardiac surgeons, cardiologists, radiologists, and engineers is constantly developing and validating new image analysis methods and tools to increase the reliability of clinical decisions.
The hybrid operating room (Hybrid OR) opened in 2011 at USZ contains state-of-the-art imaging equipment and was designed to allow for an optimal integration of the different imaging modalities in order to help surgeons and interventionists in creating a virtual image of the beating heart, the catheters, and the devices at the tip of the catheters.
Together with engineers at the ETH Zürich and Philips Healthcare in Best (Netherlands) we are exploring the capabilities offered by the new infrastructure and software available in this facility. Softwaretools for preoperative planning of TAVI procedures (Heart Navigator) as well as a navigation tool (EchoNavigator) used in MitraClip procedures are assessed in clinical studies and further developed together with Philips Healthcare. The EchoNavigator was used in 21 patients in 2012 and the results were compared to those of 21 patients treated without this software immediately before the installation of the software. The results indicate that it might facilitate the procedure, decrease the length of the procedure and the radiation dose.



The HeartNavigator was used in all TAVI patients to plan the procedures. Additionally its ability to perform intraoperative rotational computertomography scans was assessed and further developed. An own software tool was developed and validated for preoperative TAVI planning. 85 patients were retrospectively planned by clinicians involved in the heart team. The results indicate that this 3D-template tool might be an alternative tool to prevent adverse events like paravalvular leakage or atrioventricular block after TAVI implantation.

2.1.2.2 Computational models in cardiac surgery

S. Born

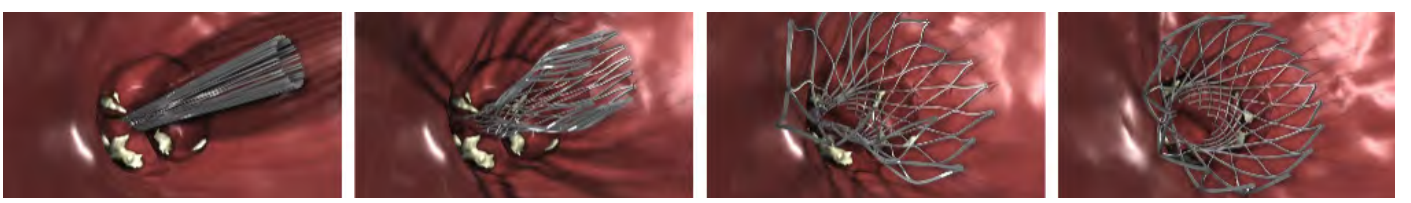
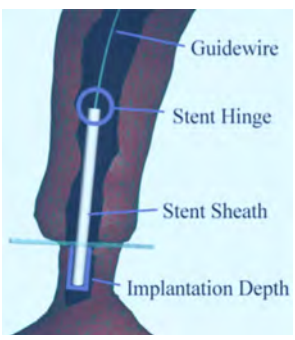
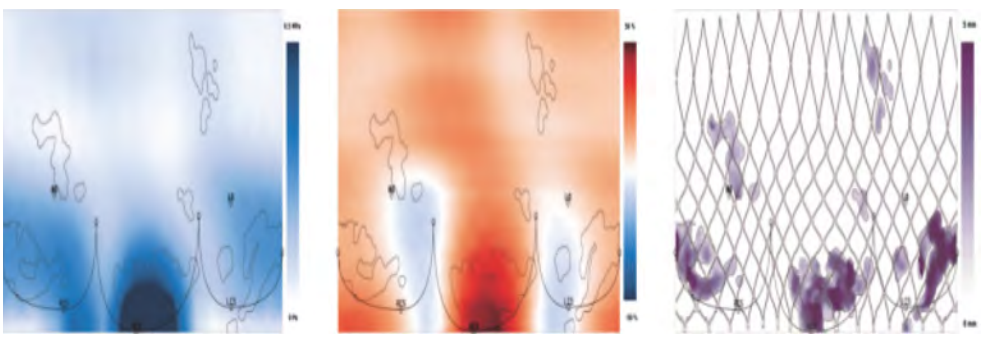


Figure 1: Maps of virtually unrolled aortic valve stents displaying radial force distribution, stent deformation and calcifications (from left to right).

The Hybrid Laboratory for Cardiovascular Technologies was installed by the Division of Cardiovascular Surgery and the Department of Surgical Research as an interdisciplinary research unit focusing on basic and translational research in the field of Computational Models in Cardiac Surgery. Computational models are in-silico representations of anatomical, physiological, and biophysical knowledge, which allow for analytical as well as predictive computational analyses and simulations. The mission of the laboratory is to promote the clinical application of computational modeling technology for surgical treatment planning and treatment outcome assessment. In close cooperation with research groups at the ETH Zurich, the laboratory provides the infrastructure for clinical evaluation of methods developed by these groups and offers clinical input to help steering the developments into a direction where they may solve real clinical problems.

Biomechanics of Transcatheter Aortic Valve Implantation
In an SNF funded project run together with the groups of Professor Mazza and Professor Székely at ETH Zurich, the biomechanical impact of stented transcatheter aortic valve implants onto the aortic root and left ventricular outflow tract and the influence of that impact on the outcome after transcatheter aortic valve implantation (TAVI) is investigated. The project aims at the development of a clinically useful system for selection of the optimal implant and placement for a particular patient. In 2014, analysis of the mechanical situation of TAVI stents after implantation was continued based on clinical data of more than 100 patients. A software, which was developed by the group, was used to extract the shape and estimate the contact forces. This information was then mapped to charts, which allowed for comparison of patterns between different patients and different groups of patients (see Figure 1). Further, we continued to work on the validation of our simulation tool by simulating TAVI cases prospectively and compare our results with the actual intervention outcome (see Figure 2, left). In this context, we also investigated the influence of stent positioning (before deployment) on the actual deployment and the final simulation result (see Figure 2. right).



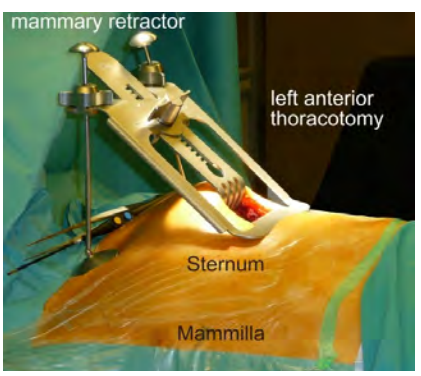


Collaborations:
- Philips Healthcare (Best, Netherlands)
- Swiss Federal Institute of Technology (ETH) Zürich, Computer Vision Laboratory (Zürich)
- Swiss Federal Institute of Technology (ETH) Zürich, Centre for Mechanics (Zürich)
- Lenox Hill Heart and Vascular Institute (New York, USA)
- Erasmus Universiteit - Thorax Center (Rotterdam, Netherlands)

2.1.2.3 Hybrid revascularization

D. Reser

Hybrid coronary artery revascularization has come to the focus of attention due to the excellent long-term patency of the left internal mammary artery (LIMA) to the left anterior descending artery (LAD). It combines the advantages of percutaneous coronary intervention (PCI) and minimally invasive direct coronary bypass (MIDCAB), providing the benefits of proven long-term patency of a LIMA-to-LAD graft. Between January 2009 and December 2014 revascularization of the LAD was performed in 46 patients with MIDCAB through a left anterior mini-thoracotomy followed by PCI of non-LAD vessels in one single procedure in our surgical hybrid suite with good results. Angiography confirmed patency of all LIMA grafts. Three of the patients died of cancer. Major adverse cardiac and cerebrovascular event free survival was 100% after 5 years.



Left anterior mini-thoracotomy (6-8cm)

2.1.3 Transplantation and Mechanical Circulatory Support

2.1.3.1 Transplantation research

H. Tolboom

***Ex-vivo* machine perfusion for recovery of hearts donated after circulatory death**

Expanding donor criteria to include organs from donation after circulatory death (DCD) could ameliorate the current shortage of donor organs, but whether DCD hearts can be safely transplanted, is unknown.

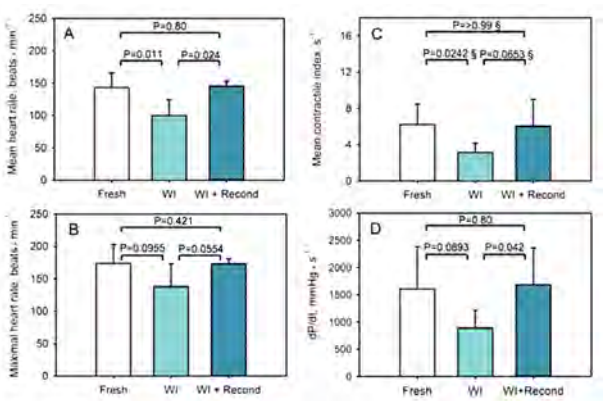


Figure 1a-d: Heart function during Langendorff perfusion

The goal of this project is:
1) To investigate the effect of global warm ischemia (WI), inherent to DCD donation, on myocardial viability.
2) To explore *ex-vivo* machine perfusion as method to improve graft function after exposure to WI. Using a small animal model, we found that even a short, 25 min. exposure to warm ischemia, had a profoundly negative impact on myocardial viability (Figure 1). If WI was followed by 60 minutes of reconditioning with *ex-vivo* normothermic machine perfusion (MP), WI's graft function improved significantly.

Our ongoing research is aimed at optimizing our reconditioning protocol (Figure 3), after which we plan further testing in a large animal model (Figure 2).

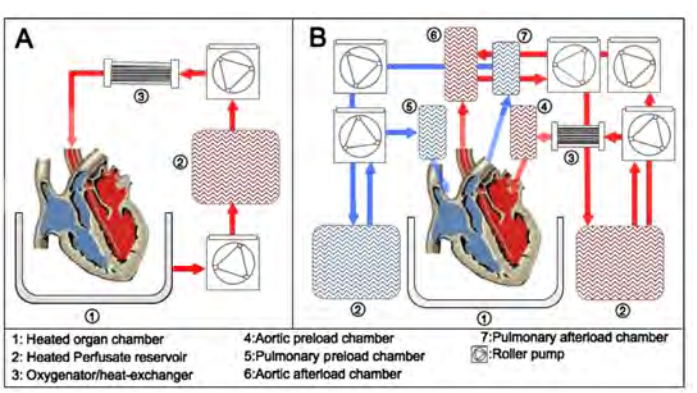


Figure 2: Full scale perfusion system

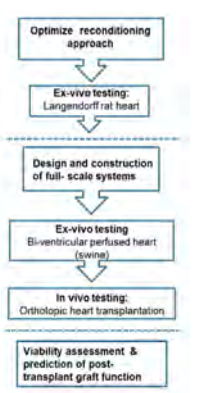


Figure 3: Project outline

We expect that our approach will enable transplantation of hearts from DCD, hereby shortening waiting times and reducing the morbidity and mortality of patients listed for transplantation.

Collaborations:

- Institute for Dynamic Systems and Control, ETH Zürich (Prof. L. Guzzella)
- Micro- and Nanosystems (Prof. C. Hierold)
- Power Electronic Systems Laboratory (Prof. J.W. Kolar)
- Metal Physics and Technology (Prof. J.F. Löffler, Prof. P.J. Uggowitzer)
- Institute for Mechanical Systems (Prof. E. Mazza)
- Institute of Energy Technology (Prof. D. Poulikakos)
- Institute for Chemical and Bioengineering (Prof. J.W. Stark)
- Laboratory of Applied Mechanobiology (Prof. V. Vogel)
- Swiss Center for Regenerative Medicine (Prof. S.P. Hoerstrup)

2.1.4 Vascular Surgery

2.1.4.1 Patient-specific virtual reality rehearsal prior to EVAR: Influence on technical and non-technical operative performance. Randomized controlled trial

L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat

Ongoing technological advances, especially in the field of image processing, have refined medical simulations to offer life-like replications of medical and surgical procedures in a variety of specialties. Patient-specific image data are incorporated into these simulations, and transformed into a 3D model. This enables the practitioner and his/her team to perform and practice 'real' cases on a virtual patient prior to performing the real procedure on the actual patient. This new technology has been referred to as 'patient-specific' rehearsal, also 'mission' or 'procedure' rehearsal.

2.1.4.2 Evaluation of the impact of DoseAware in a clinical setting

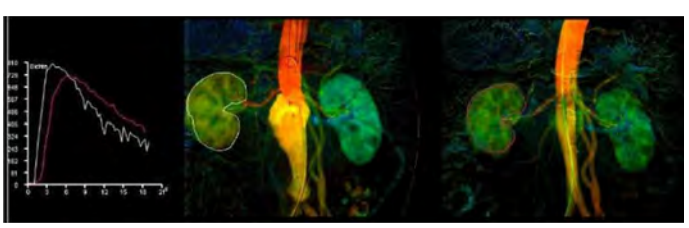
L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat

The DoseAware system allows for a real time display of the actual X-ray dose a staff member receives in addition to the monthly cumulative readouts of the TLD badges. In addition the staff member can view its personal accumulated dose directly after the procedure, at the end of the day or for any specified time range. It is expected that the shortened feedback loop and increased awareness will have direct effect on behavior of the staff towards reducing radiation dose and exposition during procedures.

2.1.4.3 Evaluation of simultaneous structural and functional imaging of the kidney using angiography in kidney artery endodebranching

L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat

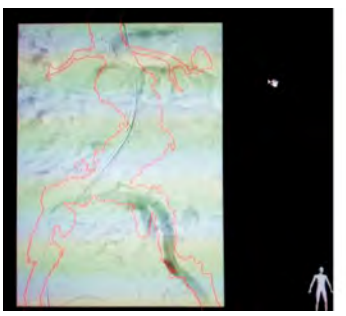
2D Perfusion typically requires only one contrast media injection and one DSA run, to obtain rich information of vessel and organ perfusion in the interventional suite. By comparing pre and post procedural images, clinicians can identify perfusion differences in the color images.



2.1.4.4 Evaluation of automated image overlay system for EVAR

L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat

The digital subtraction technique has made the digital roadmap into an indispensable tool. The roadmap can be renewed every time the X-ray tube or the table needs to be readjusted for a better view using an X-Ray view of the bones.
The aim of this study was to evaluate the feasibility of image overlay system utilizing subtraction of bone marrow image, a new image technique, during EVAR in the hybrid operating theater. Overlay view of the vessels allows to reduce the number of angiographies during EVARS and therefore to decrease the radiation dose and the volume of contrast medium.

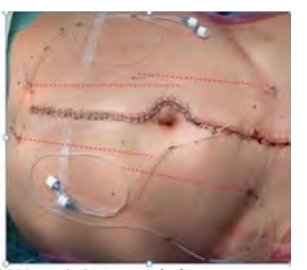


2.1.4.5 Evaluation of different methods of local anesthesia for postoperative analgesia

L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat

Postoperative analgesia with local anaesthetics via paraincisional pain catheters (PIPC) is a standard in our clinic. Our retrospective revealed that postoperative subcutaneous ropivacaine infusion was associated with significantly lower requirement of opiates and faster achievement of pain relief after open aortic aneurysm repair.

ON-Q Soaker catheter expansion kit:
- Needle with peel-away-heath
- Soaker catheter (10 in, 25 cm)

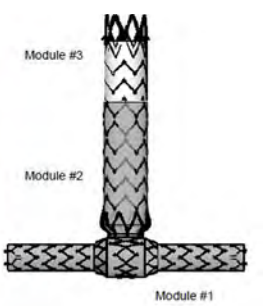


PIPC inserted subcutaneously *in situ*

2.1.4.6 A prospective open-label non-randomized single-arm first-in-man clinical study to evaluate the safety and performance of the HORIZON abdominal aortic aneurysm stent graft system

L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat

The Horizon™ AAA Stent Graft System, manufactured by Endospan Ltd. (Herzliya, Israel), is designed to treat infrarenal abdominal aortic or aorto-iliac aneurysms using an endovascular percutaneous approach. When placed within the aneurysm, the Horizon™ AAA Stent Graft System provides a permanent alternative conduit for blood flow within the patient's vasculature. Stent Graft System is modular and consists of three stent graft component configurations.



Collaborations:
- Professor Dr. Isabelle Van Herzeele, Ghent University Hospital (Gent, Belgium) and Sint - Maarten Hospital (Duffel, Belgium)
- Division of Cardiology, UniversityHospital Zurich
- Philips Healthcare (Netherlands)
- Division of Urology and Division of Visceral and Transplant Surgery, UniversityHospital Zurich
- Endospan Ltd. (Herzliya, Israel)

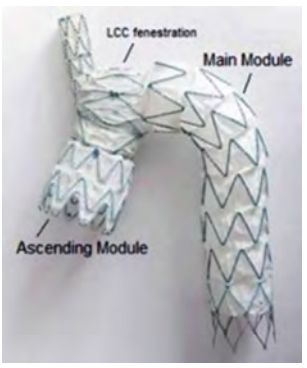
2.1.4.6 A Multicenter prospective open-label non-randomized feasibility clinical study to evaluate the safety and performance of the Nexus™ aortic arch stent graft system

L. Chaykovska, Th. Pfammatter, M. Lachat

The Nexus™ Aortic Arch Stent Graft System, manufactured by Endospan Ltd. (Herzliya, Israel) is indicated for the endovascular treatment of thoracic aortic diseases involving the aortic arch, such as (but not exclusively to):

- Aneurysm
- Dissecting aneurysm / dissection Type B and intramural hematoma (IMH)
- False / Pseudo aneurysm (uninfected)
- Residual aneurysm following Ascending Aorta open repair
- Penetrating ulcer (uninfected)

The Nexus™ system excludes the diseased area and provides a permanent alternative conduit for arterial blood.
The Nexus™ Aortic Arch Stent Graft System is comprised of two components - implantable Stent Grafts and disposable 20Fr Delivery Systems. The stent grafts are preloaded into their respective delivery system and advanced to the lesion using fluoroscopic guidance. Upon deployment, each module self-expands to conform to the shape and size of the seal zones above and below the aneurysm.



Collaborations:

- Professor Dr. Isabelle Van Herzeele, Ghent University Hospital (Gent, Belgium) and Sint - Maarten Hospital (Duffel, Belgium)
- Division of Cardiology, University Hospital Zurich Philips Healthcare (Netherlands).
- Philips Healthcare (Netherlands)
- Division of Urology and Division of Visceral and Transplant Surgery, University Hospital Zurich
- Endospan Ltd. (Herzliya, Israel)

2.2 Visceral & Transplant Surgery Research

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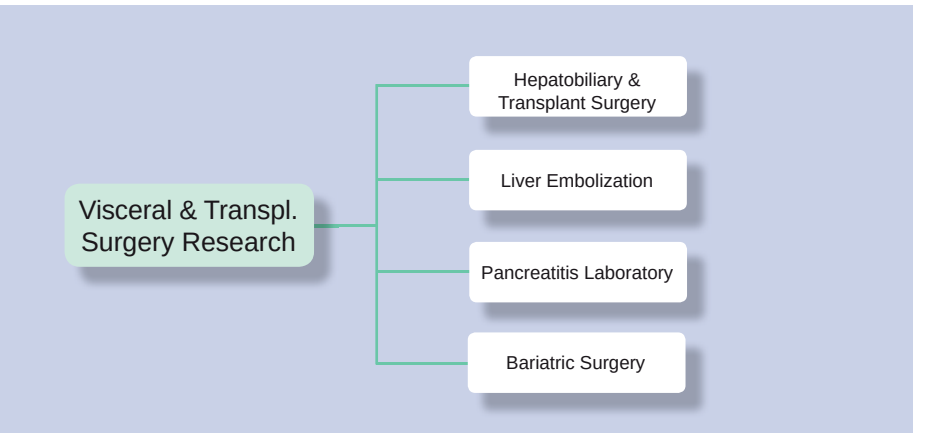
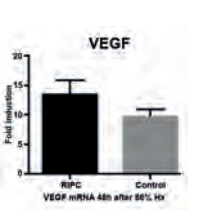


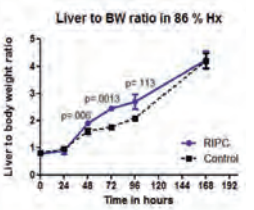
2.2.1 Hepatobiliary & Transplant Surgery

Remote ischemic precoditioning for the improvement of regeneration after hepatectomy

P. Kambakamba, C. Oberkofler, R. Graf, B. Humar & P.-A. Clavien

We have previously shown that remote ischemic preconditioning (RIPC) - a strategy to protect against ischemia reperfusion - has systemic effects mediated through a platelet-serotonin-Vegf-Il10/Mmp8 axis. Since both serotonin and Vegf can exert proregenerative action onto liver, we are exploring whether the beneficial effects of RIPC are also related to an improved recovery of liver after resection, and whether RIPC could be used to directly promote hepatic regeneration.

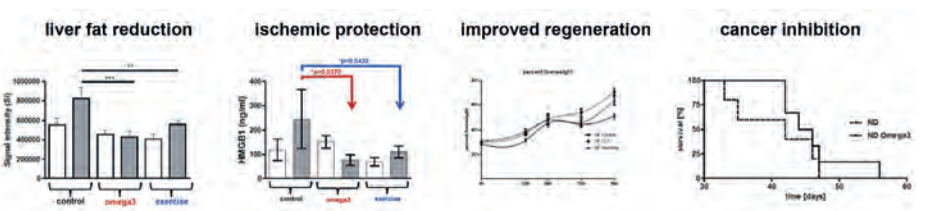




Ω3-fatty acids and exercise inhibit hepatosteatosis, protect from ischemic injury, improve regeneration and hinder liver cancer

M. Linecker, P. Limani, E. Kachaylo, N. V. Calo, P. Kambakamba, P. Kron, C.Tschuor, M. Foti, J.-F. Dufour, R. Graf, B. Humar & P.-A. Clavien

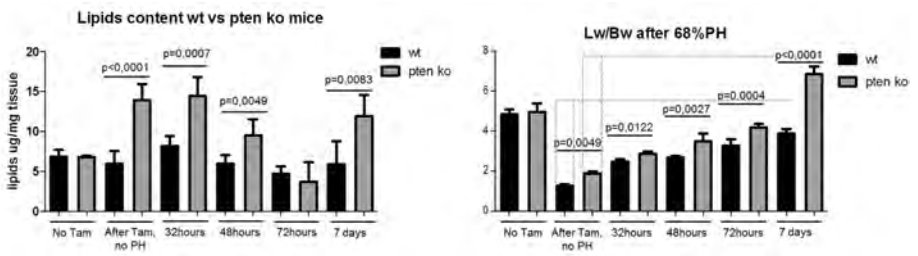
Surgical removal of liver tumors is associated with postoperative complications due to fatty liver, ischemic injury, inefficient regeneration, and a possible tumor occurrence. Ideal interventions to improve surgical outcomes would target all of these aspects. We show that Ω3-fatty acids and exercise can do all of the above, and hence may be highly beneficial when applied in association with liver surgery. The beneficial effects of Ω3-fatty acids and exercise appears to be mediated by Ampk, at least in part.



Pten downregulation during liver regeneration for the promotion of energy metabolism and hepatocyte growth

E. Kachaylo, Ch. Tschuor, N. V. Calo, P. Limani, M. Foti, J.-F. Dufour, R. Graf, B. Humar & P.-A. Clavien

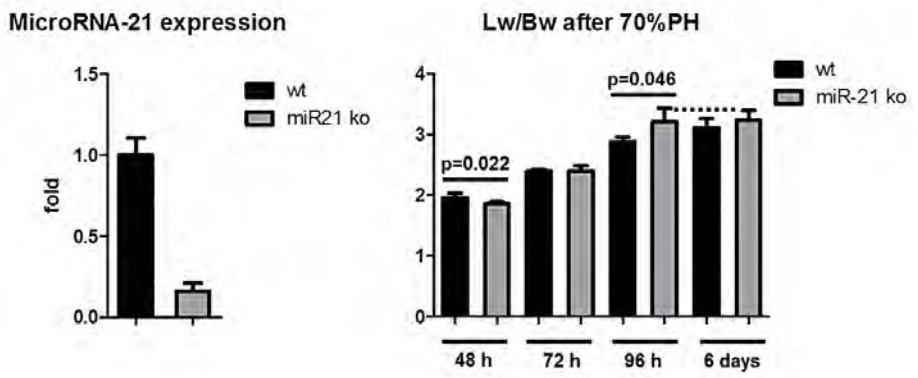
Pten is a negative regulator of the growth-promoting PI3K-Akt-mTOR axis and is uncharacterized with regards to its role in liver regeneration. Since we observed Pten downregulation during liver regeneration, we used Cre-AlbERT2-Pten$^{fl/fl}$ mice (inducible, hepatocyte-specific knockouts) to study its function. Pten loss was associated with immediate hepatic lipid accumulation, followed by hypertrophic liver overgrowth and the disappearance of lipid droplets, suggesting Pten downregulation facilitates liver regeneration through the provision of energy.



The pro-proliferative Mir21 has a function in the termination of liver regeneration following hepatectomy

E. Kachaylo, Ch. Tschuor, P. Limani, P. Ramadori, M. Foti, J.-F. Dufour, R. Graf, B. Humar & P.-A. Clavien

Mir21, overexpressed in many cancers, has been shown to promote early phases of liver regeneration. Using Cre-AlbERT2-*miR21*$^{fl/fl}$ mice, we have observed an additional function of Mir21 during late phases of regeneration, where it appears to promote the termination of the regenerative process. These findings indicate that the role of Mir21 in liver is more complex than previously assumed.

