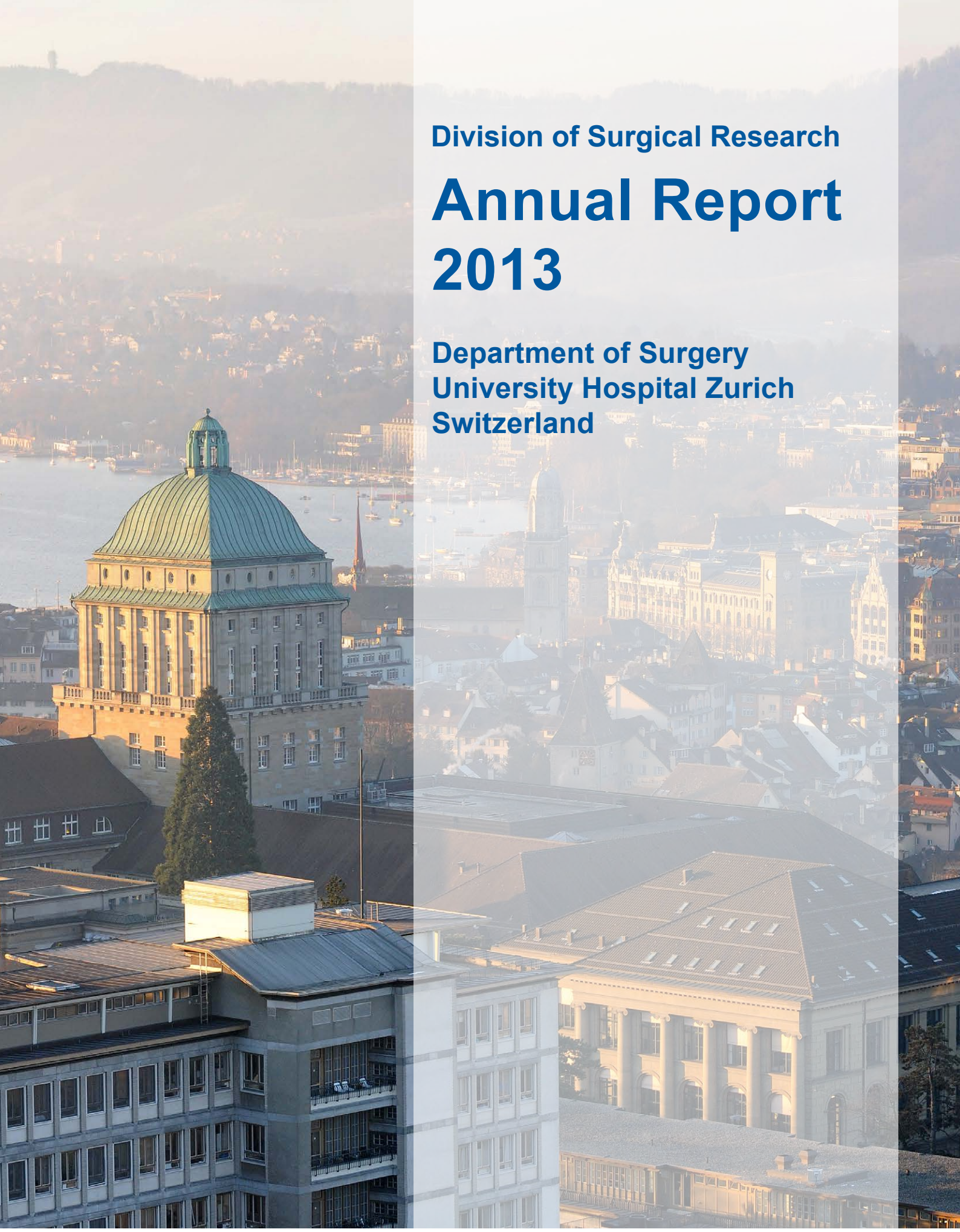


Division of Surgical Research

Annual Report 2013

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 2013 of the Division of Surgical Research at the Department of Surgery, University Hospital Zurich.

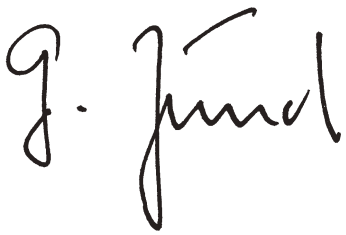
In 2013 major investments of laboratory equipment include the purchase of a real-time PCR System, two homogenizers MagNA Lyser, a NanoDrop spectrometer and a hypoxia chamber. Furthermore, we had to replace some defect equipment and acquired a CO_2 incubator and an ultra-low temperature freezer.