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Dr. Patryk Kambakamba, MD


Dr. Michael Linecker, MD


Dr. Gitta Maria Seleznik, PhD


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Marta Bombardo Ayats, PhD Student


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Magda Langiewicz, PhD Student


Ermanno Malagola PhD Student


Dr. Christian Eberhardt PhD


Kathryn Schlesinger, PhD Student

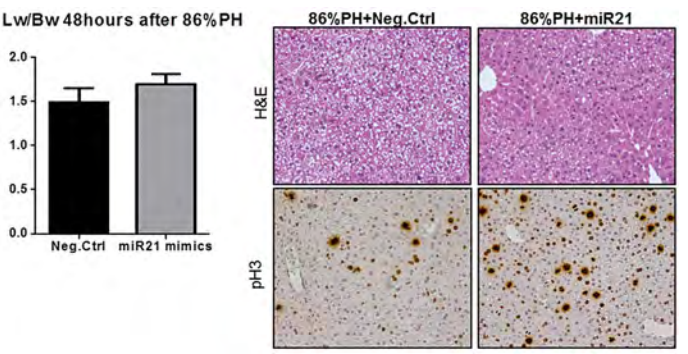

Raphael Buzzi cand. med.


Lukas Peter med. pract.

Pharmacological overexpression of Mir21 mitigates liver failure after extended tissue loss

E. Kachaylo, Ch. Tschuor, P. Limani, P. Ramadori, M. Foti, J.-F. Dufour, R. Graf, B. Humar & P.-A. Clavien

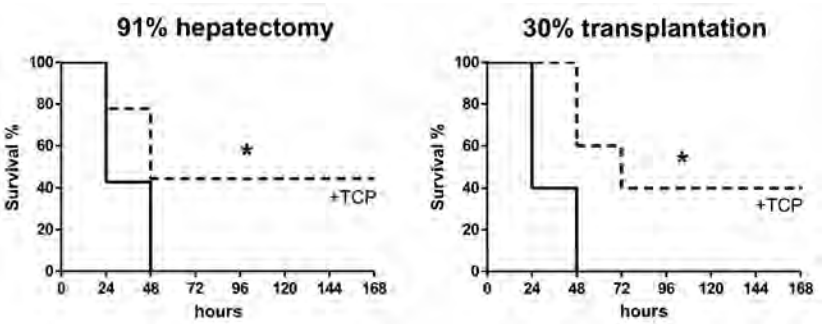
Here, we explored the pro-proliferative features of Mir21 for a potential treatment of the Small-for-Size Syndrome (SFSS, liver failure following excessive tissue loss). Transfecting mice with Mir21 mimics prior to extended hepatectomy (inducing SFSS) was effective in improving SFSS-associated abnormalities (reduced liver weight gain, cell cycle arrest, metabolic liver function), suggesting the acute treatment with Mir mimics may represent a potential strategy to improve outcomes of extended resections.

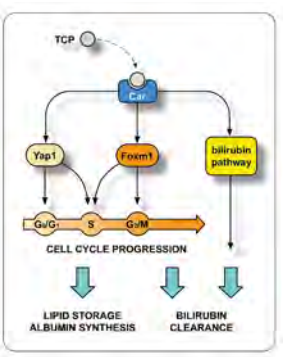


Car-driven regeneration protects liver from failure following tissue loss

C. Tschuor, E. Kachaylo, L. Perparim, D. A. Raptis, M. Linecker, Y. Tian, U. Herrmann, K. Grabliauskaite, A. Weber, A. Columbano, R. Graf, B. Humar & P.-A. Clavien

The pathobiology underlying liver failure following extended tissue loss (SFSS) is ill-understood. With the help of a novel SFSS mouse model combined with genetic models and *in vivo* siRNA knockdown approaches, we have identified deficient induction of the Car-Foxm1/Yap1 axis as a cause of SFSS. Re-activation of Car through exogenous ligands (TCP) was sufficient to normalize the SFSS phenotype. These findings indicate a key role for Car-dependent regeneration in the protection from liver failure and suggest human Car ligands may be a potent mean for the management of human SFSS.

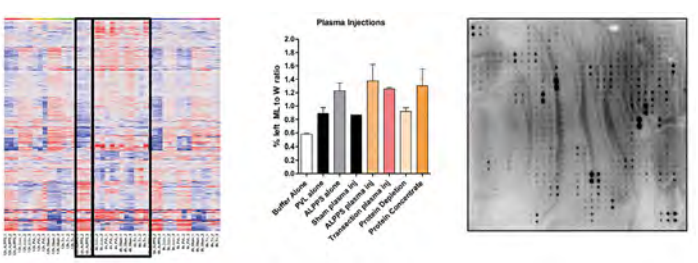




Mechanisms underlying the accelerated liver regeneration induced by ALPPS surgery

M. Langiewizc, A. Schlegel, R. Graf, B. Humar & P.-A. Clavien

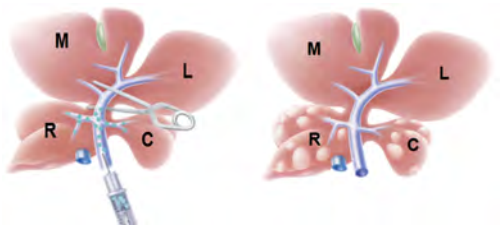
ALPPS is a novel surgical technique that markedly accelerates liver regeneration in patients. In a newly established ALPPS mouse model, we can mimic this accelerated regeneration and have identified surgery-triggered plasma proteins as the regenerative mediators. Plasma proteins with pro-regenerative function have an obvious therapeutic potential. Using a combination of genomics and proteomics approaches coupled to functional validation *in vivo*, we are aiming at tracking down individual proteins able to accelerate liver regeneration in mouse and man.

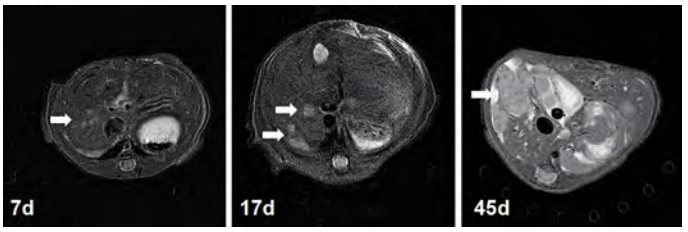


Selective portal vein injection for the design of syngeneic orthotopic mouse models of liver malignancy

P. Limani, N. Borgeaud, M. Linecker, Ch. Tschuor, E. Kachaylo, A. Schlegel, J.-H. Jang, U. Ungethüm, M. Montani, R. Graf, B. Humar & P.-A. Clavien

Various animal models of liver tumors exist. Orthotopic systems based on grafting of cancer cells yield rapid tumor development and are well-suited for studying a tumor within its physiological (micro)environment. Syngeneic grafts additionally preserve the immunological competence of the host. Here, we describe selective portal injection as a versatile tool to generate orthotopic syngeneic models of liver tumors that share a short latency and a high penetrance, are reproducible, restricted to the liver, and provide unaffected control tissue.

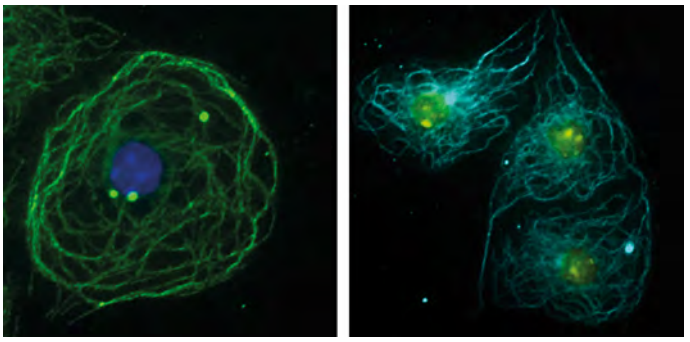




Endothelial contribution to the tumor microenvironment of hepatocellular carcinoma

N. Borgeaud, E. Kachaylo, P.-A. Clavien, R. Graf, B. Humar

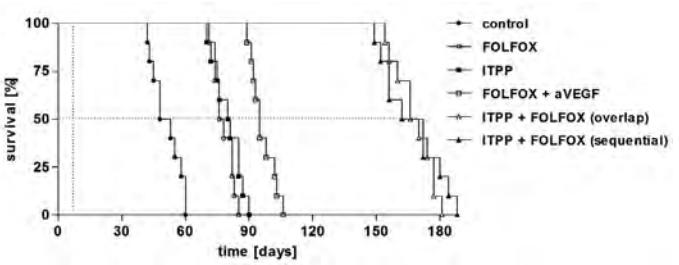
Liver endothelial cells represent the largest non-parenchymal cell population in the liver and have a key role in maintaining proper liver function. Whether and how these highly differentiated cells affect processes related to the transformation and malignant progression of hepatocytes is not known. To explore the interaction of liver cancer cells with their endothelial niche, we have established primary liver endothelial cell culture that will be expanded to hepatocellular co-culture systems. Novel insight into endothelial-parenchymal interactions may help to develop alternative cancer treatments that target the tumor microenvironment.



Inhibition of hypoxia through ITPP for an improved chemotherapy of colorectal liver metastasis

P. Limani, A. Schlegel, Ch. Tschuor, E. Kachaylo, J.-H. Jang, J.-M. Lehn, R. Graf, B. Humar, P.-A. Clavien

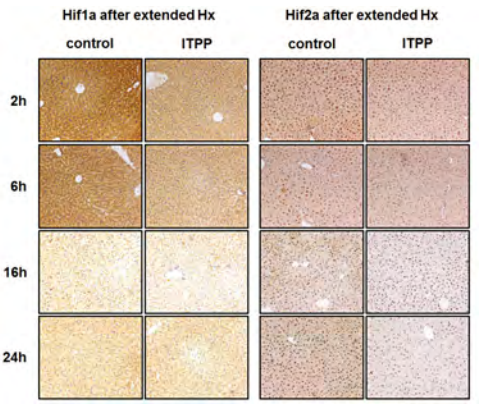
Hypoxia is a renown promoter of malignancy and is associated with many undesired effects such as endothelial dysfunction and the loss of chemotherapeutic efficacy. Using the anihypoxic molecule ITPP, we could re-establish stable normoxia in experimental liver metastases, leading to a long-lasting inhibition of the hypoxic response, the normalization of vasculature, and a markedly improved efficacy of chemotherapy when compared to chemotherapy plus anti-angiogenic agents (Avastin) as assessed by survival. An according clinical trial has been initiated.



Hypoxia and its function during liver regeneration

P. Kron, P. Limani, R. Graf, B. Humar & P.-A. Clavien

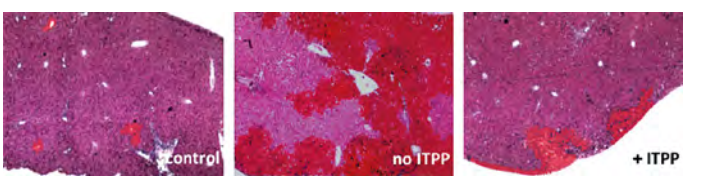
Hypoxia and its effects on tumor biology are being intensely researched, however the physiological function of oxygen during liver regeneration is unknown. We observe HIF activation during early regenerative phases that are dominated by increased inflow of oxygen-poor, portal blood. Following the assessment of hypoxic changes during the complete regenerative process, we will probe the function of hypoxia through the use of ITPP and genetic modulators of the hypoxic response. These studies should highlight fundamental processes occurring in regenerating liver.



Inhibition of hypoxia to counteract ischemia during organ preservation

A. Schlegel, P. Limani, R. Graf, P. Dutkowski, J.-M. Lehn, B. Humar, P.-A. Clavien

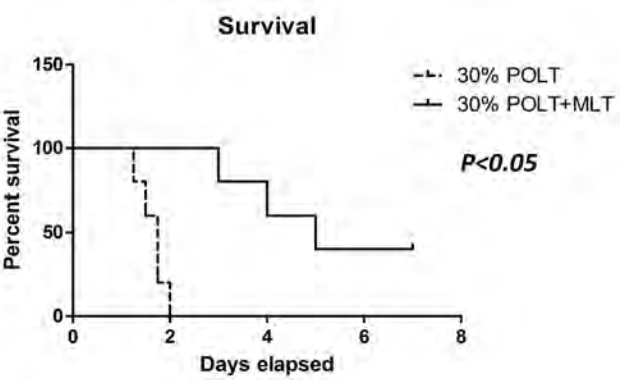
Liver transplantation requires the exposure of grafts to prolonged times of ischemia prior to implantation. To reduce ischemic stress, we designed a new model of isolated rat liver perfusion and incubated liver grafts with oxygenated blood with or without the antihypoxic molecule ITPP. ITPP-treated grafts displayed improved function and unlike untreated grafts led to long-term survival of recipients. Therefore, the nontoxic ITPP has the potential to improve transplantation outcomes.



Melatonin Rescues Small for Size Liver Graft Failure in Mice

Z. Song, E. Maurizio, B. Humar, R. Graf, P.-A. Clavien, Y. Tian

Small for size (SFS) syndrome is one of the factors which impedes the development of living donor liver transplantation (LDLT). Melatonin, as a strong antioxidant, might have protective effect on SFS graft failure in mice. We analyzed the effect of melatonin in a model combining ischemia and hepatectomy. With this model, melatonin treatment reduced liver injury and enhanced the regeneration of the liver. In a 30% partial liver transplant mice model, melatonin treatment improved the survival rate from 0% to 40%. For the next step, we will further investigate the underlying mechanism of melatonin in this process.



Collaborations/Sponsors:

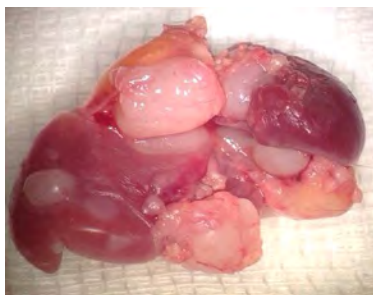
- Prof. Michelangelo Foti (University of Geneve)
- Prof. Jean-Francois Dufour (University of Bern)
- Prof. Gerald Schwank (ETH Zurich)
- Prof. Sabine Werner (ETH Zurich)
- Prof. Jean-Marie Lehn (University of Strasbourg)
- Various clinical collaborations

2.2.2 Impact of ALPPS (Associating liver partition and portal vein ligation for staged hepatectomy) on tumor growth

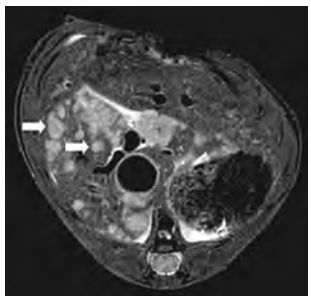
M. Lesurtel, P. Kambakamba, A. Wirsching, C. Eberhardt, N. Bain

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) is a novel two-stage hepatectomy that induces rapid growth of the liver remnant in primarily non-resectable liver tumors by combining transection of the liver with portal vein ligation. Nevertheless, there are some concerns that this unparalleled liver regeneration may also accelerate tumor growth (local and distant).

The aim of this project is to investigate in a mouse model whether ALPPS promotes tumor growth. For this purpose we combine two well-established models in our department: liver tumor cell injection and ALPPS. As in clinical routine ALPPS is mainly indicated in patients with colorectal liver metastases, we focus on the effect of ALPPS on a colorectal adenocarcinoma cell line.



Left panel: Liver tumor load 21 days after cancer cell injection in the portal vein

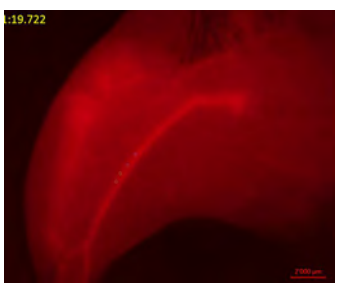


Right panel: T2 weighted small animal MRI in order to assess number of tumors and tumor volume in liver of mice (white arrows).

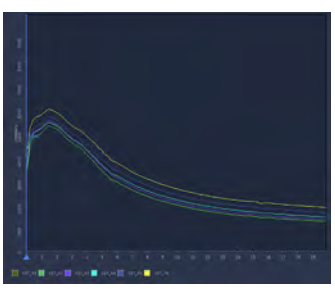
Indocyanin Green (ICG) clearance to assess liver function in mice

Indocyanin green (ICG) is a fluorescent dye which is exclusively eliminated in the bile after intravenous injection. ICG clearance test is routinely used to non-invasively assess liver function in humans before hepatectomy to assess the capacity of the liver to tolerate liver resection especially in case of chronic liver disease. This test is based on extracorporal fluorescence detection.

We aim at establishing a non-invasive, dynamic liver function test based on ICG clearance in mice in several models including normal liver, major hepatectomy, small-for-size liver, acute and chronic liver failure.



Left panel: Fluorescence camera showing ICG in inguinal vein

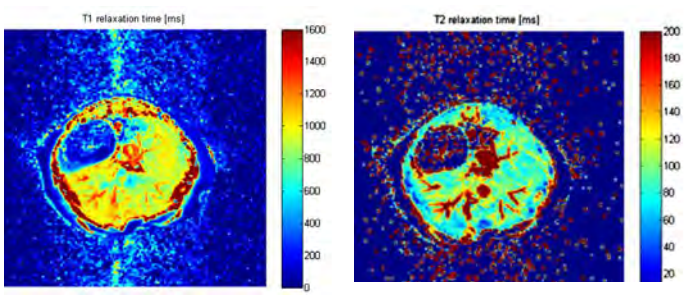


Right panel: Calculated ICG decay curve over time

Molecular Imaging of liver metabolic pathways after partial hepatectomy: Indicators of liver failure?

Post-hepatectomy liver failure (PLF) is associated with a failure of liver regeneration but the molecular mechanisms of PLF have not been elucidated yet. Using multi-modal molecular imaging techniques, the liver metabolism of glucose, pyruvate and ATP is characterized during liver regeneration in a well-established mouse model of partial hepatectomy.

We test which biomarkers of molecular imaging are best suited to provide a quantitative measure for developing PLF. Probing of metabolic pathways in regenerating liver are performed using hybrid positron-emission-tomography (PET)/magnetic resonance imaging techniques. Liver ATP synthesis is measured with ^{31}P-magnetic resonance spectroscopy, pyruvatelactate metabolism with hyperpolarized [$^{1\text{-}13}$C]pyruvate spectroscopy, and glucose metabolism with dynamic ^{18}F-fluorodeoxyglucose (FDG) PET.



Left and Right Panels: T1/T2 relaxation parameters of liver MRI representing characteristic tissue properties after partial hepatectomy in mice using a small animal MRI.

Collaborations/Sponsors:

- PD Dr. Andreas Boss, Department of Radiology, University Hospital Zurich

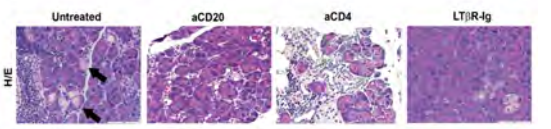
2.2.3 Pancreatitis Research Laboratory

Comparative effectiveness of immune-cell depletion in the treatment of autoimmune pancreatitis

G. Seleznik, T. Reding Graf, S. Sonda, M. Heikenwälder and R. Graf

The aim of our research is to understand the pathophysiology of autoimmune pancreatitis (AIP) and to optimize a clinically relevant, novel therapeutic strategy that AIP patients can benefit from. *Tg*(Ela1-Lta,b) mice with established AIP were treated with anti-CD20 mAb (Rituximab), anti-CD4 mAb in order to deplete B- and CD4+ T-cells respectively and with LTβR-Ig to inhibit LTβR signaling. Assessing parameters associated with AIP pathogenesis, LTβR-Ig achieved the greatest improvements.

Therapy	Format	Target
LTbR-Ig	Fusion protein	Blocking the interaction between LTbR and its ligands
aCD20 (Rituximab)	Monoclonal antibody	Depleting B-cells
aCD4	Monoclonal antibody	Depleting CD4 T-cells

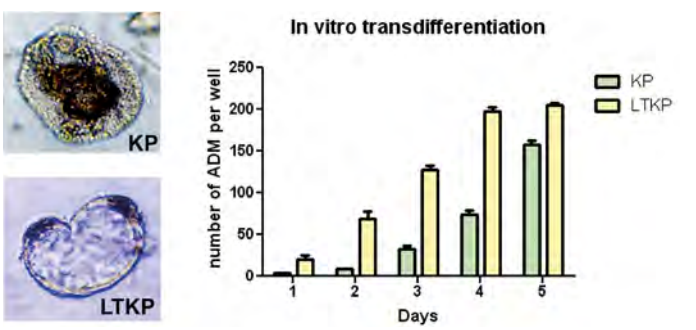


Treatments applied in Tg(Ela1-Lta,b) mice.

Lymphotoxin promotes acinar cell reprogramming and accelerates pre-neoplastic conversion in Kras induced pancreatic tumorigenesis

G. Seleznik, T. Reding Graf, S. Sonda, A. Perren, M. Heikenwälder and R. Graf

The aim of the project is to explore the inflammatory mechanisms promoting pancreatic pre-malignant lesion (ADM and PanIN) development. Therefore, we established a new genetic model for pancreatic carcinogenesis by intercrossing the commonly used $p48^{+/Cre};Kras^{+/G12D}$ (KC) model for pancreatic tumorigenesis, to a novel transgenic mouse expressing Lymphotoxin (LT) in acinar cells and developing spontaneous pancreatic inflammation at an early age. Lymphotoxin overexpression in LTKC mice dramatically accelerated the development of premalignant lesions *in vitro* and *in vivo*.

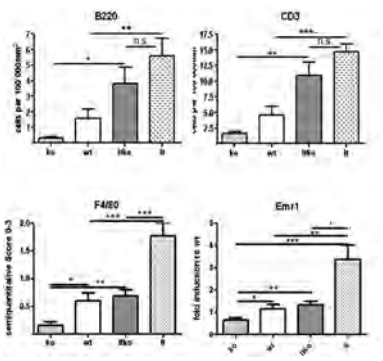


Lymphotoxin accelerates ADM development in vitro. Primary mouse pancreatic acinar cells were isolated from KP and LTKP mice and cultured in 3D collagen explant culture.

Effects of p21 deficiency on murine autoimmune pancreatitis

T. Reding, L. Peter, G. Seleznik, S. Sonda and R. Graf

The cell cycle inhibitor p21 has been described as a mediator of autoimmunity in several diseases such as lupus nephritis and rheumatoid arthritis. Here we aimed at investigating the role of p21 in autoimmune pancreatitis (AIP) development by a transgenic mouse model where mice developing spontaneous AIP (*LT*) were intercrossed with mice deficient in p21 ($p21^{-/-}$). Deletion of p21 reduced the number of infiltrating macrophages without altering the humoral response, but it did not rescue the development of AIP, suggesting that macrophages do not affect the development of this disease.

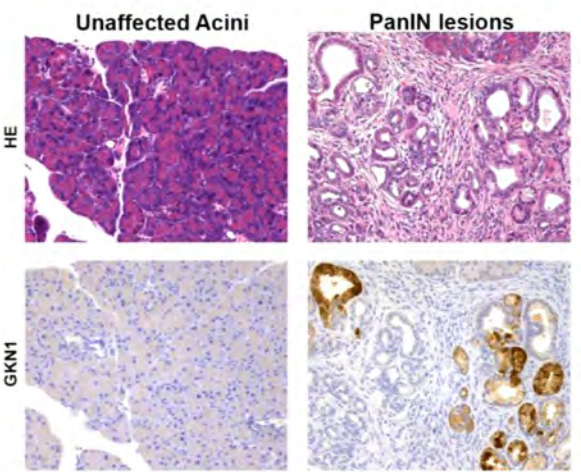


Distribution of immune cells in mouse models: ko: $p21^{-/-}$; wt: p21 wild type littermates; lt: Tg(Ela1-Lta,b) ; ltko: Tg(Ela1-Lta,b) x $p21^{-/-}$.

Gastrokine as a novel potential biomarker for premalignant pancreatic lesions

G. Seleznik, T. Reding, A. Dittmann, A. Perren, E. Angst, M. Heikenwälder and R. Graf

A whole genome microarray analysis of a mouse model for pancreatic carcinogenesis revealed striking gastrokine up-regulation in the pancreas. Therefore, we investigated gastrokine (Gkn) expression and function during pancreatic pre-malignant and malignant lesions. Gkn expression is specific for premalignant PanIN lesions and it is secreted into the pancreatic juice, furthermore Gkn is highly expressed in benign pancreatic adenomas, but is absent from malignant tumors, suggesting a tumor suppressor property.

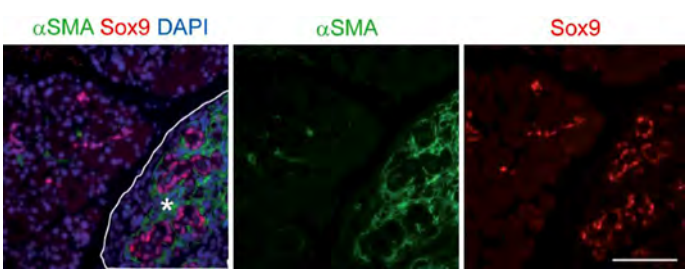


Localization of Gkn in the mouse pancreas.

p21$^{WAF1/Cip1}$ limits senescence and acinar-to-ductal metaplasia formation during pancreatitis

K. Grabliauskaite, A. Hehl, G. Seleznik, E. Saponara, T. Reding Graf, S. Sonda and R. Graf

De-differentiation of pancreatic acinar cells into ductal-like lesions, a process defined as acinar-to-ductal metaplasia (ADM), is observed during organ regeneration following pancreatitis. In addition, ADM is found in association with pre-malignant PanIN lesions and correlates with an increased risk of pancreatic cancer. We found that p$^{21WAF1/Cip1}$ acts as a molecular switch to promote quiescence of acinar cells and avoid a permanently withdraw from the cell cycle with consequent increased DNA damage, activation of senescence and ADM formation.