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 one 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 within our Division as well as our research partners of 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



Prof. Dr. Gregor Zünd, MD
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,
MD, PhD
Director Clinic of
Visceral & Transpl.
Surgery

Prof. Dr.
Hans-Peter Simmen,
MD
Director Clinic of
Trauma Surgery

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

Prof. Dr.
Volkmar Falk,
MD
Director Clinic of
Cardiovascular
Surgery

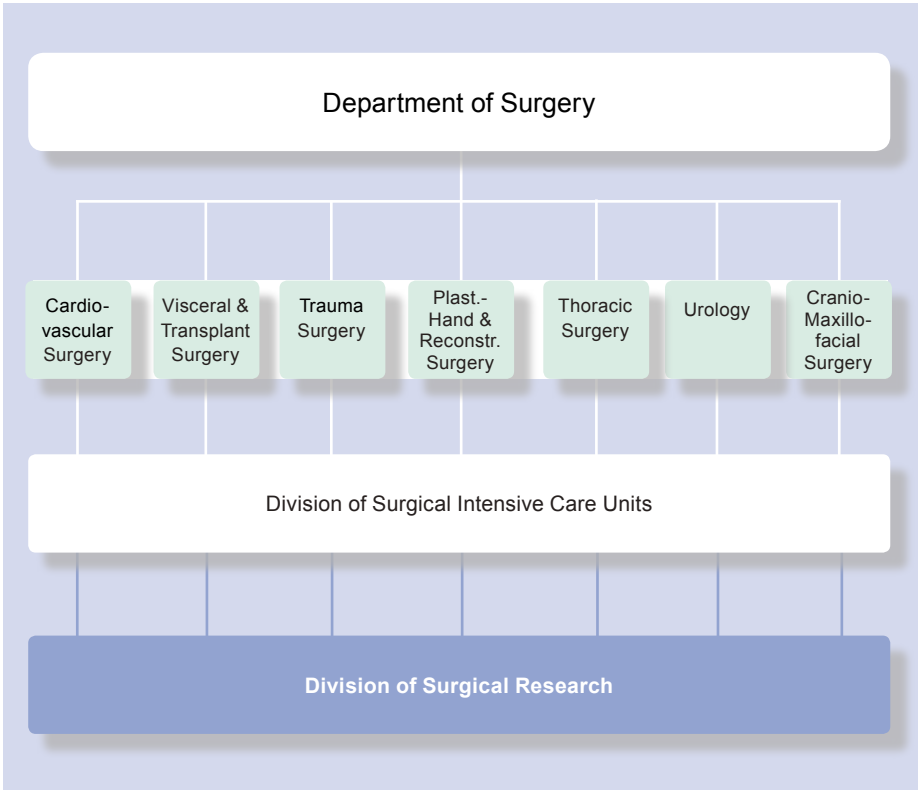
Prof. Dr.
Pietro Giovanoli,
MD
Director Clinic of
Plastic - Hand &
Reconstr. Surgery

Prof. Dr.
Tullio Sulser,
MD
Director Clinic of
Urology

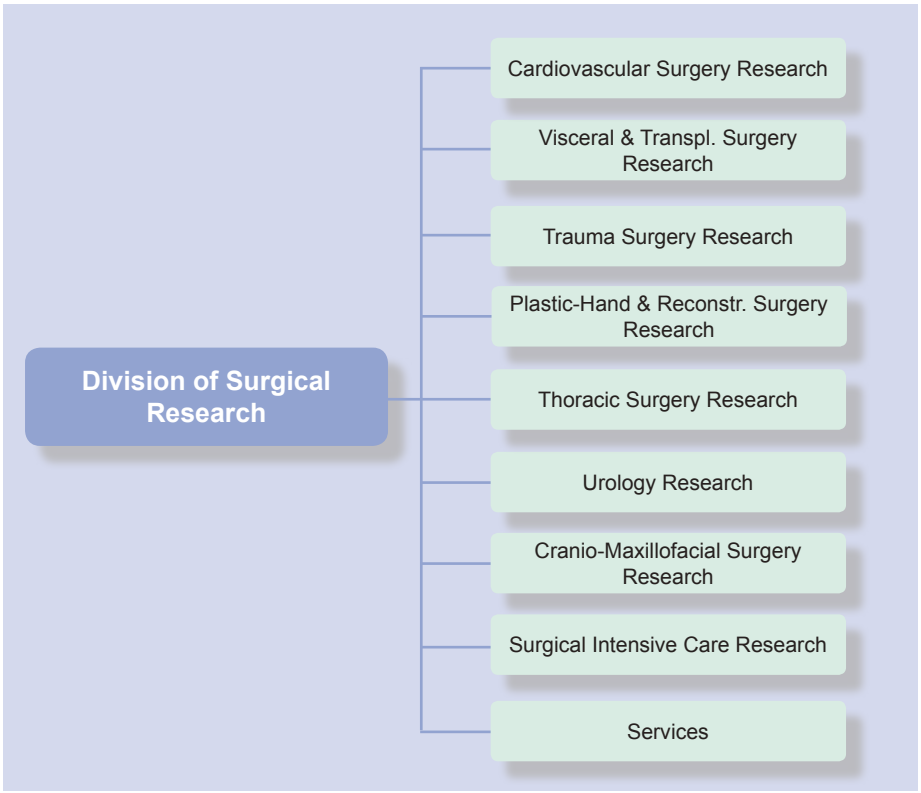
Prof. Dr. Dr.
Klaus W. Grätz, MD
Director Clinic of
Cranio-Maxillofacial
Surgery

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 Surgical Research

Prof. Dr.
Rolf Graf, PhD
Co-Head Division of Surgical Research

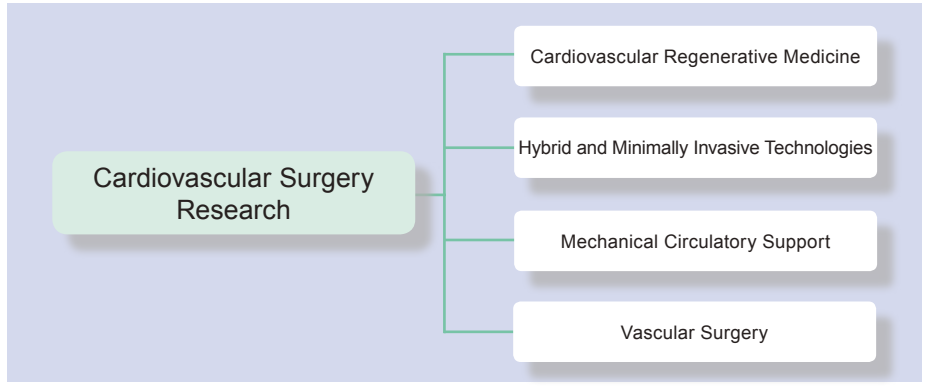
Susanne Frehner
Administration
Division of Surgical Research

2. Research and Development

2.1 Cardiovascular Surgery Research


Prof. Dr.
Simon Philipp
Hoerstrup,
MD, PhD


Prof. Dr.
Volkmar Falk,
MD, Director




Prof. Dr.
Mario Lachat,
MD


Dr.-Ing.
Michael Gessat


PD Dr.
Dieter Mayer,
MD


PD Dr.
Maximilian
Emmert,
MD, PhD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Stephan Jacobs,
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Laura Frese,
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Christoph
Starck,
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Dr.
Steffen
Zeisberger,
PhD


Dr.
Chad Brokopp,
PhD

2.1.1 Cardiovascular Regenerative Medicine

2.1.1.1 Stem cells and microtissue technology

M. Emmert, S. P. Hoerstrup

Stem cells have been repeatedly suggested as a next generation therapeutic approach for the treatment of cardiac diseases. The overall research aim is the development of translational, clinically relevant stem cell based therapy concepts for myocardial regeneration after myocardial infarction or cardiomyopathy. 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 (figure 1) was recently developed at the Swiss Center for Regenerative Medicine and is currently being tested in numerous animal disease models (mice, pigs and sheep) for cardiac cell therapy and cardiovascular tissue engineering. 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.

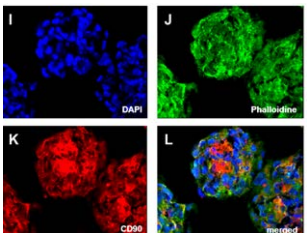
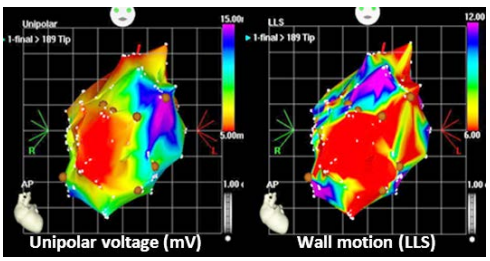


Figure 1: Mesenchymal stem cell based 3D microtissues



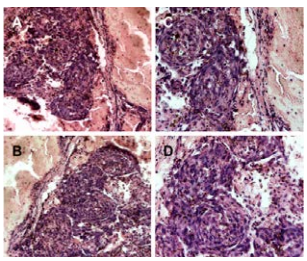


Figure 2: Intramyocardial injection of human mesenchymal stem cell based 3D microtissues using the NOGA transcatheter based three dimensional mapping (left). Histological assessment of 3D-MTs post transplantation.

2.1.1.2 Cardiovascular tissue engineering

B. Weber, 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, Hoerstrup et al. (Circulation 2006) 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.

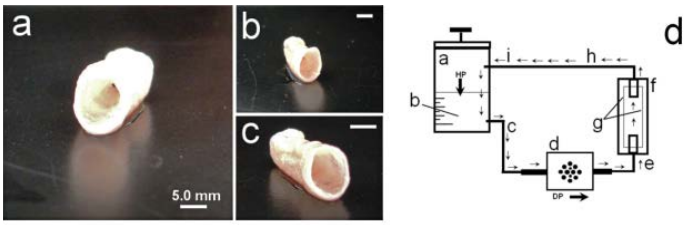


Figure: Tissue engineered vascular graft based on fetal cells (a-c) generated in a flow bioreactor system (d). Weber et al. TERM 2013

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.

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Study Coordination, Administration

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Dipl. Ing.

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Dipl.-Ing.

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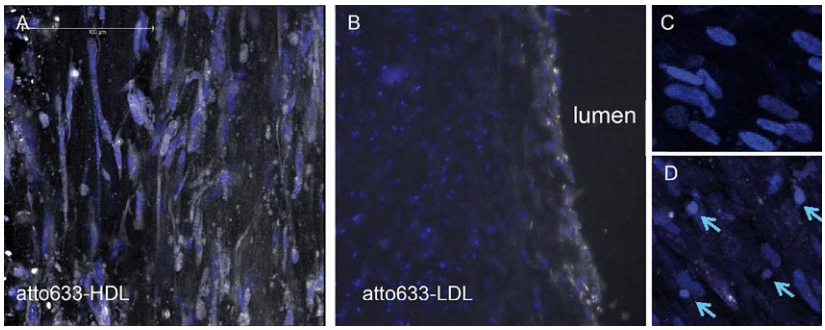
Jérôme
Robert,
PhD Student

By investigating atherogenesis in biomimetic human based tissue engineered vessels complete with haemodynamics and three-dimensional 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)



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 (arrows).