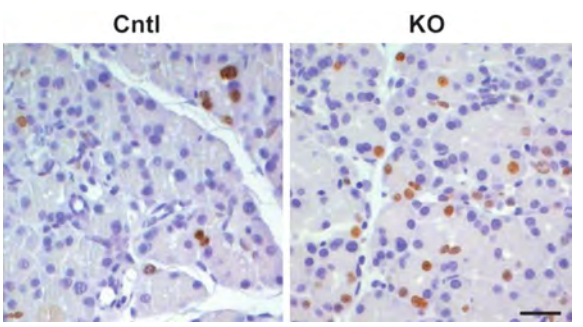


Acinar-to-ductal metaplasia (asterisk) is enhanced in the pancreas of p21$^{-/-}$ mice following pancreatitis.

Inactivation of TGF-β receptor II signalling in pancreatic epithelial cells promotes acinar cell proliferation and fibrosis during pancreatitis

K. Grabliauskaite, E. Saponara, T. Reding Graf, S. Sonda and R. Graf

TGF-β signalling is implicated in many pathophysiological functions of pancreatic cells; however, an acinar specific role of this molecule in modulating pancreatic regeneration has not been completely investigated before. By using mice deficient in TGF-β receptor II (TGFβRII$^{fl/fl}$) exclusively in epithelial cells, we showed that TGF-β signalling inhibited acinar cell cycle activation and prevented excessive ADM formation. Additionally, loss of TGF-β signalling in acinar cells potentiated the development of fibrosis during pancreatitis, suggesting the existence of a regulatory feedback between acinar and stellate cells.

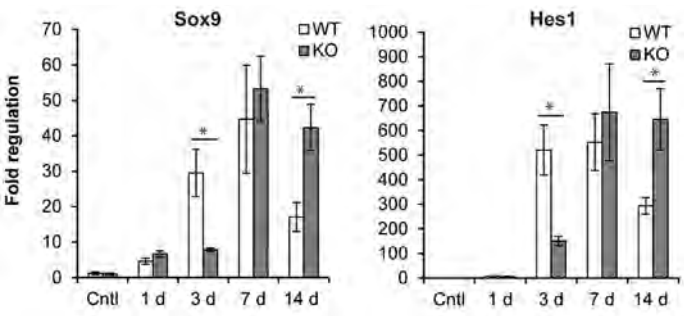


Ablation of TGF-β II signaling (KO) increases the replication of pancreatic acinar cells during pancreatitis.

Serotonin promotes acinar de-differentiation following pancreatitis-induced regeneration in the adult pancreas

E. Saponara, Y. Tian, K. Grabliauskaite, M. Bombardo, T. Reding Graf, S. Sonda and R. Graf

As serotonin has been recognized as a potent mitogen for a variety of cells and tissues, we investigated whether the molecule exerts a mitogenic effect in pancreatic acinar cells in two regenerative models, namely inflammatory tissue injury following pancreatitis and tissue loss following partial pancreatectomy. Serotonin did not affect clonal regeneration of mature acinar cells following tissue loss. However, it was required for acinar de-differentiation following inflammation-mediated tissue injury by promoting secretion of zymogen content.

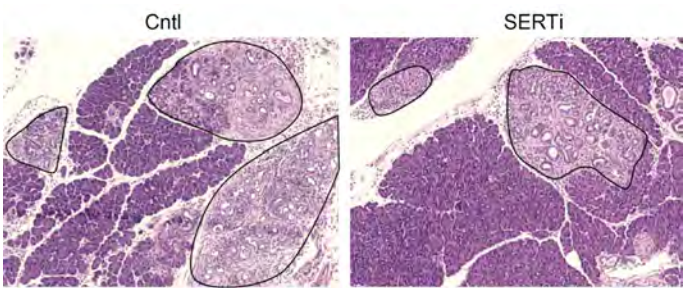


Lack of serotonin in TPH1-/- mice (KO) delays the up-regulation of de-differentiation markers following pancreatitis.

Inhibition of serotonin transporter prevents Rac1-dependent cytoskeletal remodeling and reduces pancreatic acinar-to-ductal metaplasia formation

E. Saponara, G. Seleznik, T. Reding Graf, R. Graf and S. Sonda

Acinar-to-ductal metaplasias (ADMs) are considered a prerequisite for pancreatic intraepithelial neoplasia (PanIN) development. Importantly, ADM formation depends on cytoskeletal remodeling promoted by the activity of the small GTPase Rac1. By using genetic and pharmacologic approaches, we showed that inhibition of serotonin uptake prevented Rac1 activation, cytoskeletal remodeling and the formation of ADM and PanIN lesions, without apparent drug toxicity.

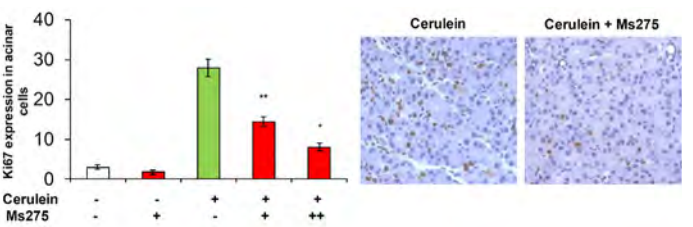


Inhibition of serotonin uptake with SERTi reduces the formation of pre-malignant lesions in the pancreas.

Class I HDAC activity promotes pancreatic regeneration following pancreatitis

M. Bombardo Ayats, E. Saponara, T. Reding Graf, R. Graf and S. Sonda

Pancreatic regeneration following inflammatory injury is associated with a robust change in gene expression. This study investigates whether epigenetic mechanisms regulated by the activity of histone deacetylases (HDACs) are activated during pancreatic regeneration and drive the observed gene regulation. We found that class I HDACs are activated following pancreatitis induction and promote proliferation of acinar cells by regulating the expression of cell cycle inhibitors.

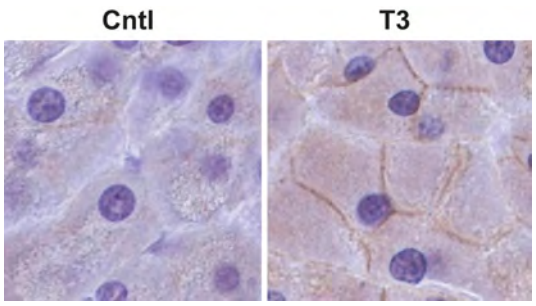


Inhibition of class I HDAC with Ms275 reduces acinar cell replication following pancreatitis.

Thyroid hormone T3 promotes acinar cells proliferation during pancreatitis

E. Malagola, K. Schlesinger, E. Saponara, K. Grabliauskaite, T. Reding Graf, R. Graf and S. Sonda

3,5,3'-triiodo-L-thyronine (T3) is considered to be the active form of thyroid hormones (THs). In the present project we wanted to evaluate the response of healthy adult pancreas to supplementation of T3; furthermore, we asked whether T3 influences the regenerative response following cerulein-induced pancreatitis. T3 robustly promoted proliferation of acinar cells in both normal and injured pancreas, likely via activation of the β-catenin (Wnt) pathway. In addition, the evidence of a regulation of THs responsive factors expression during pancreatitis points out a putative patho-physiological role of endogenous T3 in pancreatic regeneration.



T3 treatment induces up-regulation of β-catenin in pancreatic acinar cells.

Evaluation of a sepsis marker

T. Reding, P. Limani, G. Seleznik, D. Raptis, A. Dittmann, S. Sonda, R. Graf

Pancreatic stone protein (PSP) was originally identified in the pancreas. We have developed an ELISA to determine PSP in serum samples and demonstrated that PSP is highly elevated in patients with septic complications. To validate PSP as a marker of sepsis, we are conducting clinical trials in which we analyze perioperative levels of PSP in patients with infectious or septic complications.

Collaborations/Sponsors:

- Prof. Dr. Mathias Heikenwälder, PhD, (TUM Munich)
- Prof. Dr. Adrian Hehl, MD, (University of Zurich)
- Prof. Dr. Achim Weber, MD, (University Hospital Zurich)
- Prof. Aurel Perren (Universität Bern)

2.2.4 Bariatric Surgery

Rapid and body weight-independent improvement of endothelial function and HDL properties after Roux-en-Y gastric bypass: role of glucagon-like peptide-1

E. Osto, P. Doytcheva, C. Corteville, M. Bueter, C. Dörig, S. Stivala, H. Buhmann, S. Colin, L. Rohrer, R. Hasballa, A. Tailleux, C. Wolfrum, F. Tona, J. Manz, K. Spliethoff, P.M. Vanhoutte, U. Landmesser, F. Pattou, B. Staels, C.M. Matter, T.A. Lutz, T.F. Lüscher

Roux-en-Y gastric bypass (RYGB) reduces body weight and cardiovascular mortality in morbidly obese patients. Glucagon-like peptide-1 (GLP-1) seems to mediate the metabolic benefits of RYGB partly in a weight loss-independent manner. This study aimed to investigate in rats and patients whether obesity-induced endothelial and HDL dysfunction are rapidly improved after RYGB through a GLP-1-dependent mechanism.

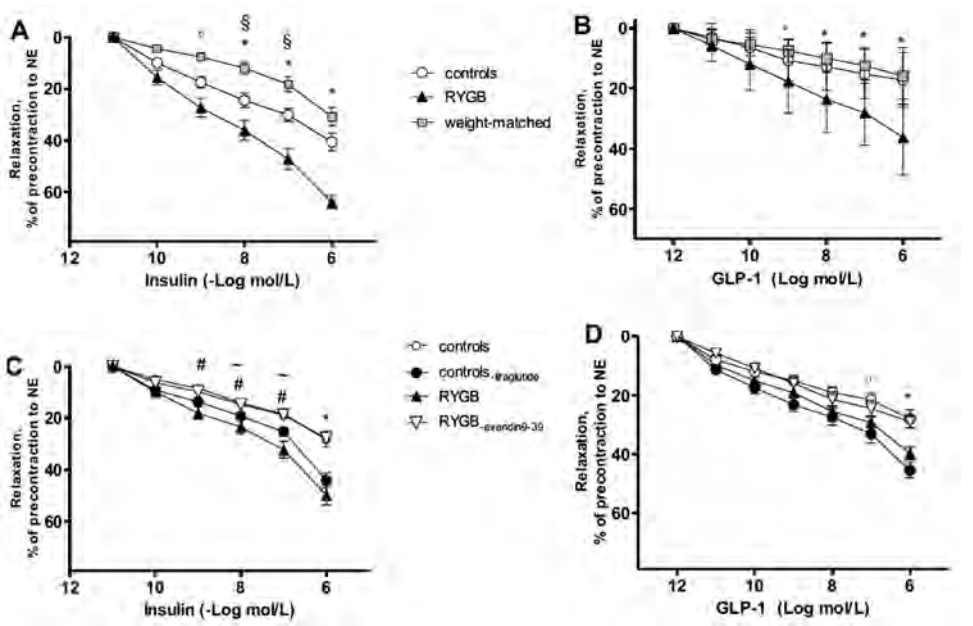


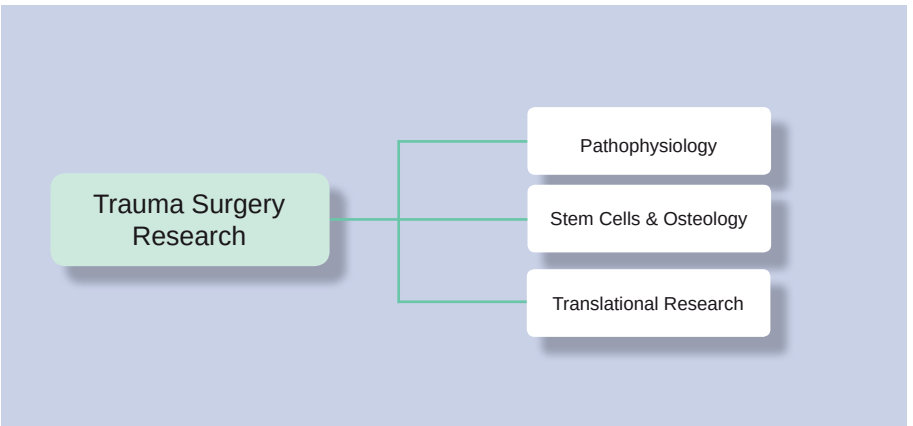
*Figure: **A** and **B**, Relaxation of aortic rings isolated 8 days after Roux-en-Y gastric bypass (RYGB) compared with sham-operated rats. Concentration-response curves during submaximal contraction to norepinephrine (NE) in response to insulin (**A**) and glucagon-like peptide-1 (GLP-1; **B**). *Sham-operated rats vs RYGB, §controls vs weight-matched, °RYGB vs weight matched, P<0.05. **C** and **D**, Effect of GLP-1 modulation for 8 days on the relaxations to insulin (**C**) or GLP-1 (**D**). #RYGB vs controls, ~RYGB vs RYGB-exendin9-39, °controls-liraglutide vs controls, *controls-liraglutide and RYGB vs other study groups, P<0.05; n=6 to 8 per group (please see Osto E et al., Circulation. 2015 Mar 10;131(10):871-81).*

We found that RYGB rapidly reversed obesity-induced endothelial dysfunction (see figure) and restored the endothelium-protective properties of HDL by a GLP-1-mediated mechanism. The present translational findings in rats and patients unmask novel, weight-independent mechanisms of cardiovascular protection in morbid obesity.

Collaborations/Sponsors:

- Prof. Dr. vet. Thomas Lutz (Institute of Veterinary Physiology, University of Zurich)
- Prof. Dr. Alan Spector, MD, (Florida State University, USA)
- Prof. Dr. Professor Carel le Roux, Experimental Pathology, University College Dublin

2.3 Trauma Surgery Research




Prof. Dr. Guido A. Wanner, MD


Prof. Dr. Hans-Peter Simmen, MD, Director


PD Dr. Paolo Cinelli, PhD

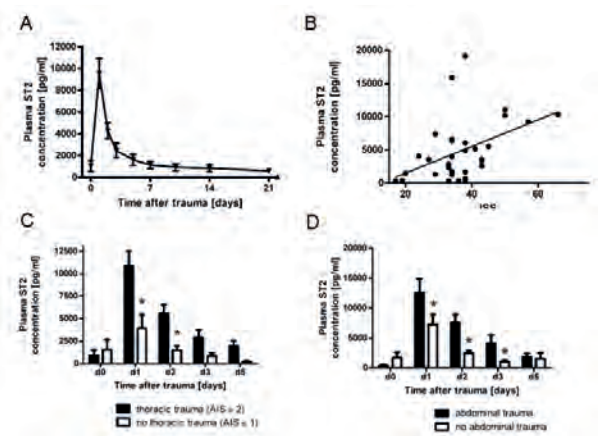

Prof. Dr. Clément Werner, MD

2.3.1 Pathophysiology

Interleukin-33 and its soluble receptor ST2 – novel players in trauma-induced systemic inflammation

D. Rittirsch, V. Schoenborn, S. Märsmann, G.A. Wanner

The inflammatory response following trauma is highly complex and still inadequately understood. Endogenous danger signals (alarmins) play a crucial role in the initiation of the immune response. The novel cytokine interleukin-33 (IL-33) is known to act as an alarmin in various inflammatory conditions. Its soluble decoy receptor sST2 functions as an endogenous antagonist of IL-33. Aim of the study was to investigate the role of IL-33 and sST2 in systemic inflammation in patients with multiple injuries. We could demonstrate for the first time that IL-33 and its soluble receptor sST2 are released during the early phase after multi-system injury. Plasma concentrations of sST2 during the early phase reflect the severity of injury and are associated with the development of sepsis. Intriguingly, the data suggest that the spleen may represent a source for sST2 and/or may be involved in the regulation of sST2 release during the late phase after trauma. In conclusion, these findings suggest that IL-33 and sST2 contribute to systemic inflammation after trauma.



(A) Plasma concentration of soluble ST2 (sST2) as a function of time. ▲= healthy volunteers (n=10), (B) Correlation of plasma sST2 concentration after trauma with the injury severity score (ISS). n=32; r2=0.2024, P<0.01. (C) Levels of sST2 in patients with thoracic injury (AIS ≥ 2; n=26) compared to patients without severe injury to the chest (AIS ≤ 1; n=6). (D) Concentrations of sST2 in plasma from trauma patients with (AIS ≥ 3; n=15) and without abdominal injury (AIS ≤ 2; n=17) at day 0-5 after trauma.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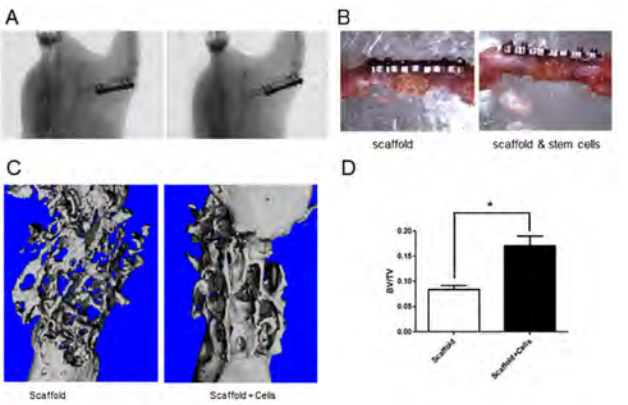
2.3.2 Stem Cells & Osteology

Perivascular Stem Cells for Bone Tissue Engineering

König M, Casanova Zimmermann E, Cadosch D, Wanner G and Cinelli P

Tissue engineering research has endeavored to search for novel sources of stem cells other than bone marrow mesenchymal stem cells (MSCs) for bone regeneration and repair. Pericytes has recently been identified as a primitive origin of human MSCs. We established an effective protocol to purify CD146+ NG2+ CD34- CD45- pericytes from adipose tissue and directly transplanted these cells without any *in vitro* expansion in a mouse model for critical bone defect. The enriched perivascular cells were able to efficiently contribute to bone regeneration as compared with the scaffold only controls animals.

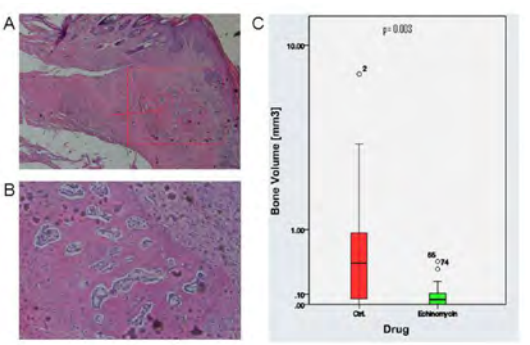


A. In vivo micro computeted tomograph picture of implanted scaffold. B. Difference between implanted scaffold and scaffold with perivascular cells. C. microCT 3D reconstructions of collagenous bone scaffold with and without perivascular cells implanted in a femoral segmental critical-sized defect in mouse, 8 weeks upon implantation. D. Quantification of bone volume to total volume in the two groups with and without stem cells.

Heterotopic Ossification: New Approaches continued

Zimmermann SM, Jentzsch T, Wanner GA, Simmen HP, Werner CML

Heterotopic ossification (HO) frequently causes complications following orthopedic and trauma surgery and may drastically reduce the postoperative outcome due to pain and joint contracture. Current therapeutic options include NSAID's and local radiation. However, both options of prevention show disadvantages such as delayed fracture healing and impaired ossification as well as other side effects. Our goal is to investigate a novel approach in the prevention of heterotopic ossification by pharmacologically interfering with the molecular signaling pathways involved in this process. We examined the effect of Echinomycin, a known inhibitor of HIF1-α, on HO formation in a murine model where an Achilles tenotomy was performed. We found a highly significant reduction in the bone volume following subcutaneous administration of Echinomycin compared to the control group.



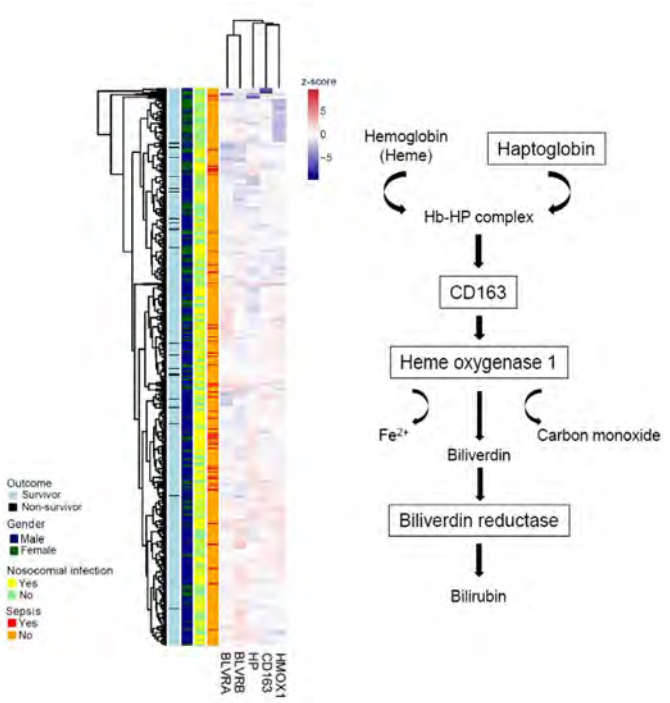
A. Islet of heterotopic bone within the soft tissue of a specimen's hind limb; B. Detailed image of islet of heterotopic bone; C. Bone volume in control and Echinomycin group.

2.3.3 Translational Research

Transcriptomic profiling in severely injured patients

D. Rittirsch, V. Schoenborn, S. Günkel, P. Cinelli, M. Bauer, G. Wanner

In severe trauma, overwhelming systemic inflammation can result in adverse events and the development of complications, including sepsis. The study was aimed to identify mechanisms linked to complicated courses after severe trauma by a systems biology approach. In a prospective study, RNA samples from circulating leukocytes from patients with multiple injury were analysed for dynamic changes in gene expression over a period of 21 days by whole genome screening (discovery set) and quantitative RT-PCR (validation set). Transcriptome profiling of a representative patient subset with either systemic inflammation or sepsis revealed the strongest changes between both groups in expression of the heme degradation pathway. Using quantitative RT-PCR analyses the key components haptoglobin (HP), cluster of differentiation (CD) 163, heme oxygenase-1 (HMOX1), and biliverdin reductase (BLVR) A and B showed robust changes following trauma. The severity of systemic inflammation was reflected by the expression of HP, and upregulation of HP was associated with the incidence of sepsis. Transfusion of allogenic blood was associated with the development of nosocomial infections and sepsis, and the risk for massive blood transfusion correlated with the expression pattern of HP. Furthermore, systemic release of myoglobin was also associated with dynamic upregulation of the heme degradation pathway.



Schematic illustration of the heme degradation pathway and correlation (cluster analysis) of the expression (ΔCT) of HP, CD163, HMOX1, BLVRA, and BLVRB with the binary outcome parameters survival, nosocomial infection, sepsis, and gender.

Collaborations/Sponsors:

- Clinical Trials Center, UniversityHospital Zurich
- Brigitte von Rechenberg, Musculoskeletal Research Unit, Vetsuisse Faculty, University of Zurich
- Center for Applied Biotechnology and Molecular Medicine (CABMM), University of Zurich
- Armin Curt, Spinal Cord Injury Center, University of Zurich and University Hospital Balgrist
- Orthopedic Research Laboratory, Biomechanics, University Hospital Balgrist, Zurich
- Beatrice Beck-Schimmer, Institute of Anesthesiology, UniversityHospital Zurich
- Institute for Biomechanics, ETH, Zurich
- Michael Bauer, Institute for Anesthesiology and Intensive Care Medicine, University Hospital Jena, Germany
- Markus Huber-Lang, Dept. of Traumatology, Hand-, Plastic and Reconstructive Surgery, University Hospital Ulm, Germany
- Jan Schwab, Klinik und Poliklinik für Neurologie & Experimentelle Neurologie, Charité Universitätsmedizin Berlin
- Michael Flierl, Philip Stahel, Dept. of Orthopaedic Surgery, Denver Health Medical Center, USA
- Peter A. Ward, Dept. of Pathology, University of Michigan Medical School, Ann Arbor, USA
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2.4 Plastic, Hand & Reconstructive Surgery Research

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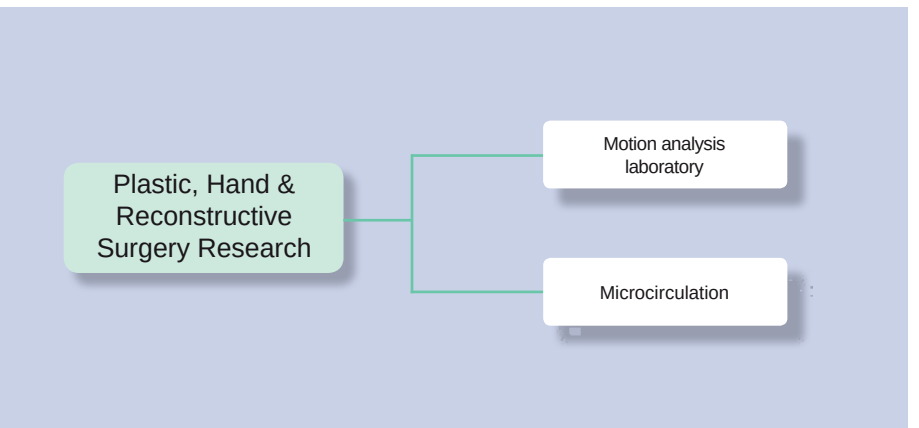
Anna Wang
med. Student



2.4.1 Tissue Engineering

Establishment of a bioactivity test for PDGF-BB intended at tendon regeneration

O. Evrova, J. Houska, E. Bonavoglia, M. Calcagni, P. Giovanoli, V. Vogel and J. Buschmann

Tendon rupture repair may be accelerated by growth factors such as PDGF-BB that is supplied to the wound site in a controlled manner. In order to test the bioactivity of PDGF-BB that is released from emulsion electrospun meshes, the released growth factor can be added to the culture medium of rabbit tenocytes. In order to enhance the sensitivity of the bioactivity test, culture medium with or without serum is tested. Tenocytes are more sensitive to aliquots of PDGF-BB when the culture medium is used without serum. We highly acknowledge the financial support of this project by *ab medica*, Italy, and EMDO Stiftung, Zürich.