2.1.1.4 Novel targets for infarction prevention strategies

C. Brokopp, S. P. Hoerstrup

The role of antiplasmin-cleaving enzyme (APCE) in myocardial infarction

APCE is a soluble serine protease found at elevated levels in patients suffering from acute myocardial infarction. Previous work indicates that a transmembrane form of APCE - Fibroblast Activation Protein - 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 APCE levels are enhanced in mice in response to intravenous injection of inflammatory cytokine - tumor necrosis factor alpha, suggesting that inflammatory triggers may enhance circulating ACPE levels. Increased levels of circulating ACPE contributed to thrombosis by impairing fibrinolysis, whereas genetic inhibition of APCE prolonged arterial-injury induced occlusion times in mice, suggesting an anti-thrombotic effect of APCE inhibition. Taken together, these findings suggest a role for APCE in thrombosis, and highlight the potential relevance of APCE as a therapeutic and diagnostic target in patients at risk of myocardial infarction.

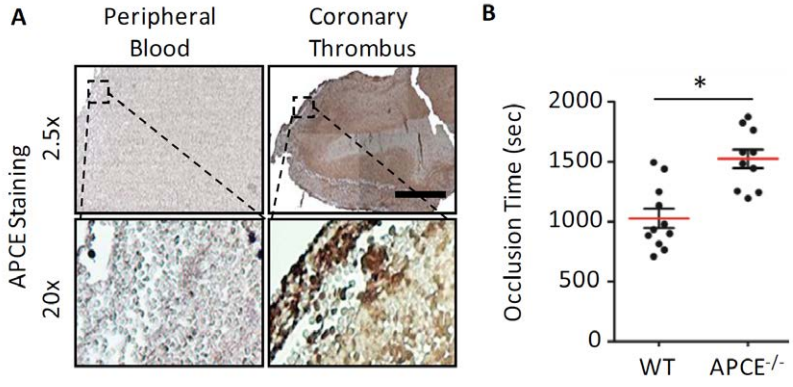


Figure: A. APCE (brown) is enhanced in obstructive human coronary thrombi vs. peripheral blood.
B. Genetic inhibition of ACPE prolongs arterial injury-induced thrombosis times in-vivo.

APCE Diagnostic and Therapeutics

An APCE blood test is currently being developed to accurately and reproducibly quantify ACPE in human blood samples with the aim of determining the diagnostic and predictive value of APCE in patients with coronary artery disease. ACPE-inhibiting monoclonal antibodies are also being developed as anti-thrombotic agents which may be useful for future infarction prevention strategies.

Collaborations:

- 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 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 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 Anatomie, 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. Sündermann

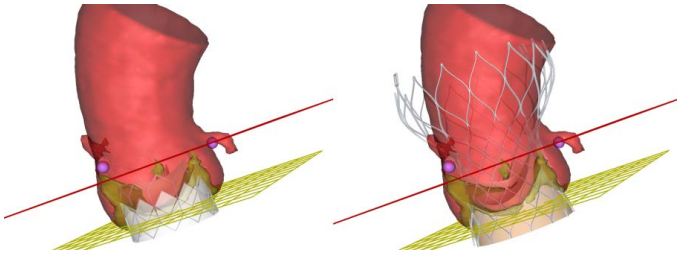
Interventional, catheter based treatment of heart valve disease has become a widely accepted alternative option for the treatment of aortic and mitral valve pathologies in patients at high risk for surgery. Pre-, intra-, and postoperative imaging is crucial because -unlike to open surgery- no direct 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

M. Gessat

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 a 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 3-year project aims at development of a clinically useful system for selection of the optimal implant selection and implant placement for a particular patient.

In 2013, analysis of the mechanical situation of TAVI stents after implantation was started with based on clinical data from 30 patients. A software, which was developed by the group, was used to extract the shape and estimate the contact forces (see Figure 1) This information was then mapped to charts, which allowed for comparison of pattern between different patients and different groups of patients.

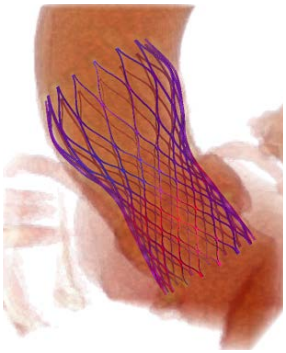


Figure 1: Postoperative TAVI stent modeling

Our framework for predictive simulation of aortic valve stent implantation which we first presented in 2012 was extended. It now contains a multi-material model of the aortic root which better reflects the inhomogeneity of tissue stiffness in the region of interest (see Figure 2). A modelling pipeline to include calcifications has tremendously increased the accuracy of the simulation (see Figure 3).