Collaborations:
- Prof. V. Vogel, ETH Zürich and ab medica, Italy

Development of an elastic, biocompatible and biodegradable protein delivery device for tendon repair: emulsion electrospun DegraPol scaffold

O. Evrova, J. Houska, E. Bonavoglia, M. Calcagni, P. Giovanoli, V. Vogel, and J. Buschmann

For tendon rupture repair, an electrospun DegraPol® tube has been developed that is biocompatible, biodegradable and very elastic, enabling the surgeon an easy handling during implantation. In order to render this device bioactive to support and accelerate the tendon healing process, emulsion electrospinning has been tested and the release kinetics of different molecules has been determined as a function of polymer concentration, flow rate and voltage. For example, the release of FITC-BSA is shown as a function of weight percentage of the polymer in the solvent (Figure 1). We highly acknowledge the financial support by *ab medica*, Italy, and EMDO Stiftung, Zürich.

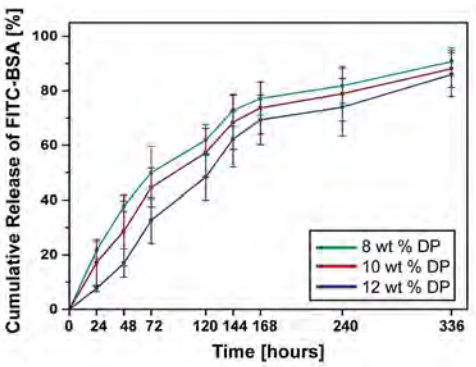


Figure 1 Comparison of cumulative release [%] between emulsion electrospun scaffolds produced with different wt % of DegraPol® in the solvent at 1 ml/h flow rate.

Collaborations:
- Prof. V. Vogel, ETH Zürich and ab medica, Italy

Tissue mechanics of biomimetic and biominerizable nanocomposites aimed at bone regeneration

W. Baumgartner, M. Welti, N. Hild, S. C. Hess, W. J. Stark, G. Meier Bürgisser, P. Giovanoli and J. Buschmann

Besides designed cell distributions and sufficient vascularity, tissue engineered bone grafts should be functional with respect to load bearing capacity at the place they will be implanted. This capacity varies by orders of magnitude between cortical and cancellous bone. Many materials intended for bone tissue engineering are therefore examined mechanically. However, the tests are often performed in a dry and cell-free state, although their tissue mechanics may be different in the wet state.
Therefore, we examined bone grafts based on electrospun nanocomposite PLGA/a-CaP seeded either with or without adipose-derived stem cells and determined their tissue mechanics including stiffness and energy dissipation in the wet state. While stiffness increased over time in cell-free scaffolds, it remained constant for cell-seeded grafts. As for energy dissipation, cell seeding led to a higher energy loss compared to cell free constructs.

Collaborations:
- Prof. W.J. Stark, ETH Zürich

2.4.2 Microcirculation and Skin Tissue Engineering

N. Lindenblatt, A. Hegglin, M. Kijanska, M. McLuckie, P. Giovanoli

New vascularization strategies for skin tissue engineering

A major challenge for both plastic surgeons and skin tissue engineers today is the limited survival of full thickness skin grafts (FTSG). The grafts often become necrotic as they undergo hypoxia due to failing to acquire a sufficient blood supply. To overcome this, we are taking a deeper look at the vascular endothelial growth factor (VEGF), known for its active role in angiogenesis. By creating a full thickness skin substitute (FTSS) with the addition of myoblasts that stably overexpress VEGF, we aim to significantly increase the speed of revascularisation and therefore decrease the hypoxic environment.

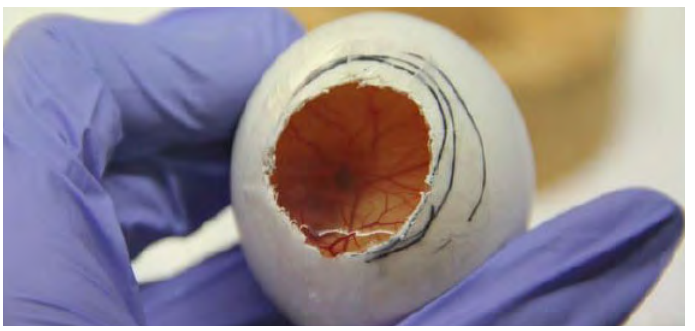


Fig. A common initial selection process consists of testing out a potential scaffold by placing it on the chorioallantoic membrane (CAM) of a chicken egg.
A way to test if the scaffold has good biocompatibility is if the CAM vasculature has grown around or towards it. If the vasculature particularly avoids the material and the vessels grow away from it, it is clearly not a good option, as the reaction will be the same in vivo.

Evaluation of the effect of fat and adipose-derived stem cells (ADSCs) on vascularisation and nerve regeneration in a new *in vivo* mouse model

The effect of fat and adipose-derived stem cells (ADSCs) on peripheral nerve regeneration will be studied in different settings in an *in vivo* situation. Based on this, novel therapeutic strategies to improve nerve regeneration and thus function of an extremity after injury could be developed.

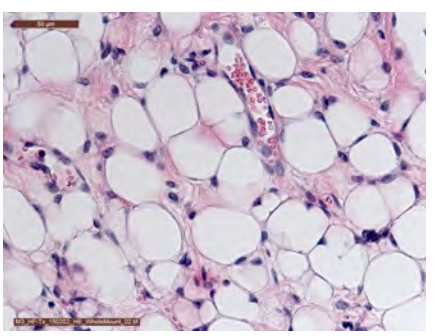


Fig. HE section of human fat. The fat is revascularized after implantation in the mouse dorsal skinfold chamber.

Characterisation of the vascularisation and integration of the silk-derived surgical scaffold SERI®

Reconstructive surgery requires continuously new acellular matrices for a wide range of applications. Acellular dermal matrices (ADMs) are frequently used today in soft tissue replacement during breast reconstruction procedures, where they contribute to implant coverage and restoration of breast aesthetics. SERI® Surgical Scaffold is a synthetic, off-the-shelf, single use, silk-derived fibroin multifilament scaffold with indications to be used for soft tissue support and reinforcement in plastic and reconstructive surgery.
Considering the complexity of the healing process and the risks associated with the use of different types of biomaterials, it is important to investigate their properties and contribution to wound healing *in vivo*.

Therefore, in order to understand how SERI® promotes wound healing we have performed an *in vivo* study basing on the model of the dorsal skinfold chamber in order to investigate the ravascularisation and the inflammatory response associated with wound closure.

The study is supported by a research grant from Allergan (Allergan Inc., Irvine, CA, USA) and partially funded by the SNSF through NCCR Kidney.CH.

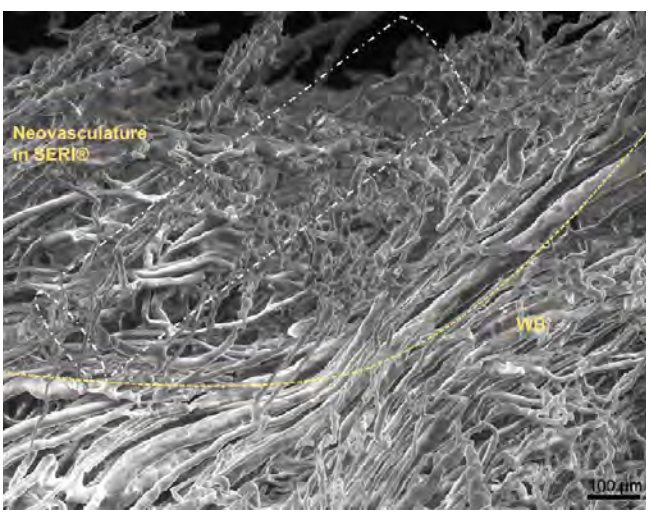


Fig. SEM images of the vascular corrosion cast representing angiogenic capillaries within regenerating granulation tissue and the SERI® matrix 21 days after implantation. White dashed line indicates a fiber of the SERI® matrix; yellow dashed line indicates the border between wound bed (WB) vasculature and the newly formed vasculature accompanying wound healing.

Evaluation of bacterial cellulose as wound dressing

Apical guidance represents an adhesion-free, material-independent strategy that can be applied to any wound shape and type (from simple mechanical abrasions to burns and chronic wounds). It is an opportunity to better manage simple everyday's wounds and burns (with standard plasters), as well as larger burns and chronic wounds (advanced wound dressing) requiring hospitalization. In this latter case, the treatment with apical guidance promise to significantly reduce the rehabilitation time.
The deployment of surface-structured bacterial cellulose substrates in model animals as skin wound dressing or body implant proves the high durability and low inflammatory response to the material over a period of 21 days, demonstrating beneficial effects of surface structure on skin regeneration. Further studies are ongoing.

The project is a cooperation with Dr. Aldo Ferrari and Dr. Simone Bottan, ETH Zurich.

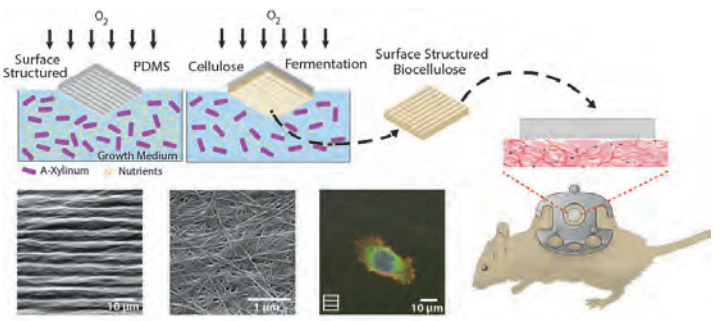


Fig. Replica molding methodology to transfer on-demand functional topographies to the surface of bacterial cellulose nanofiber textures. With this guided assembly-based biolithography (GAB), a surface-structured polydimethylsiloxane (PDMS) mold is introduced at the gas liquid interface of an Acetobacter xylinum culture. The generated bacterial cellulose nanofibers are assembled in a three-dimensional network reproducing the geometric shape. Scanning electron and atomic force microscopy are used to establish the good fidelity of this facile and affordable method. Interaction of surface-structured bacterial cellulose substrates with human fibroblasts and keratinocytes illustrates the efficient control of cellular activities which are fundamental in skin wound healing and tissue regeneration. The deployment of surface-structured bacterial cellulose substrates in model animals proves the high durability and low inflammatory response to the material (Bottan, et al., 2014).

Vascularisation of polyurethane discs

In order to replace tissue in the body, three-dimensional scaffolds are often the basis for many tissue regenerative strategies. For this kind of tissue engineered and cell engrafted constructs it is crucial to acquire sufficient oxygen and nutrient supply through an effective revascularisation. We are studying the influence of biomaterial coating with growth factors in order to improve the revascularisation of polyurethane.

The project is a cooperation with Prof. S.P. Hoerstrup and Dr. Christian A. Schmidt, University Hospital Zürich. This study is financially supported by the Swiss National Science Foundation.

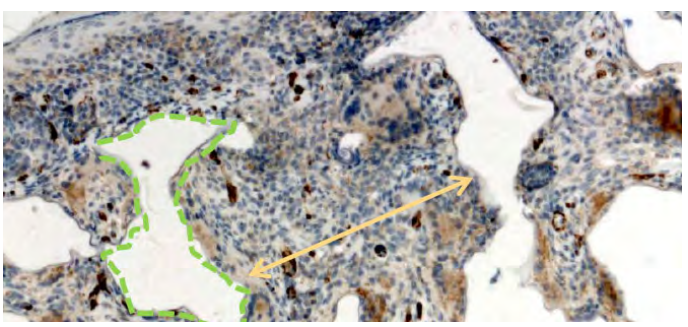


Fig. Revascularisation of polyurethane discs implanted in the dorsal skinfold chamber and stained by immunohistochemistry of CD31 positive endothelial cells (DAB). The biomaterial is fully integrated and vascularized 21 days after transplantation. Green dashed line indicates a fragment of the implanted biomaterial, the yellow arrow refers to the pore size of the biomaterial (150 µm).

Collaborations/Sponsors:

- Dr. Aldo Ferrari PhD, Simone Bottan MSc. Laboratory of Thermodynamics in Emerging Technologies. ETH Zurich
- Dr. Tomas Egana, PhD, Center for Genome Regulation, Santiago de Chile , Chile
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- Dr. Deon Bezuidenhout, MD, Cardiovascular Research Unit, University of Cape Town, South Africa
- Dr. Katrin Kerl, Department of Dermatology, University Hospital Zurich
- Prof. Urs Ziegler, Claudia Domröse, Klaus Marquardt, Center for Microscopy and Image Analysis, University of Zurich
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- Prof. Dr. Simon P. Hoerstrup, MD, PhD, Dept. of Surgical Research & Clinic for Cardiovascular Surgery, University Hospital Zurich
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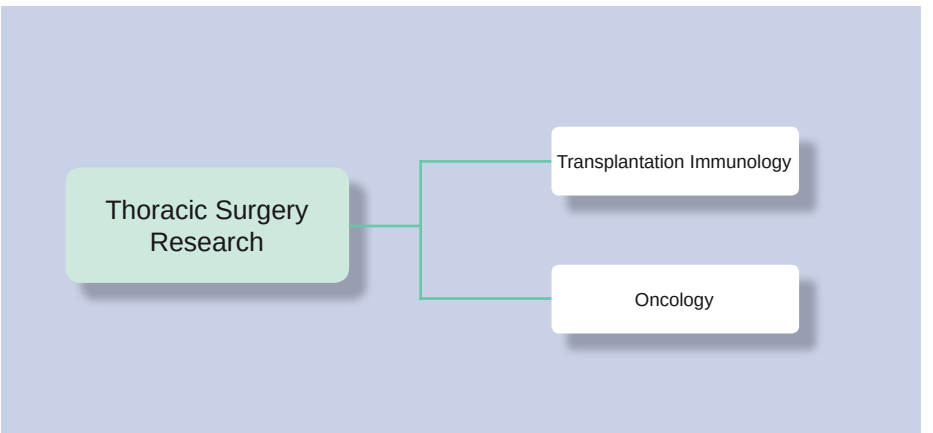


2.5.1 Transplantation Immunology

Mice lung allograft acceptance by CD26 co-stimulatory blockade is due to a balanced expression of IL17 and IL10

Y. Yamada, J.-H. Jang, I. Inci, W. Weder, W. Jungraithmayr

Previously, we have shown that the CD26 inhibitor (Vildagliptin) effectively reduced allo-reaction by both *in vitro* experiments with mixed lymphocyte reaction assays, and *in vivo* experiments with orthotropic mice lung transplantation using a combination of MHC class I and II complete mismatched mice. Functionally, blood gas analysis revealed that P/F ratio in the CD26 inhibitor group (CD26-I) and CD26 KO group (CD-26KO) were higher than control (Figure 1A). FACS analysis showed that the number of $IL10^{+}$ cells in lung grafts harvested on day 1 after the surgery were relatively higher in CD26-I and CD26KO than control (Figure 1C), and $IL17^{+}$ cells were relatively less in CD26-I and CD26KO (Figure 1B). ELISA revealed that the levels of IL10 in graft lung harvested on day 5 after the surgery in CD26-I and the CD26KO were significantly higher than control (Figure 1D). We assumed that the increased expression of the immune-protective cytokine IL10 and the reduced expression of the pro-inflammatory cytokine IL17 play an important role after CD26 co-stimulatory blockade and promotes lung allograft acceptance.

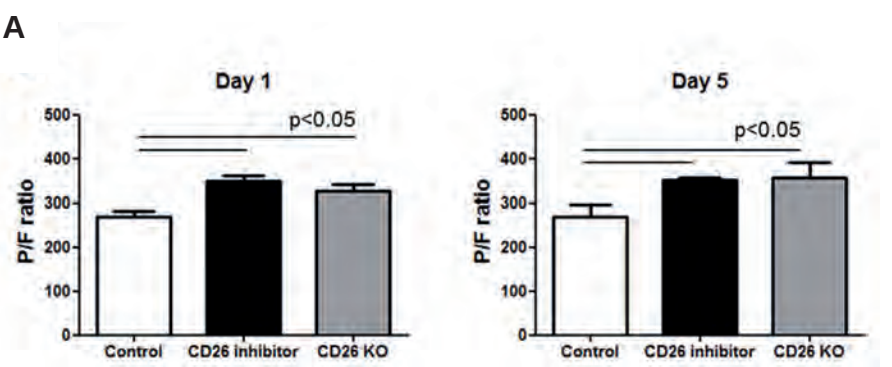


Figure 1A: Blood gas analysis. P/F ratios in CD26-I and CD26KO were higher than control.

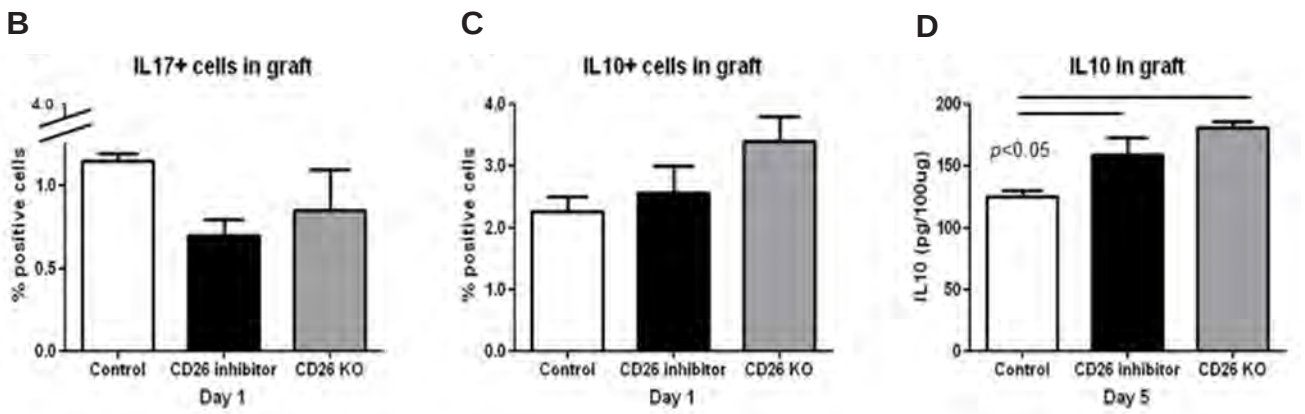


Figure 1B: The number of IL17^{+} cells in lung grafts harvested on POD1 examined by FACS. CD26-I and CD26KO showed relatively less numbers.
Figure 1C: The number of IL10^{+} cells in lung grafts harvested on POD1 examined by FACS. CD26-I and CD26KO showed relatively higher numbers.
Figure 1D: The levels of IL10 in lung grafts harvested on day 5. The levels in CD26-I and CD26KO were significantly higher than control.

Magnetic resonance imaging for the detection of chronic lung allograft rejection in mouse lung transplantation

Y. Yamada, J.-H. Jang, D. Kenkel, A. Boss, W. Weder, W. Jungraithmayr

The aim of study is to develop a technique of magnetic resonance imaging (MRI) that charaterizes and detects early chronic rejection (CR) lesions on the basis of a validated CR model of orthotopic mouse single lung transplantation. We performed orthotopic mice lung transplantations using a combination of MHC class I and II minor mismatched mice (C57BL/10 as donor and C57BL/6 as recipient) (n=15). Three of 15 samples (20.0%) showed pathological findings of bronchiolitis obliterans. Representative macro and microscopic features are shown in Figure 2. An evaluation of CR by MRI is now taken place.

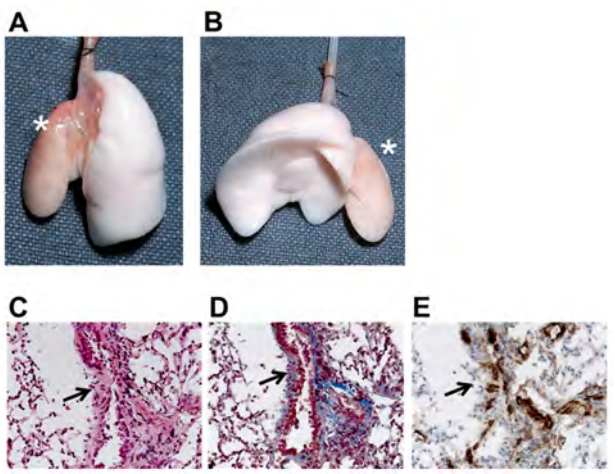


Figure 2A and B: A macroscopic view of the graft (A, dorsal side; B, ventral side). Orthotropic mice lung transplantations with a minor mismatch combination was performed and harvested on day 28. The stars indicate transplanted left lung.
Figure 2C-E: A microscopic view of the graft. Panel C shows HE staining. Panel D and E are the corresponding sites stained with Trichrome and aSMA. A fibrotic change can be seen on bronchus (arrow).

Anti-inflammatory effect of intragraft CD26/DPP4-inhibition by Vildagliptin protects mouse lung from ischemia-reperfusion injury

J.-H. Jang, Y. Yamada, W. Jungraithmayr

Ischemia/reperfusion injury (IRI) is a primary cause of organ damage after lung transplantation (Tx). CD26/DPP4 has a catalytic activity cleaving wide range of substances. It was shown that a substrate of CD26/DPP4, SDF-1, involved in alternative differentiation of macrophage. We here aimed to increase the bioavailability of SDF-1 by inhibition of CD26/DPP4 with the specific inhibitor Vildagliptin to protect syngeneic mouse lung implant from IRI.
Immunohistochemistry showed that Vildagliptin treated group decreased immune cell infiltration (Fig. 1A) and significant reduction of plasma TNF-α compared to control group seven days after Tx (Fig. 1B) which are signs of post-operative inflammation.

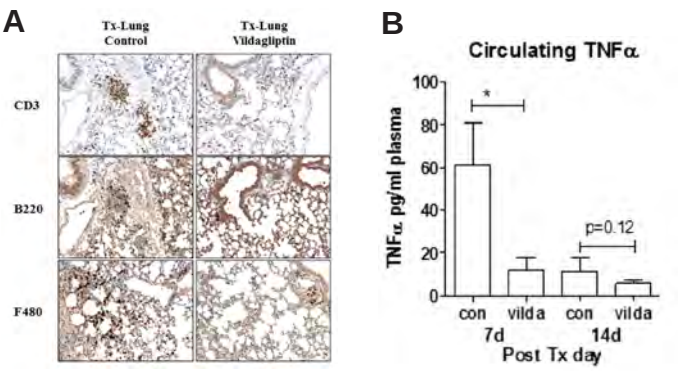


Figure 1. ***Decreased post-Tx inflammation by intra-graft CD26/DPP4 inhibition.*** *Cold-Preservation with Vildagliptin prevented immune cell infiltrations in the graft (A) and reduced inflammatory cytokine level (B) seven days after syngeneic Tx. Inflammatory immune cells (T cell, B cell, and Macrophage) are recruited around pulmonary artery (A). Circulating TNF-α was decreased by Vildagliptin flusing during cold ischemic preservation.*

To find the anti-inflammatory mechanism of CD26/DPP4 inhibition, we analyzed mouse lung grafts before Tx. Cold preservation after Vildagliptin flush inhibited catabolism of SDF1 significantly (Fig. 2A). By flow cytometry, we found IL-10 expressing macrophages are significantly elevated in CD26/DPP4 inhibited lungs (Fig. 2B, 2C).

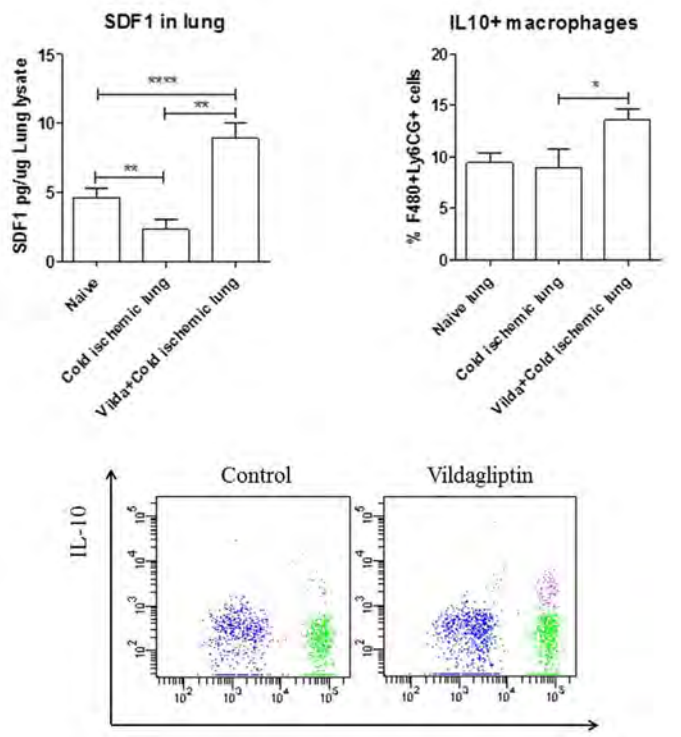


Figure 2. Anti-inflammatory effect of intra-graft CD26/DPP4 inhibition. Vildagliptin significantly preserved SDF-1 (A) and increased proportion of IL-10 expressing macrophages in cold ischemic mouse lungs (B). Representative histograms showing increment of IL-10 positive macrophage (Ly6CG positive) population (purple) by Vildagliptin in cold ischemic mouse lung (C).

Together, we found a protective modality of lung transplantation against Tx associated IRI and cold preservation by inhibiting CD26/DPP4 which enables alternative differentiation of macrophages toward phenotype of anti-inflammation.

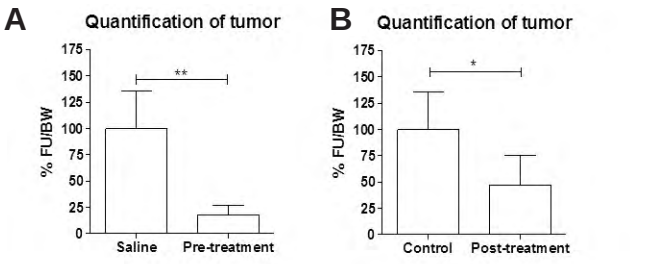
Collaborations:

- Prof. Ingrid de Meester, Department of Medical Biochemistry, University Antwerp, Belgium
- PD Dr. Andreas Boss, Dr. Moritz Wurnig, Department of Diagnostic Radiology, UniversityHospital Zurich
- Dr. Markus Weiger, ETH Zurich, Institut für Biomedizinische Technik, Zürich
- Prof. Beatrice Beck-Schimmer, Department of Anesthesiology, UniversityHospital Zurich
- Dr. Johanna Buschmann, Department of Reconstructive Surgery, UniversityHospital Zurich
- University Leuven, Belgium, Laboratory of Pneumology
- McDyer Lab, University of Pittsburgh, USA

Novel therapy for lung metastases by CD26/DPP4 inhibition

J.-H. Jang, Y. Yamada, W. Jungraithmayr

CD26/DPP4 has become the focus of cancer research and it was shown that CD26/DPP4 positive cancer cells display increased metastatic activity. We tested the inhibitor of CD26/DPP4, Vildagliptin on the development (pre-treatment) and growth (post-treatment) of mouse colorectal lung metastases established by syngeneic cell line (MC38) injection. Treatment with Vildagliptin suppressed both, the incidence and growth of lung metastases.



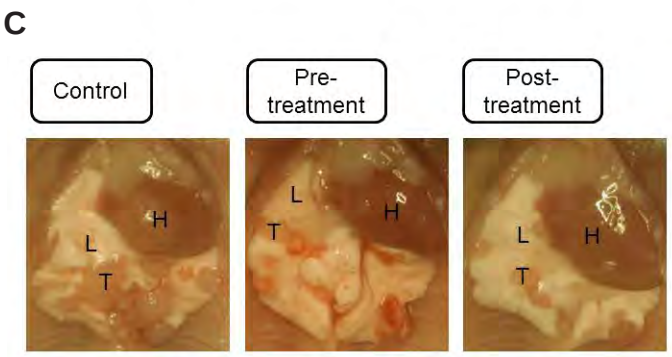


Figure 1. Vildagliptin treatment reduced lung metastases growth.
*Both, pre- and post-treatment of Vildagliptin significantly decreased the size of tumor in mice (A, and B) without change of bodyweight within these three weeks. Gross anatomy of metastases developed by MC38 cell line injection is shown (C) three weeks after the inferior vena cava injection of MC38 cell line (100x103 cells/g mouse) (n=5). L: lung, H: heart, T: tumor. (** p=0.0042, * p=0.041)*

We have analyzed molecular characteristics of tumors developed in lung (Fig. 2A) and under skin (Fig. 2B) by syngeneic cell line injection. The expression of autophagy markers (LC3, p62, and ATF4) and ID1, AKT were decreased by Vildagliptin treatment, while cellular stress markers (calpains) were increased.

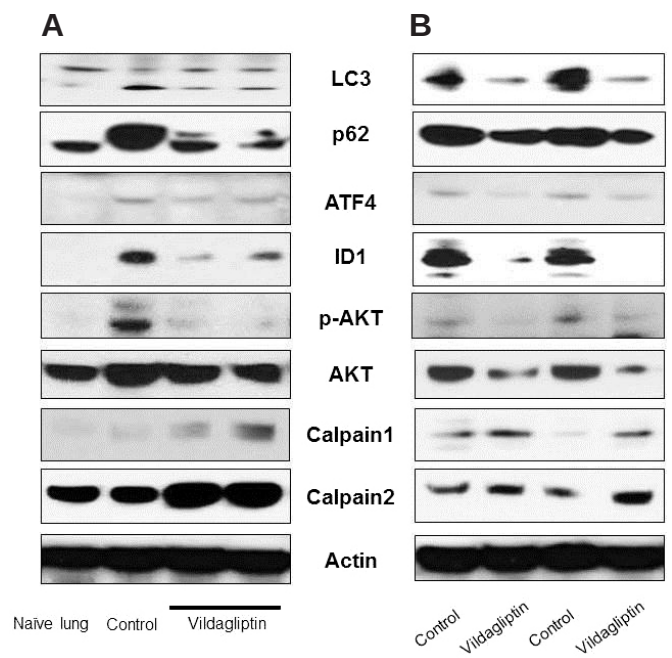


Figure 2. Molecular characteristics of tumors with or without Vildagliptin treatment in vivo. The autophagy markers LC3, p62, and ATF4 were decreased in the tumors of lungs (A) and skin (B) by Vildagliptin treatment. The expression of ID1 was also decreased together with its downstream target AKT by the treatment. In contrast, cellular injury markers (Calpain1 and 2) increased by the treatment of Vildagliptin.

In contrast with reduced expressions of autophagy markers (Fig.2), apoptosis marker (TUNEL) was significantly increased by Vildagliptin treatment (Fig. 3).

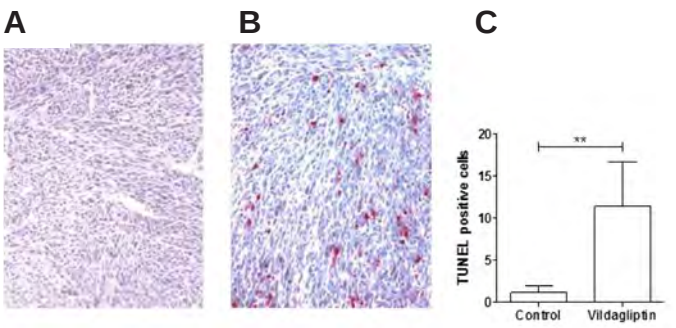


*Figure 3. Increased apoptosis in the subcutaneously implanted MC38 tumor cell line by Vildagliptin treatment. Vildagliptin reduced the tumor size in consistent manner. Compared to the control (A), Vildagliptin increased apoptotic cells (B and C) shown by TUNEL stain (n=4). (** p=0.007)*

The anti-tumor effect of Vildagliptin was conducted via reduction of autophagy and induction of apoptosis in the metastases. We propose the CD26/DPP4 inhibitor Vildagliptin as a new therapeutic approach for the treatment of colorectal cancer lung metastases.

Collaborations:

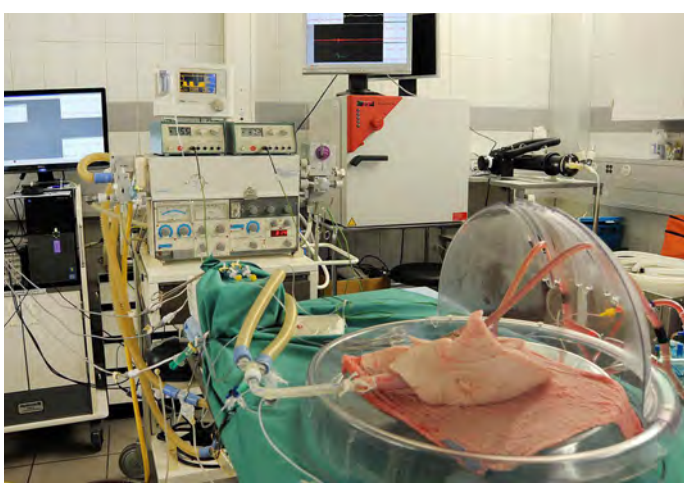
- Prof. Ingrid de Meester, Department of Medical Biochemistry, University Antwerp, Belgium
- PD Dr. Andreas Boss, Dr. Moritz Wurnig, Department of Diagnostic Radiology, UniversityHospital Zurich
- Dr. Markus Weiger, ETH Zurich, Institut für Biomedizinische Technik, Zürich
- Prof. Beatrice Beck-Schimmer, Department of Anesthesiology, UniversityHospital Zurich
- Dr. Johanna Buschmann, Department of Reconstructive Surgery, UniversityHospital Zurich
- University Leuven, Belgium, Laboratory of Pneumology
- McDyer Lab, University of Pittsburgh, USA

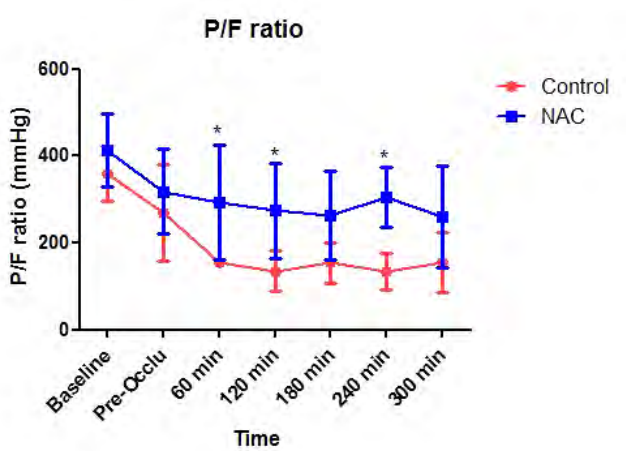
Ex vivo reconditioning of donor lungs with inhaled N-Acetyl cysteine after prolonged cold ischemia

I. Inci, S. Hillinger, S. Arni, Y. Yamada

Project Description

In order to reduce primary graft dysfunction following lung transplantation, we evaluated the reconditioning potential of our lung perfusion (EVLP) system together with direct *ex vivo* nebulization of curative N-Acetyl cysteine (NAC) into donor lungs. In a large animal setting, we used our previously developed pig single lung transplantation model and short term survival experiment to monitor, *in vivo*, several physiological and biochemical parameters of the reconditioned graft. Those experiments allowed us to better document the beneficial role of reconditioning damaged lungs with both EVLP and inhaled NAC after a prolonged cold ischemic storage.





Gas exchange during the observation period. Better oxygenation observed in the treated group.

2.5.2 Oncology

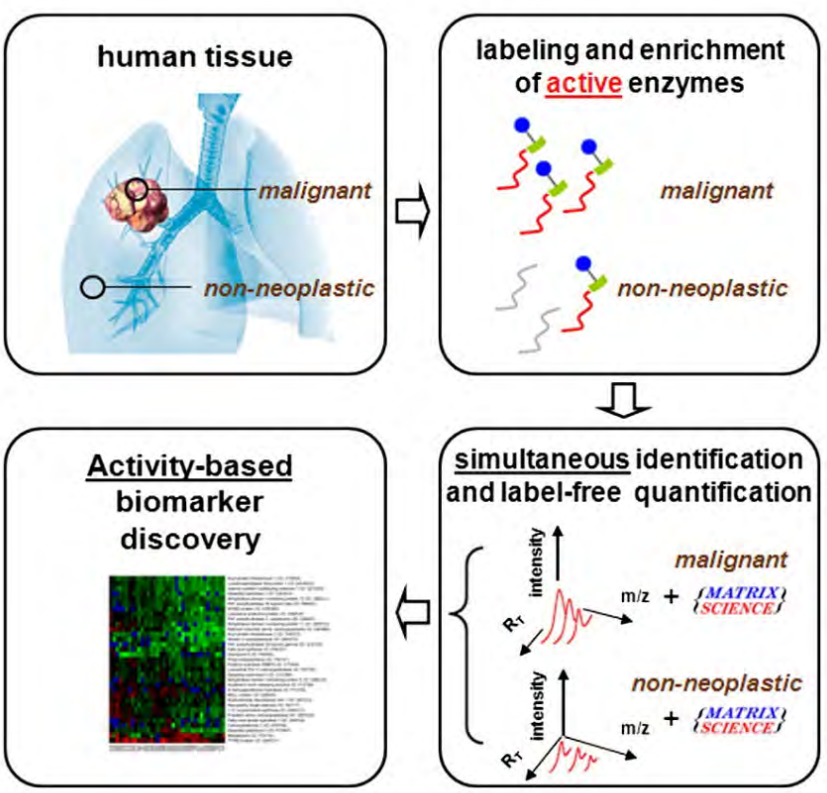
2.5.2.1 Lung cancer

Activity-based proteomics: biomarker identification in human lung adenocarcinoma

S. Arni, S. Hillinger

Project Description

In Switzerland, lung adenocarcinoma is a major cause of cancer related deaths. We previously characterized with the activity based proteomics (ABP) methodology several biomarkers in order to improve the risk stratification provided by conventional staging algorithm. We plan to now validate our biomarkers and are developing a new SWATH MS protocol for ABP of the serine hydrolase superfamily, combining both high throughput and high reproducibility.



Principle of the lung adenocarcinoma activity based biomarker discovery platform previously developed in our lab.

Collaborations:

- Dr. Tatjana Sajic and Prof. Ruedi Aebersold, Department of Biology, Institute of Molecular Systems Biology (IMSB), ETH Zurich, Switzerland

2.5.2.2 Malignant pleural mesothelioma

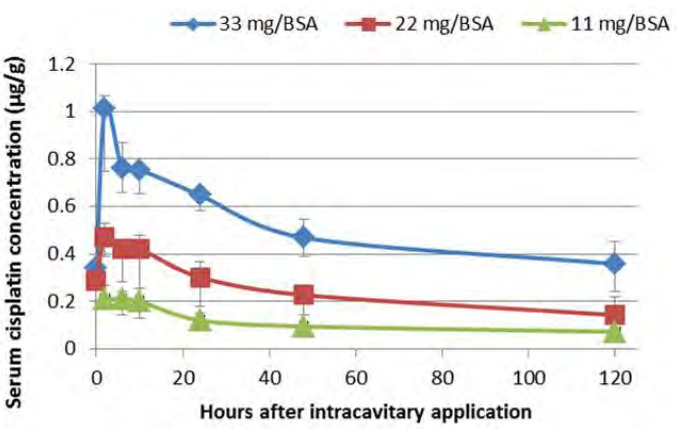
Localized intracavitary therapy for MPM – from bench to bedside

Phase I Dose-Escalation Monocentric Open Trial for the Evaluation of the Safety of ***In***tracavitary Cisplatin-***F***ibrin ***L***ocalized ***C***hemotherapy after Pleurectomy/Decortication or Extrapleural Pneumonectomy for the Treatment of Patients with Malignant Pleural ***Meso***thelioma (***INFLuenCe – Meso I***)

I. Opitz, A. Kostron, O. Lauk, M. Meerang, M. Friess, C. Bommeli, A. Jetter, D. Günther , R. Stahel, E. Felley-Bosco, G. Wuilleret, G.-M. Monsch, B. Seifert, W. Weder

Our newly developed intracavitary chemotherapy with cisplatin loaded in to a fibrin carrier for MPM was applied into clinical application (Lardinois, Jung et al. 2006; Opitz, Lardinois et al. 2007; Opitz, Erne et al. 2011). Safety and tolerability were assessed in a Phase I-dose-escalation trial including 12 mesothelioma patients who underwent prior pleurectomy/decortication (P/D). Cisplatin-fibrin was sprayed after to the chest wall and the surface of the lungs in a concentration of 11 mg/m^2 BSA (n=3), 22 mg/m^2 BSA (n=3), 33 mg/m^2 BSA (n=3) and 44 mg/m^2 BSA (n=3). The adverse events observed were in most of the cases related to the morbidity of the operation. Preliminary pharmacokinetic results showed very high concentrations of cisplatin in the local chest wall at 90 min after application of cisplatin-fibrin. In contrast, the peak of systemic cisplatin concentrations of patients receiving 11-33 mg/m^2 cisplatin-fibrin were below the nephrotoxicity limit of 6 µg/g (Figure 1), even in combination with previous intravenous induction cisplatin treatment.

Outlook: A Phase II trial for the confirmation of safety and tolerability of intracavitary cisplatin-fibrin after Pleurectomy/Decortication (P/D) or Extrapleural Pneumonectomy (EPP) is planned (Phase IIa Monocentric Open Trial for the Evaluation of the Safety of ***In***tracavitary Cisplatin-***F***ibrin ***L***ocalized ***C***hemotherapy after Pleurectomy/Decortication or Extrapleural Pneumonectomy for the Treatment of Patients with Malignant Pleural ***Meso***thelioma (***INFLuenCe – Meso II***)). In this trial, additional 20 patients will receive the maximally tolerated dose (MTD).



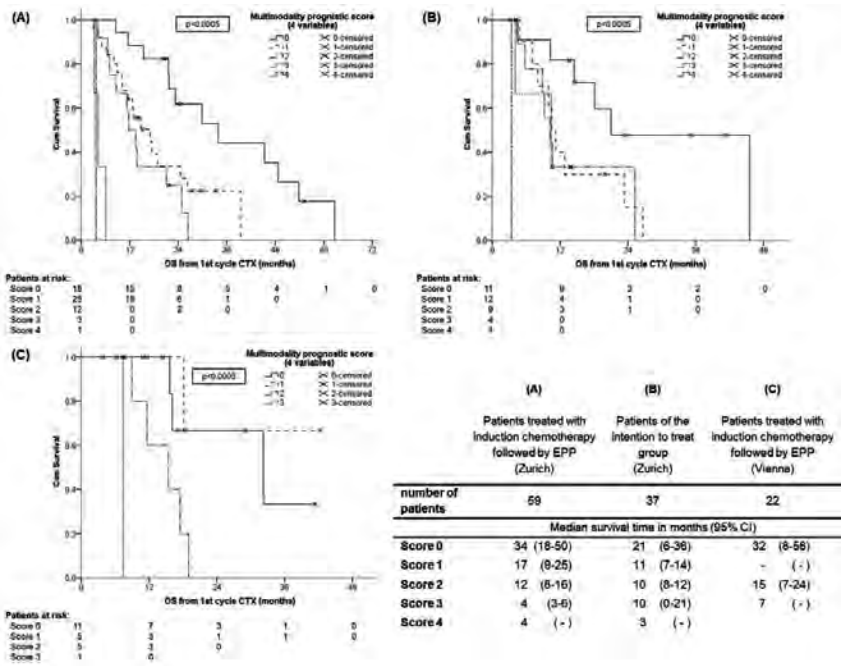
Kinetics of serum cisplatin following intracavitary administration. Data is presented in median + range (n=3 for each dosage group).

A new prognostic score supporting treatment allocation for Multimodality therapy for malignant pleural mesothelioma - A review of 12 years' experience

I. Opitz, M. Friess, P. Kestenholz, D. Schneiter, R. Stahel, T. Frauenfelder, Dan Linh Nguyen-Kim, B. Seifert, W. Klepetko, Ali-Mir Hoda, W. Weder

Selection factors for multimodal therapy of patients with malignant pleural mesothelioma (MPM) were identified based on survival data from 12 years of experience. A prognostic score was defined considering tumor volume, histology, CRP and response to chemotherapy and identified patient groups not benefitting from multimodality treatment in a cohort of patients receiving cisplatin-based induction chemotherapy followed by extrapleural pneumonectomy (EPP) at the University Hospital Zurich. The score was validated in two cohorts:

1) Patients with the intention to be treated with induction chemotherapy and EPP at the University Hospital Zurich, but did receive another kind of surgery or no surgery at all after induction chemotherapy.
2) Patients treated with induction chemotherapy followed by EPP at the Medical University Vienna.



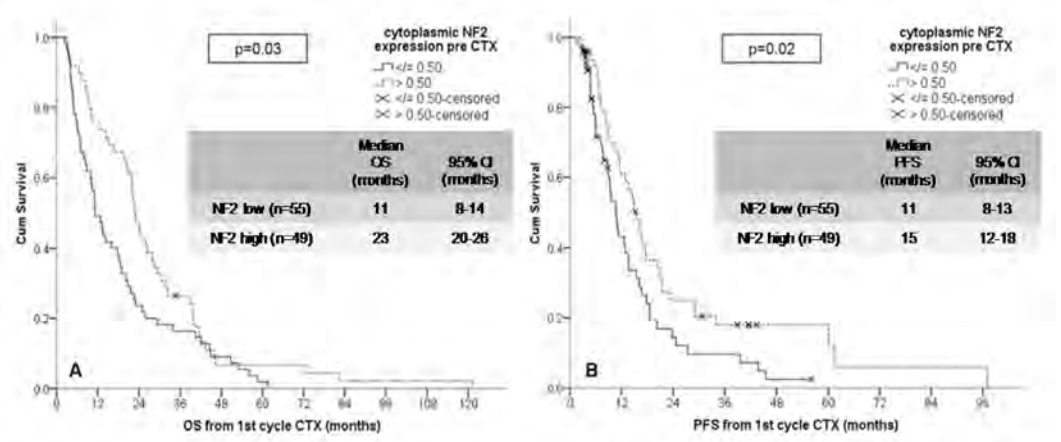
	(A) Patients treated with induction chemotherapy followed by EPP (Zurich)	(B) Patients of the intention to treat group (Zurich)	(C) Patients treated with induction chemotherapy followed by EPP (Vienna)
number of patients	59	37	22
	Median survival time in months (95% CI)		
Score 0	34 (18-50)	21 (6-36)	32 (8-56)
Score 1	17 (8-25)	11 (7-14)	- (-)
Score 2	12 (6-16)	10 (8-12)	15 (7-24)
Score 3	4 (3-6)	10 (0-21)	7 (-)
Score 4	4 (-)	3 (-)	

Kaplan-Meier curve of overall survival (OS) in months of the multimodality prognostic score (including 4 variables: volumetry pre CTX > 500ml, CRP pre CTX > 30mg/l, non-epithelioid histology in pre CTX biopsy, PD according to modified RECIST criteria)

Prognostic and Predictive Biomarkers for Malignant Pleural Mesothelioma

I. Opitz, M. Meerang, K. Bérard, M. Friess, B. Bitanihirwe

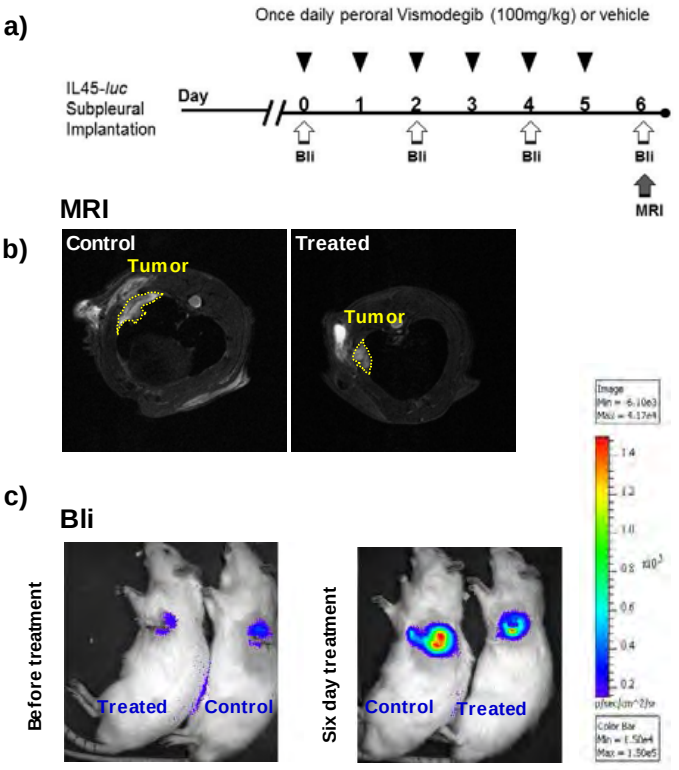
The prognosis for Malignant Pleural Mesothelioma (MPM), an aggressive tumor associated with asbestos exposure, is poor without treatment. Multimodal therapy, a combination treatment including chemotherapy followed by surgery, provides better outcomes, but a significant number of patients do not profit from the treatment. This reflects disease heterogeneity and highlights a need for biomarkers predicting outcomes and treatment effectiveness. In this project, we provided information underlining a prognostic significance of NF2 expression loss in MPM.
Outlook: We will confirm this finding in an independent MPM cohort via collaboration with Brigham and Women's Hospital, Boston.



Kaplan-Meier survival curves according to dichotomized expression of cytoplasmic NF2. High expression of cytoplasmic NF2 in associated with a prolonged OS **(A)** *and PFS* **(B)**. *CTX=Chemotherapy, OS=Overall survival, PFS=Progression free survival.*

Exploring Novel Treatment for Malignant Pleural Mesothelioma: Effects of Hedgehog Antagonist in an Orthotopic Malignant Pleural Mesothelioma Rat Model

I. Opitz, M. Meerang, K. Bérard, M. Friess, B. Bitanihirwe



Daily treatment with vismodegib effectively reduced tumor volume and growth *in vivo*.

a) Experimental scheme of orthotopic rat MPM model and the treatment with vismodegib.

b) Tumor volume visualized by magnetic resonance imaging (MRI) performed at the last day of treatment (day six)

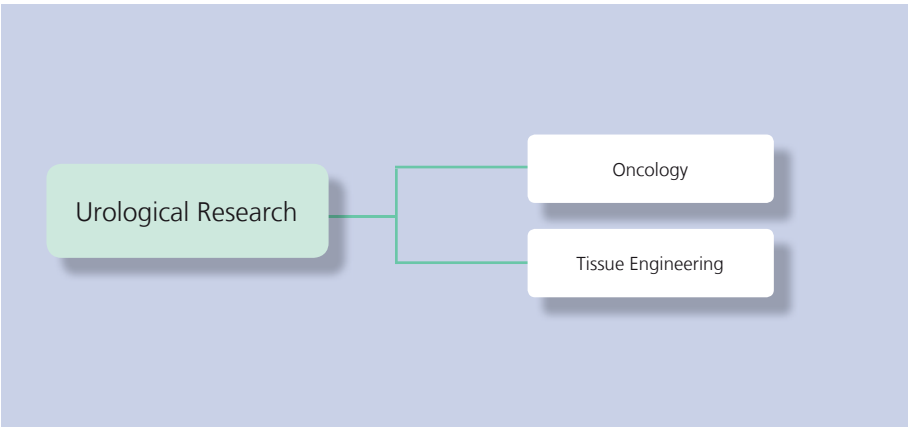
c) Tumor growth monitored by bioluminescence (Bli) before the treatment started and at the last day of treatment.