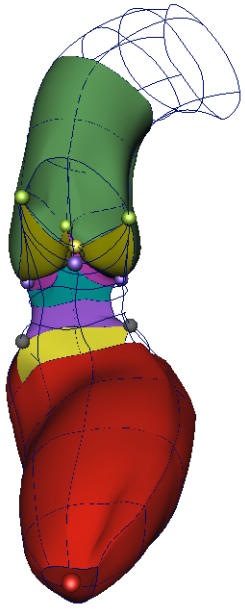


Figure 2: Multi-component model of the left ventricle and ascending aorta

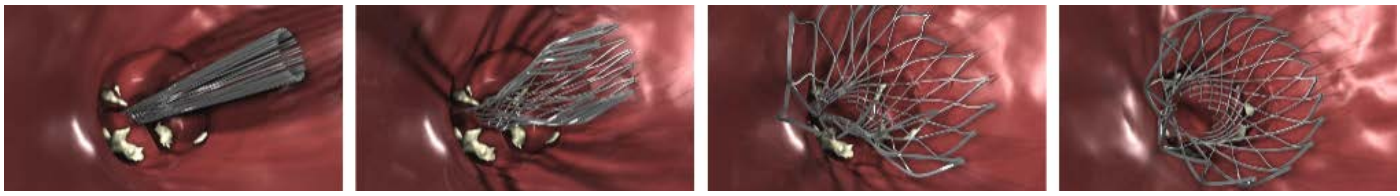


Figure 3: Prospective, patient specific simulation of TAVI stent deployment.

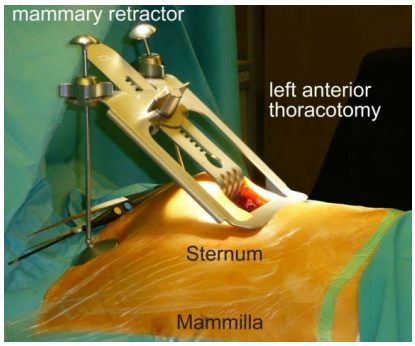
Collaborations:

- Philips Healthcare (Best, Netherlands)
- Swiss Federal Institute of Technology (ETH) Zurich, Computer Vision Laboratory (Zurich, Switzerland)
- Swiss Federal Institute of Technology (ETH) Zurich, Centre for Mechanics (Zurich, Switzerland)
- University of Stanford, Living Matter Lab (Stanford, USA)
- University of Pavia, Structural Mechanics Department (Pavia, Italy)
- Hochschule Karlsruhe, Fakultät für Informatik (Karlsruhe, Germany)
- Lenox Hill Heart and Vascular Institute (New York, USA)

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 2013 revascularization of the LAD was performed in 43 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. Kaplan-Meier survival was 100% at 5 year.



Left anterior mini-thoracotomy (6-8cm)

2.1.2.4 New minimally invasive mitral valve procedures

S. Sündermann

Mitral valve (MV) regurgitation (MR) is the second most common heart valve disease. Today, surgical MV repair is considered to be the gold standard therapy for the treatment of MR. In our center, a minimally invasive approach via a right sided mini-thoracotomy and femoral cannulation for cardiopulmonary bypass (CPB) is the preferred access. This strategy is supported by the results of a Meta-Analysis that we have performed in cooperation with the Division of Biostatistics of the University of Zurich (JTCVS 2014, in press). More than 20'000 patients were included in the underlying studies, and the results supported the right lateral mini-thoracotomy as feasible and safe access route with favorable resource related outcome compared to the median sternotomy as access route for Mitral valve surgery.

Different challenges like the choice of the correct annuloplasty ring size at the arrested heart have to be faced. One solution addressing this problem is a beating-heart adjustable ring that was used in our clinic in two multicenter studies. The Valtech Cardinal ring can be adjusted at the beating heart under echocardiographic control after implantation and closure of the left atrium. 11 rings have been implanted successfully during the CE-certification study and the following post-marketing surveillance study in 2011/2012. In 2013 the one-year and two-year follow-ups of these patients were performed and showed very good results with almost no re-regurgitations of the mitral valve.

Going one step further, the same company developed a transcatheter mitral valve annuloplasty device that can be implanted without the use of the cardiopulmonary bypass. In our new animal hybrid OR (figure 1), opened in 2012, more than 20 animals have been implanted (figure 2) so far, and further implantations are scheduled already. Besides the training and improvement of the device, methods for the preoperative planning of the procedure were developed in cooperation with the Institute of interventional and diagnostic radiology of the UniversityHospital Zurich.

Figure 1: Hybrid OR

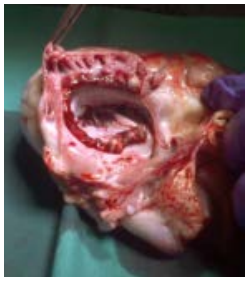


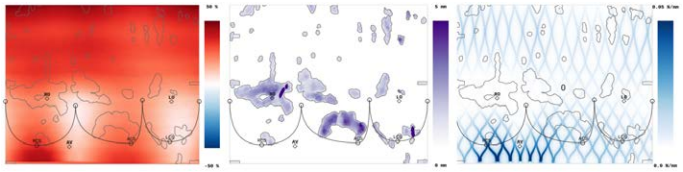
Figure 2: Cardioband

The data from these experiments were used to define the currently used protocol before human implantation that are already going on in different international centers and will also start in our institution in the beginning of 2014. The positive vote of the local IRB is already available.
An established transcatheter therapy for MR is the implantation of the MitraClip device which has been performed more than 120 times in the USZ. To further improve this technique, a newly introduced software tool, called EchoNavigator is under investigation in our institution. This tool is the first software for echocardiography-angiography fusion to facilitate the challenging navigation of catheters during this procedure. The results of 21 patients included in a feasibility study were compared to the results of 21 patients treated before the installation of the EchoNavigator. Even with this low number of patients the length of the procedure and the radiation dose could be decreased. A prospective, randomized trial to validate these results is ongoing.

2.1.2.5 Visualization strategies for cardiovascular research and therapy

S. Born

Data visualization is an important step in the knowledge generation from medical data of various sources.
Besides the acquisition, simulation, or processing of these data, visualization allows to get deeper insight into the data, reject or confirm hypotheses or generate new theories. Currently, we develop new strategies for the visual analysis of flow-sensitive 4D-MRI data to help understand aneurysm development as side effect of aortic valve stenosis. In a second project, we visually incorporate mechanical simulation and anatomical CT data to predict paravalvular leakages and cardiac arrhythmia after transcatheter aortic valve implantations (TAVI, see Figure).



Stent map visualization showing the virtually unrolled stent and aortic valve anatomy of a TAVI patient. The colors depict several properties of interest: Compression of aortic valve stent in comparison to original stent shape (left), calcium thickness (middle), and radial force distribution on the stent (right).

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.

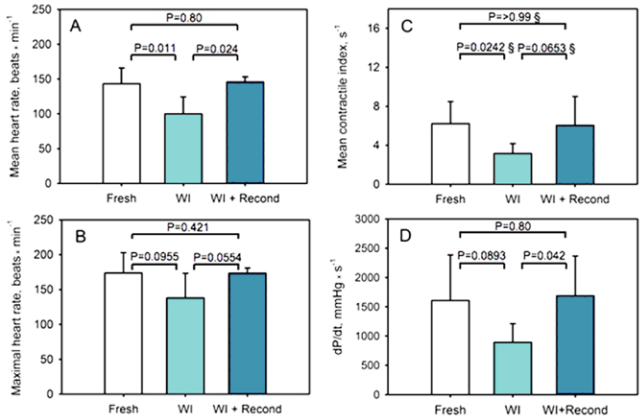


Figure 1a-d: Heart function during Langendorff perfusion

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 (fig. 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).

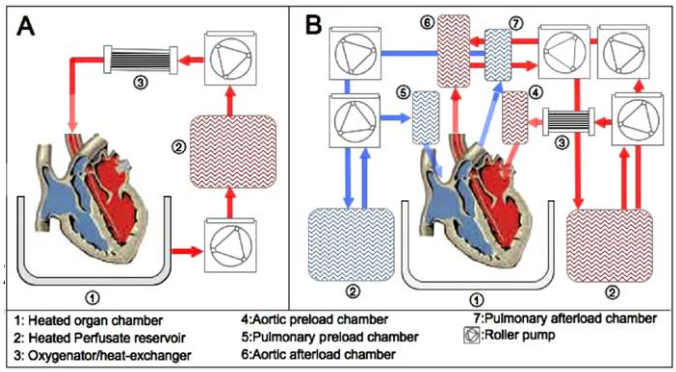


Figure 2: Full scale perfusion system

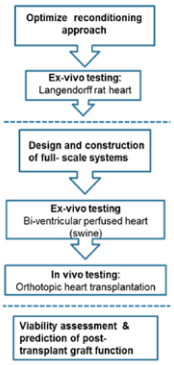


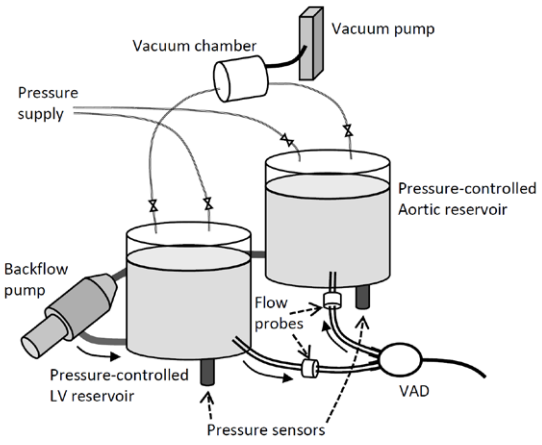
Figure 3: Project outline

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.

2.1.3.2 Mechanical circulatory support

C. Starck, M. Wilhelm

The Zurich Heart project, a collaboration with several research groups at the ETH, is working on improvement of current assist devices, such as transcutaneous energy- and information transfer, physiological regulation, modification of inner surfaces, as well as the development of new device concepts, such as biomimetic partial ventricular assist devices with tissue engineered heart valves. A novel interface for hybrid mock circulations was developed to evaluate ventricular assist devices. With this new tool, a physiological controller for turbodynamic ventricular assist devices was designed based on a measurement of the left ventricular volume. A new ferromagnetic assist device concept for extra-aortic counterpulsation based on magnetic field responsive polymer cuffs was developed and first test series were performed with the use of a silicone aorta model.