The Hedgehog signaling pathway has been found to be activated in Malignant Pleural Mesothelioma (MPM) and was associated with poor prognosis. We investigated the efficacy of Vismodegib, a FDA approved hedgehog antagonist, in a pre-clinical rat model of MPM. The treatment with Vismodegib reduced tumor volume potentially by modulating MPM stroma.

Collaborations:

- Prof. Dr. R. Stahel, PD Dr. E. Felley-Bosco, Labor für Molekulare Onkologie, UniversitätsSpital Zürich
- Dr. S. Gray, Translational Cancer research Group, Trinity Centre for Health Sciences, Institute of Molecular Medicine, St. James's Hospital, Dublin, Ireland
- Prof. Dr. H. Moch, PD Dr. A. Soltermann, Dr. B. Vrugt, Institut für klinische Pathologie, UniversitätsSpital Zürich
- Prof. Dr. M. de Perrot, Dr. G. Allo, Dr. M. Tsao, Division of Thoracic Surgery, Toronto General Hospital and Princess Margaret Hospital, University of Toronto, Toronto, Canada
- Dr. V. Serre Beinier, Département de chirurgie, Université de de Genève
- Prof. Dr. W. Klepetko, Dr, M. Hoda, Division of Thoracic Surgery, Medical University Vienna
- Prof. Dr. R. Bueno, Department of Surgery, Brigham and Women's Hospital, Boston
- Dr. A. Jetter, Institut für Pharmakologie und Toxikologie, UniversitätsSpital Zürich
- Prof. Dr. D. Günther, Labor für organische Chemie, ETH Zürich
- Prof. Dr. B. Seifert, Department of Biostatistics, Epidemiology, Biostatistics and Prevention Institute, University of Zürich
- PD Dr. T. Frauenfelder, Dr. D. Nguyen-Kim, Institut für diagnostische Radiolgie, UniversitätsSpital Zürich
- Prof. Dr. M. Pruschy, Dr. A. Broggini-Tenzer, Institut für molekulare Radiologie, UniversitätsSpital Zürich

2.6 Urological Research




PD Dr.
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Damina Balmer,
Scientific
Coordination

2.6.1 Oncology

The relationship between the humoral and cellular immune response against polyomavirus BK (BKPyV) and the development of prostate cancer (PCa)

E.X. Keller, M. Provenzano

By characterizing preoperative humoral and cellular immune responses against the BKPyV main regulatory protein LTag in PCa patients undergoing radical prostatectomy, we found an unprecedented epidemiological evidence to support an association between BKPyV infection and the clinical course of the disease. Our next goal is to define the role of the virus in the development of PCa by evaluating definite immune responsiveness to LTag during the follow-up after prostatectomy.

The prognostic value of correlations between lymphangiogenesis, cancer metastasis and tumor staging in bladder cancer

C. Poyet, M. Provenzano

We aim at defining the role of lymphangiogenesis in bladder cancer for both diagnostic and therapeutic purposes. So far, we have found that overexpression of VEGF-D in the serum of patients predicts a nodal positive disease in invasive bladder cancer. The evaluation of the expression of lymphangiogenesis specific markers in this malignancy and their clinical implementation may be valuable in the identification of high-risk patients with more invasive or nodal positive diseases.

Prostate cancer related tumor derived soluble factors (PCa-TDSFs) in urine of PCa patients

T. Schmidli, M. Provenzano

The detection of factors involved in PCa development in the urine of patients might contribute to the discrimination between indolent and aggressive tumors. By testing their gene expression levels in the urine of 15 patients undergoing the first prostate needle biopsy for PCa diagnosis, we found an interesting and significantly higher expression of factors involved in tumor immune escape and tumor progression in the patients bearing PCa positive biopsies. If validated in additional cancer biomarker studies, these factors may allow for better preoperative treatment decisions.


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Collaborations:
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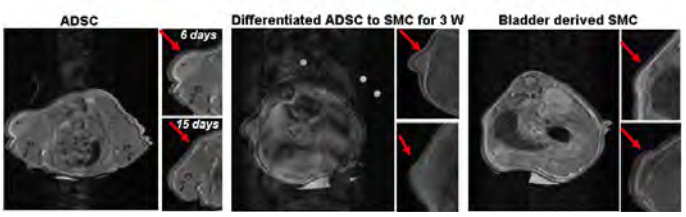
- Institute for Surgical Research and Hospital Management, Oncology section, University Hospital of Basel
- Department of Biomedical, Surgical and Dental Sciences, University of Milan, Italy
- Institute of Pharmaceutical Sciences, ETH, Zürich

2.6.2 Tissue Engineering for Urologic Tissue

Differentiated Adipose Derived Stem Cells for Functional Smooth Muscle Bioengineering

S. Salemi, D. Keller, D. Eberli

Adipose derived stem cells might be a key instrument to bioengineer contractile bladder tissue when differentiated to smooth muscle cells. However, it is uncertain whether these cells maintain their cell fate long term *in vivo*. It is our aim to evaluate different combinations of cells to improve the bladder tissue formation, by improving the microenvironment and cell-to-cell interactions.

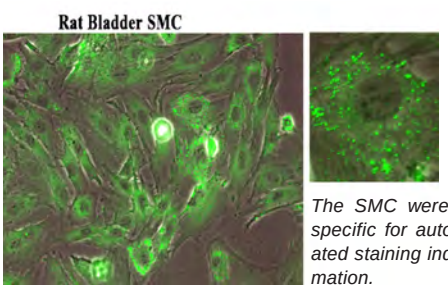


MRI scanning of injected rat ADSCs, engineered cells in vivo. ADSC differentiated for 3 weeks and bladder derived SMCs. The cells were tracked by MRI after 5 and 15 days of injection. The arrow indicates cellular bulge under the skin of nude mice.

The Role of Autophagy during the Differentiation of Adipose Derived Stem Cells to Smooth Muscle

S. Salemi, D. Eberli

As autologous smooth muscle cells (SMC) cannot be harvested from organs with end-stage disease and tissue regeneration requires large amount of functional SMC, there is urgent need for other cell sources. Adipose derived stem cells (ADSC) are suitable cell source for SM tissue engineering. We investigated the functional role of autophagy during differentiation and remodeling of ADSCs to SMC *in vitro*.

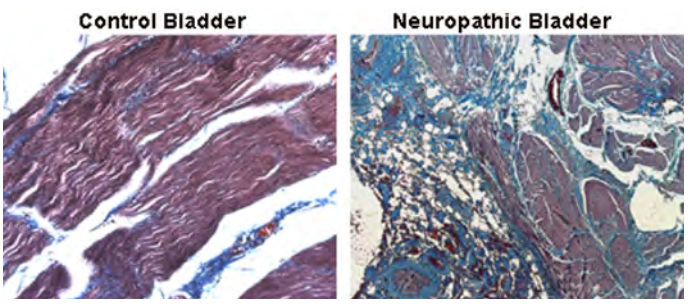


The SMC were stained with autodot dye specific for autophagy. The green punctuated staining indicates autophagosome formation.

Remodeling and optimization of bladder smooth muscle cells for functional bladder engineering in children with neuropathic disorders

S. Salemi, D. Eberli

Neurogenic bladder dysfunction is the result of disease or injury to the neural pathways and commonly occurs in patients with meningomyelocele or after spinal cord injury. We hypothesize that autophagy may play an important role in remodeling of bladder smooth muscle cells in children with neuropathic bladder.



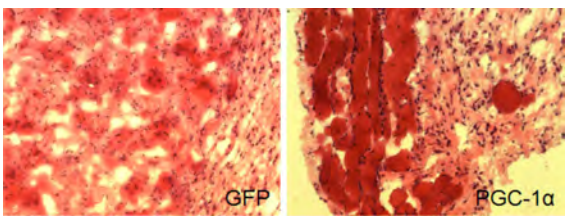
Masson's Trichrome staining of normal and neuropathic bladder. Collagen fibers stained in blue and muscle stained in red.

Collaborations:
- Prof. Rita Gobet, Division of Pediatric Urology, University Children's Hospital Zurich
- Prof. Hans Uwe Simon, Pharmacology Institute, Bern

The effect of PGC-1α on bioengineered muscle tissue formation

D.Haralampieva, S.Salemi, I.Dinulovic, C.Handschin, D.Eberli

In this project we analysed the impact of PGC-1α-genetically modified human muscle precursor cells on muscle tissue bioengineering. The cells were obtained from human *rectus abdominis* muscle biopsies, expanded in culture, infected with PGC-1α adenoviruses and injected subcutaneously on both sides of the back of nude mice for investigation of *ex situ* muscle tissue formation.



Ex situ bioengineered muscle tissue, showing enhanced muscle fiber formation in samples overexpressing PGC-1 α after 1 week.

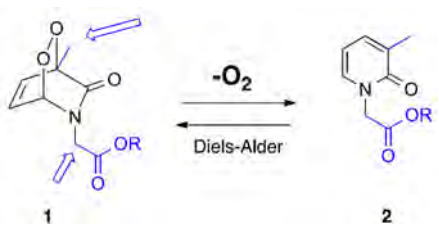
Collaborations:

- Prof. Dr. Simon M. Ametamey
- Dpt. Pharmaceutical Sciences, ETHZ, Zurich, Switzerland
- Prof. Dr. Christoph Handschin
- Biozentrum Basel, Basel, Switzerland

Tailor-made polymeric endoperoxide conjugate scaffolds for controlled oxygen delivery in regenerative medicine

S. Nötzli, D. Eberli

The goal of this joint project of chemistry and specialized medicine is to develop a polymer / biomaterial, which releases oxygen over a longer period of time. Thus necrosis would be reduced and the first critical growth phase of larger tissue implants better overcome before they are enough innervated with new vessels. We are continuously optimizing the chemical structures, conducting promising *in vitro* experiments und normoxic and anoxic conditions as well as about to establish an appropriate animal model.



*Pyridone endoperoxides **1** can release oxygen in aqueous environment over many hours. This process initially releases singlet oxygen and the parent pyridone **2**. Important positions in order to stabilize the endoperoxide are indicated in blue.*

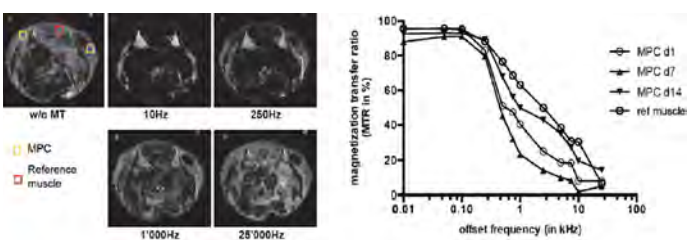
Collaborations:

- Prof. Dr. Jay Steven Siegel, Tianjin University, China
- Dr. Henning Jacob Jessen, Department of Chemistry, University of Zurich, Switzerland

In vivo characterization of differentiating muscle precursor cells applying multi-modal molecular imaging

M. Rottmar, D. Keller, M. Wurnig, A. Boss, D. Eberli

Tissue engineering therapies utilizing muscle precursor cells (MPC) may provide alternative treatments for diseases such as urinary sphincter dysfunction. A central concern associated with the use of any cell source for tissue engineering is the non-invasive monitoring of *in vivo* tissue formation. In this project we apply magnetic resonance imaging (MRI) to directly assess muscle fiber formation.



MT during myogenic in vivo differentiation. *MR-images without and with MT-pulse at increasing offset frequencies and development of MT for a range of offset frequencies during 2 weeks post-injection of MPCs.*

Collaborations:

- PD Dr. med. Andreas Boss, Institute for Diagnostic and Interventional Radiology, USZ

2.7 Cranio-Maxillofacial Surgery Research

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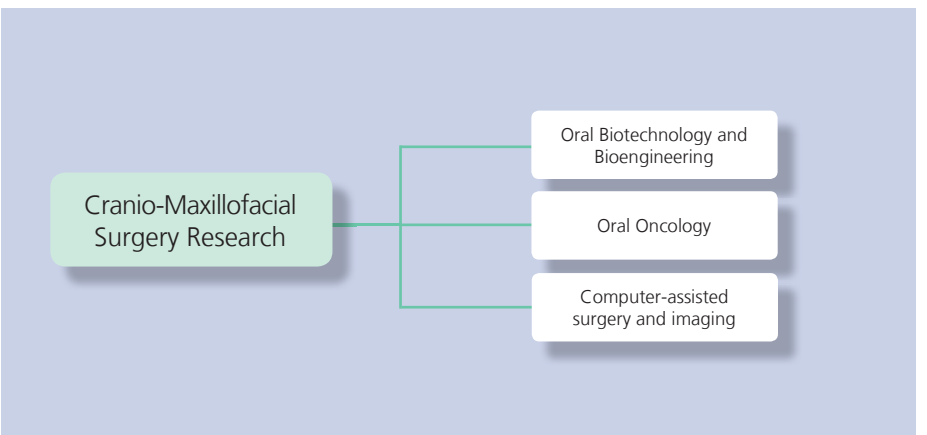


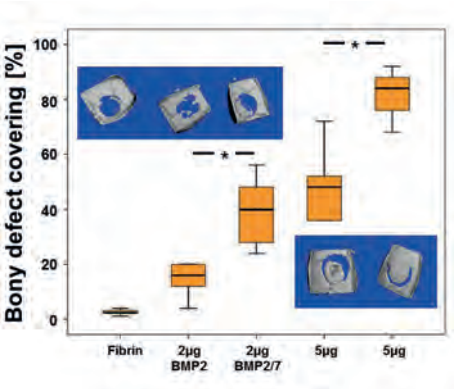
2.7.1 Oral Biotechnology and Bioengineering

Bone, cartilage and tooth regeneration

F. Weber, Ch. Ghayor, N. Roungsawasdi, B. Gjoksi, B. Siegenthaler, O. Schätti, A. Tchouboukov, Y. Bloemhard

Osteoinduction for bone regeneration

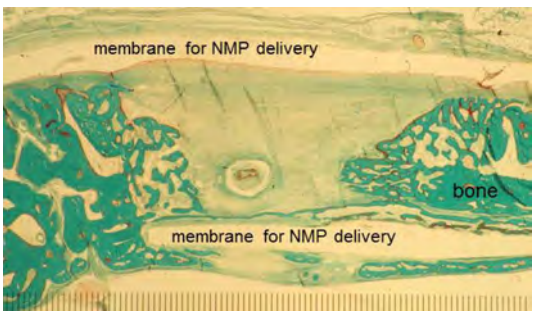
Bone morphogenetic proteins (BMPs) are hetero- or homodimers deposited in bone and responsible for osteoinduction. Despite the fact that BMP are clinically used there is still a need for the reduction of the BMP dosage to limit various side effects. To that end we have engineered a BMP2/7 heterodimer which covalently binds to fibrin hydrogels and were able to show that this heterodimer induces bone regeneration at a third of the normal dose of the BMP2 homodimer.



Healing of critical size calvarial defects in the rat. The ability of BMP2 and BMP2/7 in fibrin matrices to promote healing. The area of the defect filled with calcified tissue after 35 days of healing shown along with µCT (upper panel).

Epigenetically active small chemicals in bone regeneration

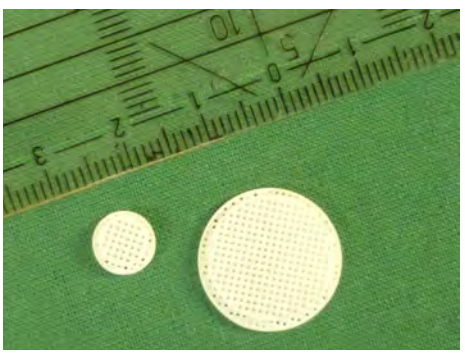
Heritable changes in gene expression or cellular phenotype not linked to changes in the underlying DNA sequence are studied in epigenetics. Acetylations are one kind of heritable changes. At present high affinity inhibitors of readers of acetylations are in clinical trials. The small chemical N-methyl pyrrolidone (NMP) is a low affinity inhibitor for reading acetylations. We have shown that NMP is an enhancer of bone regeneration and reduces osteoclast maturation and osteoclast activity and therefore bone degradation. At present we test the efficiency of NMP for the treatment and prevention of osteoporosis and test scaffolds for the delivery of NMP *in vivo*.



Polylactide/Glycolide based membrane for the delivery of NMP. Non critical size defects were created in the calvarial bone of rabbits and a membrane releasing NMP was used to enhance bone regeneration.

Osteoconductive bone substitute materials

Bone substitute materials are developed to substitute for the use of autologous grafts, which are associated with a second site of surgery, morbidity, pain and additional discomfort for the patient. Since bone is mainly composed of hydroxyapatite the majority of synthetic bone substitute materials contain 60-80% hydroxyapatite. In a SNF funded project our group together with Prof. M. de Wild (Fachhochschule Nordwestschweiz) and Prof. H. Man and Prof. M. Savalani (Hong Kong Polytechnic University, Kowloon) we characterize and develop novel osteoconductive bone substitute materials including titanium, magnesium and calcium phosphate based 3D scaffolds.



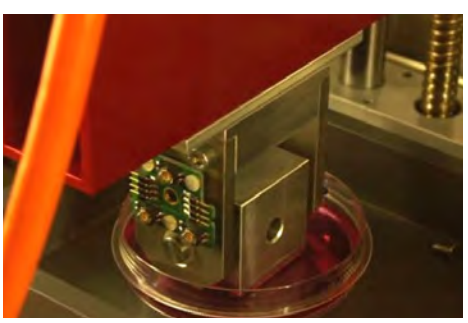
Calcium phosphate based degradable scaffolds produced by additive manufacturing.

Biomimetic nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative disc disease

The main objective of this EU-project is to develop a biomimetic substitute for the nucleus pulposus for immediate and short term treatment. The synthetic scaffold will be integrated with a bioactive-nano-polymer highly potent in supporting Nucleus Pulposus cells (EPCs) for long-term cure. In addition growth factors will be integrated into the material in a way so that their release suits the needs of this avascular site.

Mechanobiology of cartilage and cartilage tissue engineering

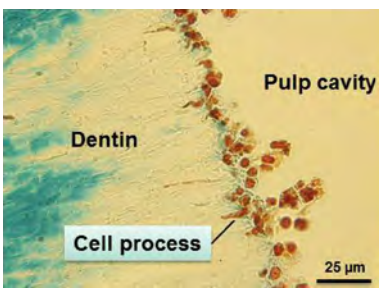
Degenerative joint disease (DJD) of the temporomandibular joint (TMJ) afflicts up to 10% of people with temporomandibular disorders (TMD). Objective of this project is a more specific analysis of the effect that different rolling/plowing conditions have on chondrocyte metabolism.



Static loading of cartilage samples as control for ploughed cartilage treated by the same machine.

Pulp regeneration

Regeneration of dental tissues is in direct competition to the placement of dental implants. Among the regenerative dental procedures, revascularization of a necrotic pulp space appears to be the treatment option that holds the most promise for the immediate future. The goal of this project is to establish a new soft tissue in the pulp space that is capable of continuing hard tissue formation. This project is based on our vast experience in hydrogels and growth factor delivery and on a close collaboration to clinical partners at the ZZM (Prof. Matthias Zehnder and Prof. Thomas Attin).



Cells exposed to dentin extend cell processes and appear odontoblast-like.

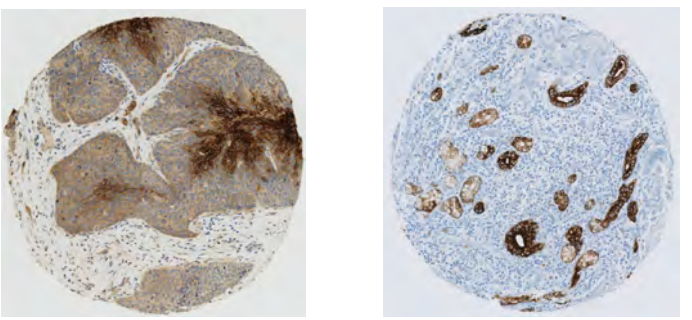
2.7.2 Oral Oncology

M. Bredell, D. Zweifel, D. Schumann, J. Ernst

Head and Neck Oncology:

Patients with hypoxic tumors have been shown to have a poorer prognosis than patients with a well oxygenated tumor. Knowledge of the tumors hypoxia status will assist in optimal treatment of Head and Neck Cancer. In a multidisciplinary project, several translational studies have been established with the goal to determine tumor oxygenation in a non-invasive manner. Two retrospective studies have been approved, a large clinical database has been built and multiple biomarkers have been correlated with clinical data. A new comprehensive tissue microarray (TMA) for tongue cancer patients has been developed and a second TMA for head and neck cancer is under construction.Anemia (<12g/dl) was confirmed as a negative predictor, and diabetes was shown to be a positive predictor for overall survival.

Various biomarkers have been identified that play a role in the hypoxia process and predict certain histological features. Some of the biomarkers also seem to be predictive for poor prognosis within subgroups of traditionally good prognosis patients.
A prospective clinical study with the aim to observe and verify the role of established and novel imaging methods in determining tumor oxygenation has been designed and approved in 2014 and patient recruitment has started. In this unique study, various MRI sequences and PET-CT will be correlated with tissue microdialysis, tissue histology and a panel of innovative biomarkers as well as saliva and serum factors in the quest to establish non-invasive methods to determine tumor hypoxia.



Expression of CCIX (left) and CK19 (right) in squamous cell carcinoma of the tongue.

2.7.3 Computer-assisted Surgery (CSS)

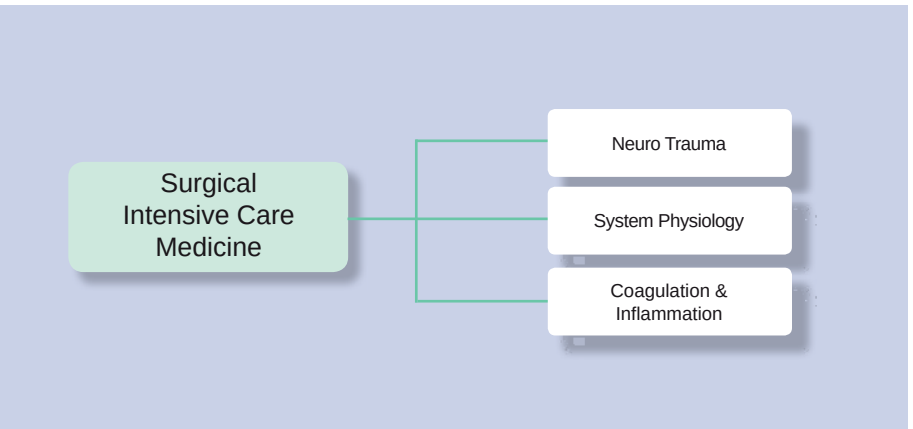
M. Rücker, H. Essig, P. Schumann, T. Gander

Enhancing CAS is a focus in the area of clinical research. In doing so, three core problems take center stage: first, existing limitations in pre-surgery digital planning, secondly, automating processes within the workflow for computer-assisted surgery as regards planning and quality control and, thirdly, the implementation of patient-specific implant and osteosynthesis material design, which is still very laborious. In our CAS research group, a statistical shape model is currently being developed that should also enable a patient-customized digital reconstruction of complex deformities. The close collaboration within the Center of Dental Medicine is of exceptional significance for the special consideration of dental occlusion. In the imaging / navigation area, apart from the quantitative assessment within quality assurance, there is an additional focus on the development of a partially automated planning platform for customized surgical treatment for reconstructions of sustained and congenital deformities.

Collaborations:

- Department of Fixed and Removable Prothodontics and Dental Material Science, University of Zurich, Switzerland (Prof. Ch. Hämmerle, Prof. Dr. Ronald Jung, PD Dr. Daniel Thoma).
- Division of Preventive Dentistry, Periodontology, and Cariology, University of Zürich Center of Dental Medicine, Zurich, Switzerland (Prof. T. Attin, Prof. M. Zehnder, Prof. P. Schmidlin).
- Department of Masticatory Disorders, University of Zurich, Switzerland (Prof. L. Gallo)
- Division of Obstetrics (Prof. R. Zimmermann, Dr. Martin Ehrbar).
- EPFL Institute of Bioengineering (Prof. M. Lütolf).
- ETH Zürich, Department of Chemistry and Applied Biosciences (Prof W. Stark).
- ETH Zurich, Cartilage Engineering + Regeneration (Prof. M. Zenobi-Wong).
- Universität Hongkong (Prof. R. Zwahlen).
- AO Research Institute, Davos Switzerland (Prof. M. Alini).
- Surgical Planning Laboratory, Brigham & Women's Hospital, Harvard Medical School, Boston (MA), USA
- VU University Medical Center, Amsterdam (Netherlands) (Dr. M. Helder, Prof. Th. Smit).
- University of Sheffield (UK) (Prof. Ch. Sammon).
- Hong Kong Polytechnic University Kowloon (Prof. H. Man).