Mock circulation setup

Collaborations:

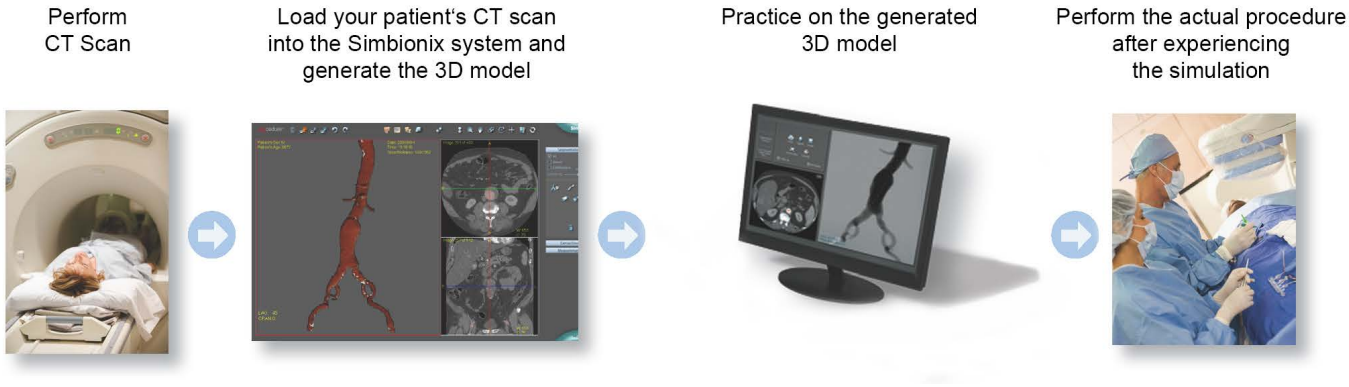
- Institute for Dynamic Systems and Control, ETH Zürich (Prof. L. Guzzella)
- Micro- and Nanosystems (Prof. C. Hierold)
- Power Electronic Systems Laboratory (Prof. J.W. Kolar)
- Metal Physics and Technology (Prof. J.F. Löffler, Prof. P.J. Uggowitzer)
- Institute for Mechanical Systems (Prof. E. Mazza)
- 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 nontechnical 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

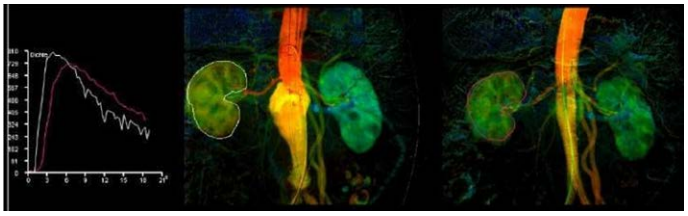
L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat

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

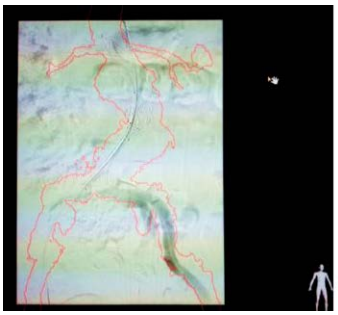
2D Perfusion typically requires only one contrast media injection and one DSA run, to obtain rich information of vessel and organ perfusion in the interventional suite. By comparing pre and post procedural images, clinicians can identify perfusion differences in the color images.

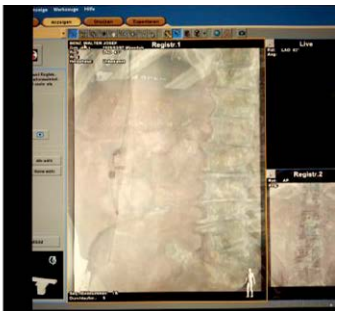


2.1.4.4 Evaluation of automated image overlay system for EVAR

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.



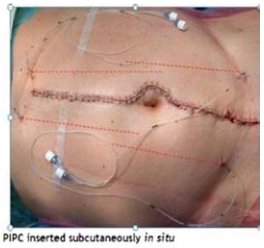


2.1.4.5 Evaluation of different methods of local anesthesia for postoperative analgesia

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)

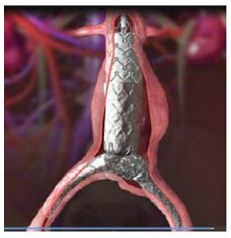


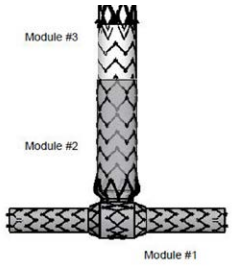
PIPC inserted subcutaneously *in situ*

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)