2.8 Surgical Intensive Care Medicine




Dr.
Peter Steiger,
MD


PD Dr.
Reto Schüpbach,
MD, M.Sc.


PD Dr.
Markus Béchir,
MD

2.8.1 Neuro Trauma

P. Steiger, G. Brandi , St. Klinzing

The research group Neurotrauma focuses on how to monitor cerebral blood flow in severe neurotrauma patients, since the main therapy aim is optimization of cerebral perfusion.

Project 1
CO2 reactivity detected by transcranial colour-coded duplexsonography and risk for hyperventilation induced ischemia in traumatic brain injury.

Hyperventilation is a recommended rescue therapy in case of elevated intracranial pressure in patients with traumatic brain injury. Hyperventilation reduces cerebral blood volume, leading to an efficient reduction of intracranial pressure –with a potential risk to cause cerebral ischemia as a result of vasoconstriction. This issue is addressed by a controlled moderate hyperventilation and assessment of surrogates for ischemia such as reduced brain tissue oxygen pressure and markers in cerebral microdialysis. Transcranial colour-coded duplex sonography allows measurement of flow velocities in the basal cerebral arteries, allowing an estimation of cerebral blood flow. Its applicability for detection of hyperventilation induced changes is investigated.

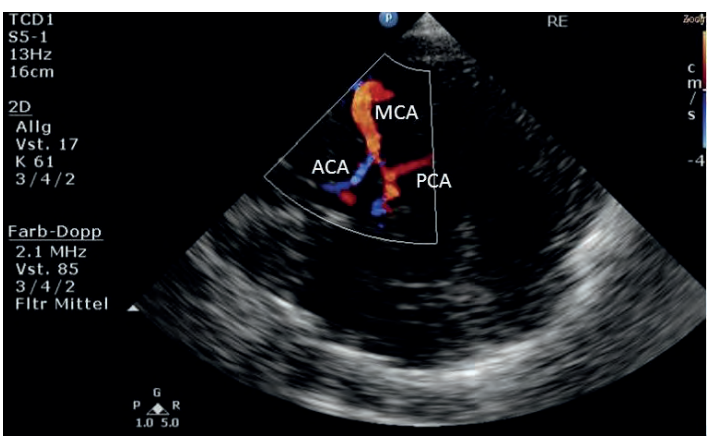


Figure 1: TCCD image of the circle of Willis. MCA middle cerebral artery; ACA anterior cerebral artery, PCA posterior cerebral artery.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Dr.
Jerzy Madon


Renato Lenherr

Postdoctoral Fellows and Students


Dr.
Alessandro
Franchini,
PhD


Dorothea
Heuberger,
PhD Student


Laura
Vazquez Rojo,
MS Student


Dr.
Giovanna
Brandi,
MD

Project 2:
Pharmacokinetics of Daptomycin in patients after burn injuries

Pharmacokinetics are altered in patients after burn injuries. Therefore, dosing recommendation that are valid for nonburn patients may not be directly applicable to burn patients. In order to avoid underdosing of daptomycin, an antibiotic against gram-positive organism, we will measure the pharmacokinetic in blood and soft tissue (by microdialysis) after a single dose of daptomycin in burned patients at 3 different periods of time during their course of disease.

2.8.2 System Physiology

M. Béchir (since 2/2013 Research Associate), P. Stehberger, B. Zoller

Rational appliance of therapeutic efforts is expected to improve outcome in critically ill patients. The group of M. Béchir searches for treatment options in which expert recommendations are directly contradictive or elusive. The team analyzes either prospectively or retrospectively which of treatment options should preferentially be prescribed in critically ill patients.
In burn patients, vascular leakage requires intravascular volume replacement. So far it was controversial whether colloids should preferentially be transfused or strictly avoided. Either product has potential advantages. Crystalloids are less expensive and do not contain non physiological molecules whereas colloids are contained for prolonged time within the blood compartment in patients suffering from vascular leakage however might negatively affect clotting and kidney function. In a randomized single centre controlled, double-blind trial, enrolling 48 patients with severe burn injuries fluid replacement by crystalloids only and colloids (6% hydroxyethyl starch 130/0.4) in combination with crystalloids respectively was compared. Outcome was found to be unaffected by the type of fluid prescribed (Table 1).

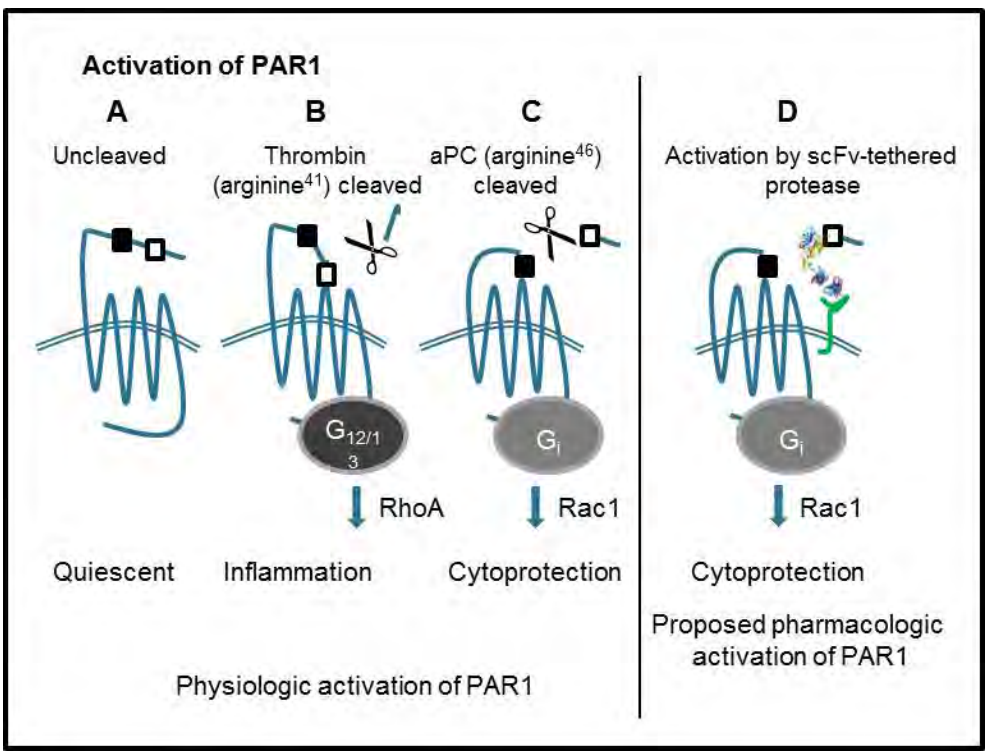
Outcome	HES (n = 23)	Lactated Ringer's (n = 22)	Difference
Primary outcome			
Total volume at days 1–3, mL			−1,213 (95% CI −3,975 to 1,549)
Secondary outcomes			
Creatinine at day 1, μmol/L	77 (66, 99)	74 (55, 90)	
Creatinine at days 1–3, μmol/L			0.4 (95% CI −18.7 to 19.5)
Urinary output at day 1, mL/d	1,360 (1,020, 1,770)	1,430 (970, 2,225)	
Urinary output at days 1–3, mL			−58 (95% CI −400 to 283)
Incidence of ARDS	6 (26.1%)	6 (27.3%)	
Risk ratio for ARDS with HES			0.96 (95% CI 0.35 to 2.64)
28-day mortality	4 (17.4%)	4 (18.2%)	
Risk ratio for 28-day mortality with HES			0.96 (95% CI 0.27 to 4.45)
In hospital mortality	8 (34.8%)	5 (22.7%)	
Hazard ratio for in-hospital death with HES			1.86 (95% CI 0.56 to 6.19)
Length of stay in ICU, days	28 (10, 58)	24 (11, 49)	
Length of stay in hospital, days	31 (18, 58)	29 (14, 61)	

Table1: Group comparison between burn patients receiving fluid replacement consisting of colloids (HES) as compared to the group receiving only crystalloids (lactated Ringer). Data are represented as median (25th and 75th percentiles) or number of patients (percentage) or risk ratio (confidence interval) or hazard ratio (confidence intervals, or CIs). Group comparison revealed no significant differences for any of the parameters analyzed.

2.8.3 Coagulation and Inflammation

R. Schüpbach, A. Franchini, J. Madon, D. Heuberger, L. Vazquez Rojo

Project title
Cytoprotection through non Anticoagulant Engineered Chimeric Activated Protein C



Scheme: Activation of PAR1: *Physiologically PAR1 is activated by removal of a short N-terminal peptide. The novel N-terminus serves as a tethered activation ligand.* ***(B)*** *Whereas thrombin cleaves at arginine 41 and uncovers a inflammation inducing ligand (open box) activated protein C (aPC)* ***(C)*** *cleaves at arginine 46 and provides a cytoprotective ligand (black box).* ***(D)*** *Proposed mechanisms for pharmacological activation of PAR1 via scFv tethered aPC. (endothelial protein C receptor; EPCR; green).*

The research efforts of our group aim to understand clotting protease dependent pro- and anti-inflammatory pathways in more detail in order to identify targets for treating inflammatory driven diseases in clinics. We recently discovered that the protease activated receptor 1 (PAR1), a major extracellular receptor sensing for clotting protease activity harbors two distinct cleavage sites for receptor activation. Cleavage at arginine 41 causes the receptor to mediate proinflammatory stimuli whereas our newly discovered cleavage site at arginine 46 activates PAR1 towards protective, anti-apoptotic and vascular barrier protecting pathways (Scheme 1a-c). This novel finding directly links clotting proteases to pro- and antiinflammatory pathways and opens up therapeutic options on how PAR1 could be pharmacologically used in inflammatory driven diseases such as sepsis.

Collaborations:
- PD Dr. A. Zinkernagel, Klinik für Infektionskrankheiten und Spitalhygiene, UniversitätsSpital Zurich, Switzerland.
- Prof. Dr. A. Oxenius, Institute of Microbiology, ETH Zurich, Zurich, Switzerland.
- Prof. Dr. M. Riewald, Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, USA.

2.9 Animal Welfare in Biomedical Research

PD Dr.
Margarete Arras,
DVM

Dr.
Nikola Cesarovic,
DVM, PhD

Flora Nicholls,
Dipl. biol.

Dr.
Miriam Lipiski,
DVM

Dr.
Paulin Jirkof,
PhD

Dr.
Thea Fleischmann,
DVM

Mareike Sauer,
cand. vet med.

To ensure high-quality scientific outcomes and humane treatment of laboratory animals reliable alleviation of post-operative pain is essential. Therefore a wide range of effective analgesia protocols for laboratory rodents are developed and validated by our group.

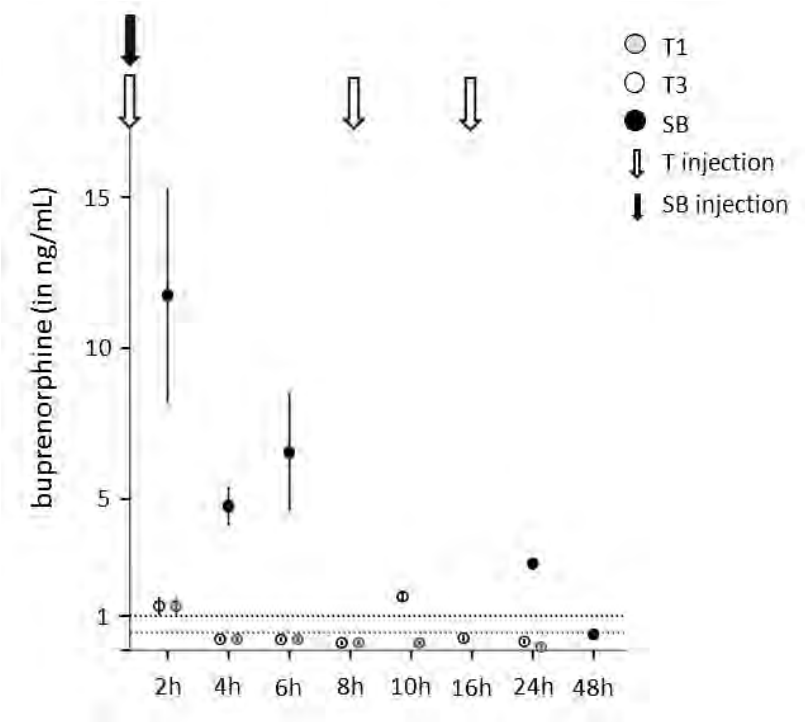
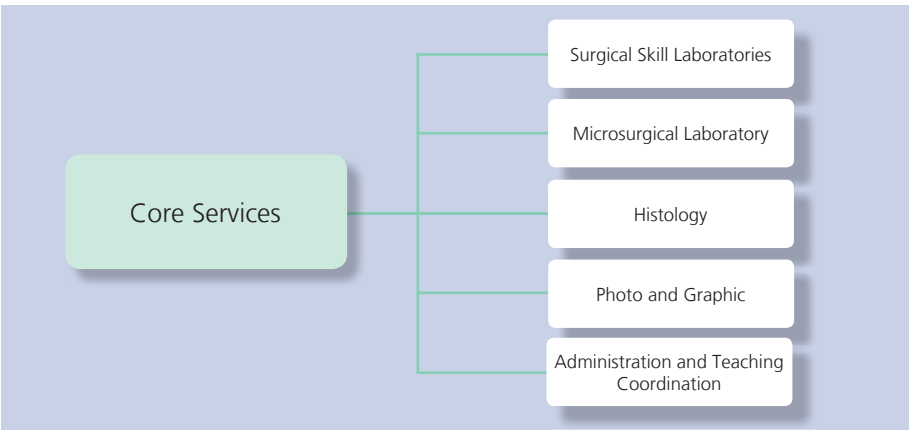


Figure 1: Characterization of an in-house developed sustained-release formulation of buprenorphine for analgesia in mice: Mean (+/-SEM) serum concentration of buprenorphine in mice given either Temgesic (T1, commercially available water-soluble buprenorphine) or sustained-release buprenorphine (SB) at the time points shown. T3 animals were injected with Temgesic every 8 h. Effective levels in humans and rodents (0.5 - 1 ng/ml) are indicated by grey dotted lines.
The sustained-release formulation offered a sound relief of post-surgical pain for 24-48 hours without causing additional stress to the animal. In contrast, commercially available water-soluble buprenorphine showed less than 8 hours of analgesia while the frequent injections required for this treatment protocol induced substantial stress, shown by significant reduction of food intake and body weight.

Collaborations:

- Alain Rudiger, Department of Anesthesiology, UniversityHospital Zurich
- Annemarie Lang, Clinic for Rheumatology and Clinical Immunology, Charite Berlin
- Arnaud Tourvieille, Humanvet, Lausanne
- Daniel Konrad, Stephan Wüest, Department of Pediatrics, Endocrinology, University Children`s Hospital Zurich
- Johannes Vogel, Institute of Veterinary Physiology, Vetsuisse Faculty, University of Zurich
- Knut Husmann, Orthopädische Universitätsklinik Balgrist und Schweizerisches Paraplegikerzentrum, University of Zurich

3. Core Services



3.1 Surgical Skill Laboratories

Surgery requires a number of practical and manual skills that can be trained in skill laboratories. In our facilities which are open to all members of the department we provide a number of tools and machines in a surgical environment. To perform operations under conditions similar to the clinical situation, technical help is provided by our staff which is also responsible for the maintenance of our facilities.

3.2 Microsurgical Laboratory

The microsurgery laboratory is a separate section in which several operating microscopes are available to all members of the department requiring special equipment. Maintenance of this laboratory includes all aspects of preparation of surgical instruments, sterilization and handling of waste materials. In addition, an intravital microscope including video equipment is available. This facility also provides for histological work-up.

3.3 Histology

The laboratory for Histology provides a histological work-up from preserved specimen to sectioning and staining. The laboratory contains an embedding machine, several microtomes, cryostat and staining devices. Several techniques including paraffin embedded, frozen and plastic embedded tissue can be processed.

3.4 Administration

- Administrative office management
- Financial accounting of the Research Divison
- Organisation, planning and coordination of workshops and vocational training
- Workshop, tutorials and seminars
- Quarterly reports
- Meeting organisation and coordination
- Personnel administration

3.5 Teaching Coordination

- Coordination and organization of the learning and teaching units in the Department of Surgery from 1st to 6th years of study including lectures and clinical courses in the compulsory part of the curriculum as well as in the electives.
- Coordination, organization of the clinical rotations during the 5th year of study.
- The work is done in cooperation with the University of Zurich and the University-Hospital Zurich for the Department of Surgery.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Corinne Renold,
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Surgical
Research

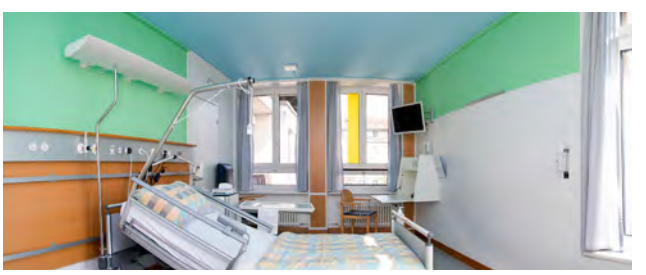

Susanne
Frehner,
Administration
Division of
Surgical
Research

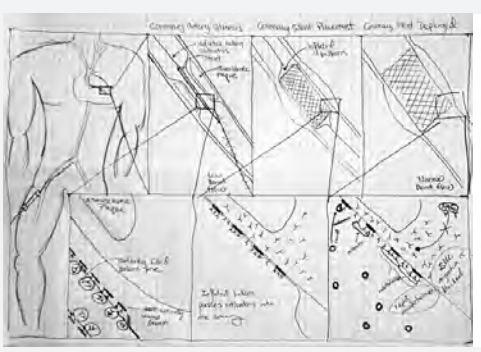
3.6 Photo and Graphic Services

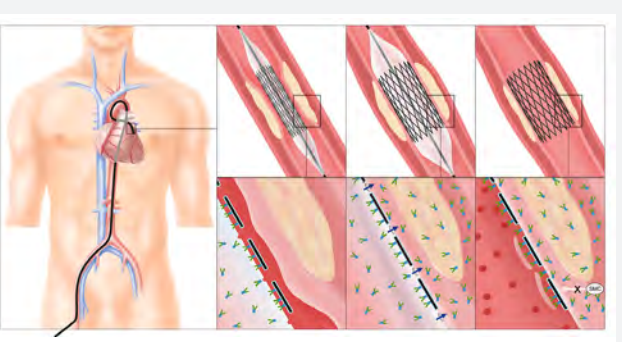
A quick, flexible, versatile and professional service.

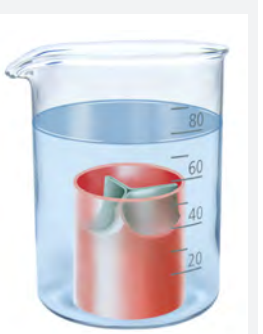
We offer

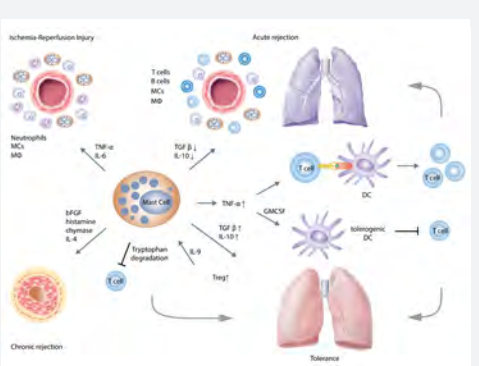
- photographic documentation of patients and events
- technical photography, on location or in our studio
- graphic and design of illustrations for papers and books
- reproduction and digitalization of any original
- layout of printing matters
- preparation of files for external printing
- print service
- cutting and converting of video-files for presentation and web
- construction and maintainance of websites
- maintainance of the digital image archives

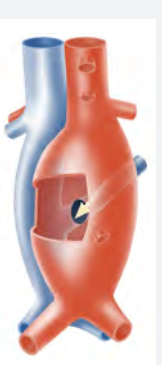


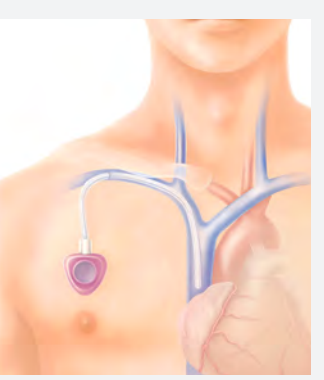


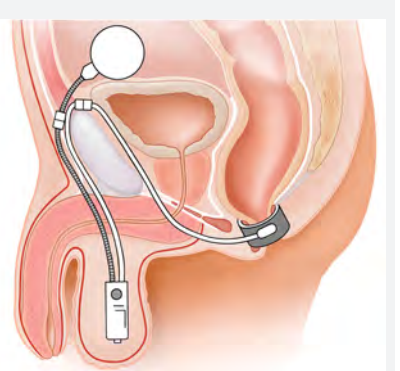








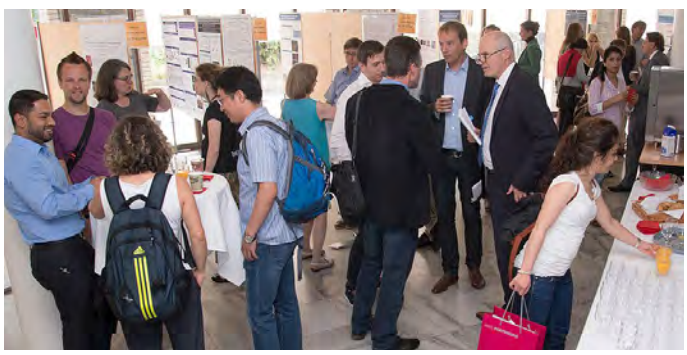




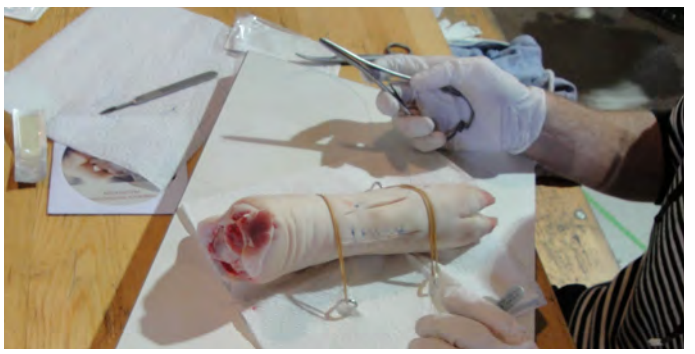
4. Events and Workshops at the Division of Surgical Research 2014

Turkish-Swiss Clinical Research Exploratory Workshop, January 24

13th Day of Clinical Research, June 12



Surgical Suture Skills Course, USZ, April 11



Surgical Suture Skills Course, Winterthur, May 21

CTC Symposium, November 6

Lab Retreat, Vulpera, January 10 - 12

Christmas Party, December 19

5. Publications 2014

Cardiovascular Surgery

- Holubcova, Z; Kunes, P; Mandak, J; Kolackova, M; Andrys, C; Krejsek, J; Holubec, T (2014).
  Could pentraxin 3 be a new diagnostic marker for excessive inflammatory response in cardiac surgery?
  Thoracic and Cardiovascular Surgeon, 62(8):670-676.
- Holmannova,D;Kolackova,M;Mandak,J;Kunes,P;Holubcova,Z;Krejsek,J;Vlaskova,D;Andrys,C(2014).
  Inhibitory CD200R and proapoptotic CD95/CD95L molecules on innate immunity cells are modulated by cardiac surgery.
  Perfusion [Epub ahead of print]
- Robotti, F; Franco, D; Bänninger, L; Wyler, J; Starck, Ch T; Falk, V; Poulikakos, D; Ferrari, A (2014).
  The influence of surface micro-structure on endothelialization under supraphysiological wall shear stress.
  Biomaterials, 35(30):8479-8486.
- Pavo, N; Emmert, MY; Giricz, Z; Varga, ZV; Ankersmit, HJ; Maurer, G; Hoerstrup, SP; Ferdinandy, P; Wu, JC; Gyöngyösi, M.;
  On-line visualization of ischemic burden during repetitive ischemia/reperfusion.
  JACC Cardiovasc Imaging. 2014 Sep;7(9):956-8
- Karar, M E; Merk, D R; Falk, V; Burgert, O (2014).
  A simple and accurate method for computer-aided transapical aortic valve replacement.
  Computerized Medical Imaging and Graphics. [Epub ahead of print]
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- Gessat, M; Hopf, R; Pollok, T; Russ, Ch; Frauenfelder, T; Sündermann, S H; Hirsch, S; Mazza, E; Székely, G; Falk, V (2014).
  Image-based mechanical analysis of stent deformation: Concept and exemplary implementation for aortic valve stents.
  IEEE Transactions on Bio-Medical Engineering, 61(1):4-15.
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  Cell therapy, 3D culture systems and tissue engineering for cardiac regeneration.
  Advanced Drug Delivery Reviews, 69-70:254-269.
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  Comparison of NOGA endocardial mapping and cardiac magnetic resonance imaging for determining infarct size and infarct transmurality for intramyocardial injection therapy using experimental data.
  PLoS ONE, 9(11):e113245.
- Starck, Ch T; Becker, J; Fuhrer, R; Sündermann, S; Stark, J W; Falk, V (2014).
  Concept and first experimental results of a new ferromagnetic assist device for extra-aortic counterpulsation.
  Interactive Cardiovascular and Thoracic Surgery, 18(1):13-16.
- Chaykovska, L; Zientara, A; Reser, D; Weise, A; Reichert, W; Hocher, B (2014).
  Development and validation of a macroarray system - MutaCHIP ARTERO - for the detection of genetic variants involved in the pathogenesis of atherosclerosis.
  Clinical Laboratory, 60(5):873-878.
- Weber, B; Robert, J; Ksiazek, A; Wyss, Y; Frese, L; Slamecka, J; Kehl, D; Modregger, P; Peter, S; Stampanoni, M; Proulx, S; Falk, V; Hoerstrup, S P (2014).
  Living-engineered valves for transcatheter venous valve repair.
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- Daryadel, A; Bogdanova, A; Gassmann, M; Mueller, X; Zünd, G; Seifert, B; Lehalle, Ch; Frossard, N; Tavakoli, R (2014).
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  Transcatheter aortic valve implantation using anatomically oriented, marrow stromal cell-based, stented, tissue-engineered heart valves: technical considerations and implications for translational cell-based heart valve concepts.
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- Driessen-Mol, A; Emmert, M Y; Dijkman, P E; Frese, L; Sanders, B; Weber, B; Cesarovic, N; Sidler, M; Leenders, J; Jenni, R; Grünenfelder, J; Falk, V; Baaijens, F P T; Hoerstrup, S P (2014).
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Visceral and Transplant Surgery

- Lutz, T A; Bueter, M (2014).
  The physiology underlying Roux-en-Y gastric bypass: A status report. American Journal of Physiology.
  Regulatory, Integrative and Comparative Physiology, 307(11):R1275-R1291.
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- Oberkofler, Ch E; Limani, P; Jang, J-H; Rickenbacher, A; Lehmann, K; Raptis, D A; Ungethuem, U; Tian, Y; Grabliauskaite, K; Humar, R; Graf, R; Humar, B; Clavien, P-A (2014).
  Systemic protection through remote ischemic preconditioning is spread by platelet-dependent signaling in mice.
  Hepatology, 60(4):1409-1417.
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  p21(WAF1) (/Cip1) limits senescence and acinar-to-ductal metaplasia formation during pancreatitis.
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6. Grants 2014

Cardiovascular Surgery

Source	Title of Project	Project Leader
Commission of the European Communities	Living autologous heart valves for minimally invasive implantable procedures - LifeValve	S. Hoerstrup
Commission of the European Communities	Intelligent materials for *in-situ* heart Valve tissue engineering - ImaValve	S. Hoerstrup
EU intra-European Fellowships	Improvement of the clinical applicability of tissue-engineered vascular grafts as new regenerative therapy for children with congenital cardiovascular malformations - LivaGraft	S. Hoerstrup
Swiss National Science Foundation	Prenatal minimally invasive implantation of fetal cell-based autologous living heart valves - a novel approach using naive and amniotic fluid-derived induced pluripotent stem cells	B. Weber
Schweizerische Herzstiftung, Bern	Living Heart Valves for the few	S. Hoerstrup
Schweizerische Herzstiftung, Bern	Imaging based *in vivo* evaluation of human mesemchymal stem cell-based three dimensional microtissues in a unique immunotolerant fetal sheep myocardial infarction model	S. Hoerstrup
ETH Grant	Hyperelastic hybrid membrane for biomimetic blood propulsion	B. Weber
KTI, Bern	Proof of concept: Human FAP-targeting Antibodies as Infarction Prevention Medications	S. Hoerstrup
Kommission für Technologie und Innovation KTI via Hauptgesuchsteller F-42402-04-01	Early detection of microscopic epithelial tumors: *In-vivo* Proof-of-Concept	S. Hoerstrup
Olga Mayenfisch Stiftung	NOGA mapping guided, trans-catheter based intramyocardial transplantation and *in vivo* tracking of human mesenchymal stem cell derived three dimensional microtissues in the porcine heart	S. Hoerstrup
Olga Mayenfisch Stiftung	Assessment of human amniotic fluid-derived stem cell-based tissue engineered heart valves in a murine model - Establishment of a SCID/bg model for the investigation of human stem cell fate *in vivo*	S. Hoerstrup
BioMedical Materials	iValve	S. Hoerstrup
Mäxistiftung und Baugartenstiftung	Tissue engineered hybrid heart valves and interfaces	S. Hoerstrup
Schweizerische Universitätskonferenz	LifeMatrix - Engineered, Dynamically Evolving Living Tissues for Repairing the Child's Heart	S. Hoerstrup
Fonds für Medizinische Forschung	Nogo-A is a negative regulator of CNS angiogenesis – molecular mechanisms and applications in brain tumors.	T. Wälchli
OPO-Stiftung	Nogo-A is a negative regulator of CNS angiogenesis – molecular mechanisms and applications in brain tumors	T. Wälchli
Baasch-Medicus-Stiftung	Nogo-A is a negative regulator of CNS angiogenesis – molecular mechanisms and applications in brain tumors	T. Wälchli
Forschungskredit 2014 (Stiftung für Forschung an der Medizinischen Fakultät)	Improved long-term *in vivo* functionality of stented tissue engineered heart valves	P. Dijkman
Forschungskredit 2014	Development of a murine model for the *in vivo* assessment of orthotopically integrated human bioartificial decellularized heart valves in heterotopically transplanted fully loaded heart grafts	B.Weber
Fonds für Medizinische Forschung	Fabrication and functional performance of human living autologous tissue engineered heart valves based on amniotic fluid cell-derived induced pluripotent stem cells.	B. Weber
Stiftung Forschung 3R	*in vitro* engineering of a dynamic threedimensional atherosclerotic lesion disease model	S. Hoerstrup
Commission of the European Communities	European Clinical Study for Application of Regenerative Heart Valves	M. Hübler
Swiss National Science Foundation	Biomechanische Simulation der katheterbasierten Aortenklappenimplantation	M. Gessat

Cardiovascular Surgery

Philips Electronics North America Co.	Evaluation and development of image-based technologies for cardiovascular therapy	V. Falk
Terumo Europe NV Leuven/Belgium	Oxygenator performance and biocampatibility comparison of two commercially available coated oxygenators and circuits	M. Wilhelm
CardioGard Medical Ltd./Israel	CardioGard: Klinische Studie zur Begutachtung der Sicherheit und der Funktion der CardioGard-Kanüle	Ch. Starck
St Jude Medical Coordination Center BVBA, Zaventem Belgium	Trifecta Durability Study. Studie zur Langlebigkeit von Trifecta	V. Falk
Schweizerische Herzstiftung, Bern	The clinical value of 3D template based planning for percutaneous aortic valve implantation	M. Gessat
Edwards Lifesciences / USA	Carpentier-Edwards / Perimount Magna / Mitral Periocardial Bioprostheses	V. Falk
Valtech Cardio Ltd., Israel	"Valtech Cardinal adjustable Semi-Rigid annuloplasty Ring System for Treatment of Mitral Valve Regurgitation in Open Surgical Repair" and "Valtech V-Chordal adjustable System for chordal repair in Mitral Valve Insufficiency due to leaflet prolaps"	V. Falk
Schweizerische Herzstiftung	CAST (Comprehensive ASsessment of frailty Test) and FORECAST (Frailty predicts death One yeaR after Elective Cardiac Surgery Test) validation study	S. Sündermann
Baugartenstiftung	Project: Zurich Heart	V. Falk
Mäxi-Stiftung	Zurich Heart	V. Falk
Uniscientia Stiftung	Zurich Heart	V. Falk
Edwards Lifesciences	Assessing standard of care and clinical outcomes using the Edwards intuity valve System in an european multi-center, active, post-marked surveillance study	S. Jacobs
Wyss Translational Center Zurich	Zurich LifeMatrix (Engineered, dynamically evolving living tissues for repairing the child’s heart)	K. Schlinkmann

Visceral & Transplant Surgery

Source	Title of Project	Project Leader
Hepatobiliary Laboratory		
SNF Sinergia Grant	Metabolic pathways governing liver carcinogenesis and regeneration	Bostjan Humar, Pierre-Alain Clavien
SNF Bonus of Excellence	Serotonin and regeneration in the normal, old and diseased liver	P.-A. Clavien, Bostjan Humar
Swiss National Science Foundation	Combining portal vein ligation with liver parenchyma transection to accelerate liver regeneration in liver surgery	M. Lesurtel
Swiss National Science Foundation	Reversible portal vein embolization for safer liver surgery and transplantation	M. Lesurtel
Swiss National Science Foundation	Uzbekistan International Cooperation: Transition to Modern Hepato-Pancreato-Biliary Surgery	M. Lesurtel
Swiss National Science Foundation	Establishment of a Morbidity Index to Assess Surgery	K. Slankamenac
Swiss National Science Foundation	Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable Pancreatic Cancer: a randomized multicenter phase III study (NEOPAC study).	P.-A. Clavien
Swiss National Science Foundation	Konditionierung mit volatilen Anästhetika in der Lebertransplantation	S. Breitenstein
Swiss National Science Foundation	Machine liver perfusion for protection from biliary injury	P. Dutkowski
Swiss National Science Foundation	Metal Nanomagnets - towards single cell surgery	B. Beck-Schimmer, P.-A. Clavien
National Institutes of Health (R01DK 092608-01A1)	Intestinal satiation in Roux-en-Y gastric bypass rats: brain mechanisms and sex differences	M. Bueter (Co-Principal Investigator)
ZIHP - Zurich Center for Integrative Human Physiology	Immediate improvement of lipid metabolism, liver and endothelial function after Roux-en-Y gastric bypass (RYGB) surgery in obese humans and rodents	M. Bueter (Co-Applicant)
ETH Zürich as the Swiss Leading House for the SSSTC	Sino-Swiss Science and Technology Cooperation	P.-A. Clavien
Krebsliga Schweiz	Inositol tris-pyrophosphate (ITPP) – treating cancer by increasing oxygen supply	Pierre-Alain Clavien, Bostjan Humar, Perparim Limani
University of Zurich (Klinische Forschungsschwerpunkte)	Non-resectable liver tumors: from palliation to cure	P.-A. Clavien
University of Zurich (Klinische Forschungsschwerpunkte)	Molecular Imaging Network, Zürich	M. Lesurtel / A. Boss
Olga Mayenfisch Stiftung	Versagen der Leberregeneration nach ausgedehnter Leberresektion als Ursache des 'Small-for-Size Syndroms'	K. Lehmann
Sassella-Stiftung	Adjuvant gemcitabitabine versus neoadjuvant gemcitabine / oxaliplatin and adjuvant chemotherapy with gemcitabine in patients with resectable pancreatic cancer	P.-A. Clavien
Sassella Stiftung	ALPPS versus Two- Stage Hepatectomy in colorectal liver metastases (monitoring and translational research)	Michael Linecker
Forschungskredit Candoc	Inositol trispyrophosphate (ITPP) and its anti-hypoxic potential in colorectal metastases of the liver	Perparim Limani
Sassella Stiftung	Myo-inositol trispyrophosphate (ITPP) and its anti-hypoxic potential in colorectal metastases of the liver	Perparim Limani, Bostjan Humar
Pancreatitis Laboratory		
Swiss National Science Foundation	Serotonin regulates secretion and regeneration of pancreatic acinar cells	R. Graf & S. Sonda
Gebert Rüf Stiftung, Basel	PSP and Sepsis	R. Graf & G. Seleznik

Visceral & Transplant Surgery

Waring Foundation	Novel insights into the etiology of pancreatic cancer	R. Graf & S. Sonda
Baugarten Stiftung	Mechanisms of Disease: chronic inflammation and cancer in the pancreas – a potential role for Lymphotoxin signalling	R. Graf & G. Seleznik
Zürcher Krebsliga	Inflammation contributes to the regression of acinar-to-ductal metaplasia (ADM) during pancreatitis	K. Grabliauskaite & S. Sonda
Novartis Foundation	Serotonin regulates cytoskeletal remodeling driving the formation of pancreatic acinar-to-ductal-metaplasia	S. Sonda & E. Saponara
Sassella Foundation	Serotonin regulates cytoskeletal remodeling driving the formation of pancreatic acinar-to-ductal-metaplasia	S. Sonda & E. Saponara

Trauma Surgery

Source	Title of Project	Project Leader
Novartis Stiftung für Biologisch-Medizinische Forschung	The role of Pramel7 in chromatin remodeling during the switch from pluripotency to differentiation	P. Cinelli
Theodor und Ida Herzog-Egli Stiftung	The switch between pluripotency to differentiation: The role of Pramel7 in embryonic stem cells	P. Cinelli
Edoardo R., Giovanni, Giuseppe und Chiarina Sassella-Stiftung	Role of the PRAME Gene Family in Cancer Stem Cells	P. Cinelli
Empiris Stiftung	Osteoinduktive Faktoren in SH Trauma	P. Cinelli
Stiftung für wissenschaftliche Forschung an der UZH	Trauma Transcriptome	G. Wanner
Synthes GmbH	Humerus Synthes - Zementverschraubungen	H.P. Simmen / C. Werner
Bayer (Schweiz) AG	Xamos-Xarelto in the Prophylaxis of post surgical venous thromboembolism after elective major orthopedic surgery of hip or knee	H.-P. Simmen
Theodor und Ida Herzog-Egli-Stiftung	Prevention of heterotopic ossification - new approaches	H.P. Simmen / C. Werner
B. Braun AG	Randomized, double-blind, controlled clinical trial on the antiseptic efficacy and tolerability of Lavasept 0.04% on acute traumatic wounds	H.P. Simmen / C. Werner
Dr. h.c. Robert Mathys Stiftung	Prevention of heterotopic ossification - new approaches	C. Werner
Synthes GmbH	Klinische Nachkontrollstudie. Proximaler Humerus, Schrauben-osteosynthese medialer Schenkelhalsfrakturen	H.P. Simmen / C. Werner
Emdo Stiftung Zürich	Neue Strategien in der Prävention Heterotoper Ossifikationen	C. Werner
AO Research Fund	Assessment of soft-tissue and periosteal microcirculation in severely open fractures using orthogonal polarization spectral imaging	G. Wanner
SUVA Luzern FG-Zellweger	Knochenmetabolismus	G. Wanner
Stiftung für wissenschaftliche Forschung an der UZH	Genetic profiling of severely injured patients - transcriptomics of inflammation for opening the "window of opportunity"	G. Wanner
CABMM (Center of Applied Biotechnology and Molecular Medicine) UZH	Identification of tenocyte specific markers in the horse	P. Cinelli
Olga Mayenfisch Stiftung	From pluripotency to differentiation: the role of Pramel7 in murine embryonic stem cells	P. Cinelli

Plastic, Hand and Reconstructive Surgery

Source	Title of Project	Project Leader
Swiss National Science Foundation	Cellular and molecular mechanisms of vascular maturation for therapeutic angiogenesis	A. Banfi, Basel; N. Lindenblatt (Co-Applicant)
Swiss National Science Foundation	New vascularization strategies for skin tissue engineering	N. Lindenblatt
Research Grant Olga Mayenfisch Stiftung, Zürich, Schweiz	Effect of fat and adipose-derived stem cells (ADSCs) on vascularisation and nerve regeneration in a new *in vivo* mouse model	N. Lindenblatt
Research Grant Allergan, Irvine, USA	Evaluation of the vascularisation and inflammatory reaction of the silk-based synthethic surgical scaffold SERI *in vivo*	N. Lindenblatt
Hartmann Müller-Stiftung für Med. Forschung	Fat grafting nerve	N. Lindenblatt
Forschung und Nachwuchsförderung der Universität Zürich	Hauttransplantate	N. Lindenblatt
Swiss Life Research Grant, Zurich	Skin grafting and tissue engineering of skin substitutes in burn surgery - what we can learn from nature	N. Lindenblatt
Hartmann Müller-Stiftung für Med. Forschung	Effect of moderate anemia in free vascular tissue transfer	N. Forster
Wolfermann-Nägeli-Stiftung	Sehnenreparatur mit einem reversibel expandierbaren Schlauch - Kaninchenmodell *in vivo*	J. Buschmann
EMDO Stiftung, Zürich	Fabrikation eines Polymerschlauches zur Sehnenreparatur	J. Buschmann
AbMedica, Lainate (Italy)	Sehnenreparatur mit einem reversibel expandierbaren Schlauch - Kaninchenmodell *in vivo*	J. Buschmann
UZH - Matching Funds	CAM Assay für high-field MRI (DFL 1127)	J. Buschmann
Hartmann-Müller Stiftung	Sehnenreparatur unter Zuhilfenahme eines mit PDGF-BB bestückten Degrapol-Rohrs	J. Buschmann
Kurt und Senta Hermann Stiftung	Fabrikation eines Polymer-Trägers: Bioaktivität und Release-Kinetik des Wachstumsfaktors Platelet-Derived Growth Factor-BB (PDG-BB) vom elektrogesponnenen Träger DegraPol ®	J. Buschmann

Thoracic Surgery

Source	Title of Project	Project Leader
Swiss National Science Foundation	The role of CD26/DPP IV and SDF-1 in pulmonary ischemic injury in a mouse	W. Jungraithmayr
Swiss National Science Foundation	Magnetic resonance imaging for the detection of chronic lung allograft rejection in mouse lung transplantation	W. Jungraithmayr (Co-Applicant) Applicant: PD Dr. A. Boss
Swiss National Science Foundation, Förderungsprofessuren	Malignant Pleural Mesothelioma - an integral approach for better outcome	I. Schmitt-Opitz
Hartmann-Müller Stiftung Zürich - 2012	Improvement of ischemia-reperfusion injury in muring lung transplants by stem cells via inhibition of DPP4 (Ges-Nr: 1591)	W. Jungraithmayr
Lungenliga Zürich	Rekonditionierung durch Magensäure geschädigter Lungentransplantate Nicht-Herz-schlagenden Spendern	I. Inci
Lungenliga Zürich	*Ex vivo* reconditioning of donor lungs with inhaled N-Acetyl cysteine after prolonged cold ischemia	I. Inci
Dr. Arnold U. u. Susanne Huggenberger-Bischoff Stiftung zur Krebsforschung (Krebsstiftung)	*In vivo* study of the efficacy of a dual phosphatidylinositol-3-kinase (PI3K)-/mTOR-inhibitor in the treatment of malignant pleural mesothelioma	W. Weder, I. Schmitt-Opitz
Matching Fund UZH 2011	Malignant Pleural Mesothelioma - an integral approach for better outcome	I. Schmitt-Opitz

Thoracic Surgery

Matching Fund UZH 2012	Preclinical investigation of the role of hedgehog signaling on mesothelioma recurrence	I. Schmitt-Opitz
Matching Fund UZH 2011	Prognostic Marker for Malignant Pleural Mesothelioma	I. Schmitt-Opitz
Krebsliga Zürich	Prognostic Marker for Malignant Pleural Mesothelioma	I. Schmitt-Opitz
BECON AG Foundation	Prognostische Marker für das Maligne Pleuramesotheliom	I. Schmitt-Opitz
Vontobel Stiftung	MikroRNAs als prognostische und prädikative Tumormarker für die multimodale Behandlung des malignen Pleuramesothelioms	I. Schmitt-Opitz
Krebsliga Zürich	Activity based protein profiling in human lung cancer biopsies	W. Weder, S. Hillinger, S. Arni
Novartis Pharma AG Basel	Identification and validation of drug targets and biomarkers for COPD/emphysema and other end-stage lung disease	W. Weder, S. Hillinger
Matching Fund UZH 2012	Improvement of ischemia-reperfusion injury in murine lung transplants by regenerative stem cells via inhibition of CD26/DPPIV	W. Jungraithmayr
EMDO-Stiftung 2013, Zurich, Switzerland	Impact of sevoflurane anesthesia on primary graft dysfunction after experimental mouse lung transplantation	W. Jungraithmayr
Universität Zürich, Projektförderung (Abt. I-III)	Suppression of lung tumor growth by CD26/DPP4-inhibition	W. Jungraithmayr

Urology

Source	Title of Project	Project Leader
Swiss National Science Foundation	Adult Muscle Progenitor Cells for the Treatment of Urinary Incontinence	D. Eberli
Swiss National Science Foundation Sinergia funding	Improving human muscle engineering by PGC-1alpha expression and molecular imaging using positron emission tomography (PET).	D. Eberli
Research Grant from “Novartis Stiftung für Biologisch-Medizinische Forschung”	Improving human muscle engineering by PGC-1alpha overexpression	D. Eberli
Max & Hedwig Niedermayer Stiftung	The Role of Autophagy in the Differentiation of Adipose Derived Stem Cells for Functional Smooth Muscle Bioengineering	D. Eberli
Klinischer Forschungsschwerpunkt "Molecular Imaging Network Zurich", *Co-Applicant*	*In-vivo* characterization of differentiating muscle precursor cells applying multi-modal molecular imaging	D. Eberli
Promedica Stiftung, Chur	Improving human muscle engineering by PGC-1 alpha overexpression	D. Eberli
Matching Fund, UZH	Improving human muscle engineering by PGC-1alpha expression and molecular imaging using positron emission tomography (PET).	D. Eberli
Institutional Grant from “Baugarten Stiftung”, Zürich	MPCs for the treatment of urinary incontinence.	D. Eberli, T. Sulser
Fonds zur Förderung des akademischen Nachwuchses (FAN) der ZUNIV	Antitumor effect of Abiraterone and autophagy inhibition in prostate cancer cells	D. Eberli
Helmut Horten Stiftung	The role of autophagy in the differentiation of adipose derived stem cells for functional smooth muscle tissue bioengineering	S. Salemi
Research Grant Innovations-Fond University Zürich for the clinical research project	Focal Therapy for Prostate Cancer	D. Eberli
Research Grant from Hartmann Müller-Stiftung für Medizinische Forschung	Non-invasive monitoring of myogenic *in vivo* differentiation of MPCs by magnetization transfer imaging and 1H magnetic resonance spectroscopy	Markus Rottmar, Andreas Boss

Cranio Maxilla Surgery

Source	Title of Project	Project Leader
Swiss National Science Foundation	The potential of N-methylpyrrolidone to prevent osteoporosis and to enhance bone regeneration	F. Weber
Swiss National Science Foundation	Osteoconductive and osteoinductive customized implants for large mandibular defects	F. Weber
CABMM (UZH) Starting grant	DMA for bone regeneration and inhibition of bone resorption	F. Weber
AO-CMF Grant	Hydrogel-titanium composites for mandibular reconstruction	F. Weber
EU-Grant (FP7-NMP-2009-SMALL-3)	Biomimetic nano-fiber-based nucleaus pulposus regeneration for the treatment of degenerative disc disease	F. Weber for UZH, M. Helder from the University of Amsterdam
Swiss National Science Foundation	Catabolic and anabolic reaction of dynamically loaded chondrocytes under biomimetic conditions	F. Weber from USZ, L. Gallo from ZZM

Intensive Care Unit

Source	Title of Project	Project Leader
Swiss National Science Foundation	Cytoprotection through non Anticoagulant Engineered Chimeric Activated Protein C	R. Schüpbach
Hartmann Müller-Stiftung für med. Forschung	Activation of Protease Activated Receptors by Bacterial Proteases	R. Schüpbach
Fresenius Kabi (Schweiz) AG Stans	Early fluid resuscitation with balanced HES 130/0.4 (6%) in severe burn injury	M. Béchir

Veterinary Services

Source	Title of Project	Project Leader
ECLAM-ESLAV Foundation, London	Characterization of isoflurane and sevoflurane for anesthesia of mice and optimization of balanced anesthesia regimens comprising surgical tolerance	M. Arras
Swiss Federal Food Safety and Veterinary Office (FSVO)	Etablierung von effizienten Schmerzbehandlungsmethoden für die Labormaus	Paulin Jirkof, Margarete Arras

7. Awards 2014

- Simon P. Hoerstrup
  Venture 2014
  Top 2 Ventures, Zurich, Switzerland

- Nicole Lindenblatt
  Götz Preis der Universität Zürich
  “Tissue engineering von Haut - was wir von der Natur lernen können”
  Universität Zürich

- Ekaterina Kachaylo
  Young Investigator Bursary to ILC
  EASL, Vienna, April 2015

- Magda Langiewicz
  Young Investigator Bursary to ILC
  EASL, Vienna, April 2015

- Gitta Seleznik
  UEG Top Abstract Prize
  “Lymphotoxin promotes acinar cell reprogramming and accelerates pre-neoplastic conversion in Kras induced pancreatic tumorigenesis”.
  United European Gastroenterology Week (UEGW), Vienna, 18th-22th October 2014

- Gitta Seleznik
  “Best of EPC” award
  Annual Conference of the European Pancreatic Club, Southampton, 24th – 28th June 2014

- Enrica Saponara
  Young Investigator Award
  Annual Meeting of the Swiss Physiological Society, Fribourg, 9th September 2014

- Isabelle Schmitt-Opitz
  Wissenschaftspreis 2014
  der Gertrud Siegenthaler Stiftung
  Zürich, 26.04.2014

- Lauk O., Hoda MA, de Perrot M., Friess M., Klikovits T., Klepetko W., Keshavjee S., Weder W., Opitz I.
  SGT Preis für die Publikation: „Extrapleural Pneumonectomy after Induction Chemotherapy: Perioperative Outcome in 251 Mesothelioma Patients from Three High-Volume Institutions“
  Bern, 26.11.2014

- Matthias Hilty
  „Best Poster“ Award
  Hämodynamische Untersuchungen
  Kongress der Schweiz. Gesellschaft für Intensivmedizin, Interlaken 29.-31.10.2014

- Wolfgang Jungraithmayr
  1st prize for basic research – Swiss Transplant Research Award 2014
  “Cytokine complex-expanded natural killer cells improve allogeneic lung transplant function via depletion of donor dendritic cells”
  Swiss Society of Transplantation

- Daniel Eberli
  SIWF-Award 2014 für besonderes Engagement in der Weiterbildung
  Schweizerisches Institut für ärztliche Weiter- und Fortbildung SIWF

- Ashkan Mortezavi
  Filling the Gap 2014-2015
  Laufbahnförderungsprogramm medizinische Fakultät der Universität Zürich

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