2.2 Visceral & Transplant Surgery Research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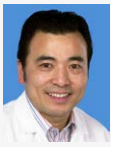
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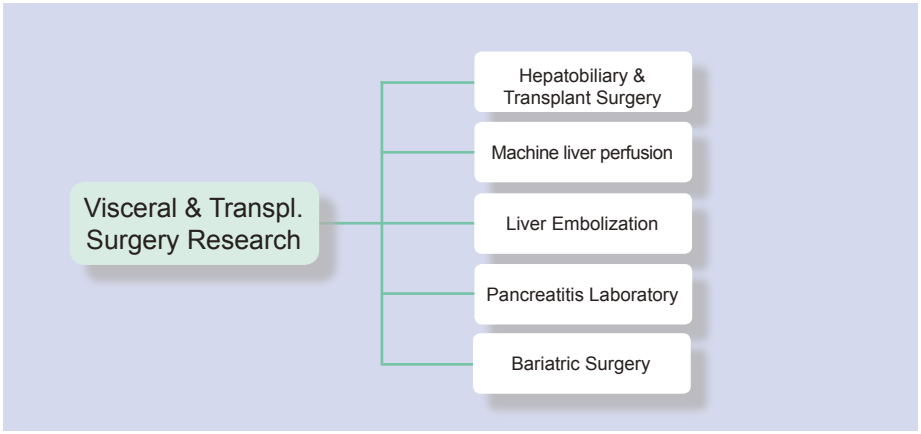
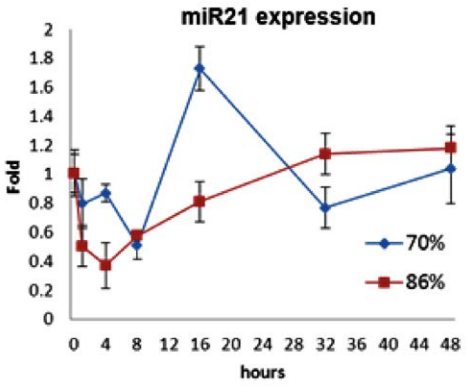


2.2.1 Hepatobiliary & Transplant Surgery

miR-21 and the control of liver regeneration in the Small-for-Size Syndrome

E. Kachaylo, Ch. Tschuor, M. Linecker, J.-H. Jang, P. Limani, P. Ramadori, M. Foti, R. Graf, B. Humar, P.-A. Clavien

Small-for-Size Syndrome (SFSS) puts patients at risk of post-operative death and can develop (i) following transplantation of critically small grafts or (ii) following extended hepatectomy leaving marginal remnants. We have identified delayed liver regeneration as a cause of SFSS, however the underlying molecular events remain ill-understood. miR-21, an oncogenic microRNA associated with proliferative states, is induced after standard (70%) hepatectomy (Hx), but not after extended (86%) Hx, which leads to SFSS in mice. Using miR-21 mimics injected before 86% hepatectomy, we could accelerate liver regeneration and rescue mice from SFSS, whilst loss of miR-21 (Cre-AlbERT2-miR21$^{fl/fl}$ mice) provoked SFSS-like features after 70%Hx. Molecular studies suggest miR-21 deficiency may be due to suboptimal Stat3 activity downstream of exaggerated Il6 signaling. These experiments will contribute towards a molecular definition of the SFSS and reveal novel targets & diagnostics for its potential management.

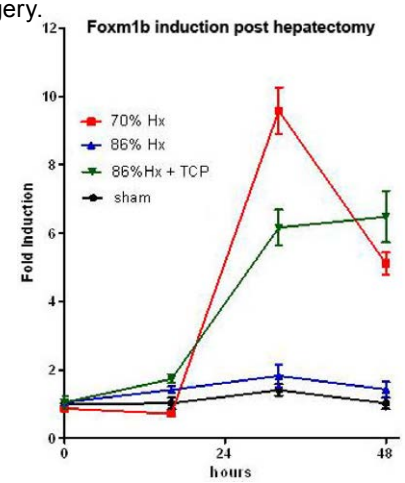


Constitutive androstane receptor agonism in the mitigation of the Small-for-Size Syndrome

Ch. Tschuor, E. Kachaylo, P. Limani, A. Schlegel, J.-H. Jang, D. A. Raptis, E. Melloul, M. Linecker, A. Vuck, Y. Tian, R. Graf, B. Humar, P.-A. Clavien

Activation of the constitutive androstane receptor (Car) through its agonist TCPOBOP (TCP) induces liver growth without the need for resection or injury in rodents. Indeed, TCP also induces liver growth in experimental models of SFSS, overriding the regenerative deficits of marginal liver grafts or remnants. In SFSS models of transplantation and resection, a single dose of TCP was able to rescue 40% of otherwise moribund mice, even when given a few hours after surgery.

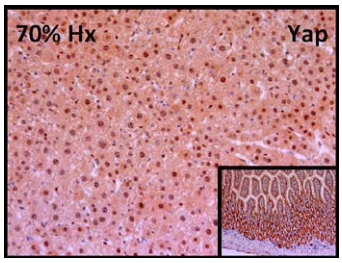
Interestingly, Car$^{-/-}$ mice develop SFSS after standard (70%) resection; indeed, SFSS developing after extended resection is associated with deficient Car induction, which is normalized by TCP. Car-normalization leads the re-induction of Foxm1b and Yap, both central mediators of the TCP effects in SFSS. Of note, human biopsies confirmed deficiencies in CAR, FOXM1B and YAP as a feature of SFSS. The effects of the human CAR agonist CITCO on *ex vivo* human liver slice cultures will reveal whether CAR agonism may also be a viable strategy to mitigate human SFSS.

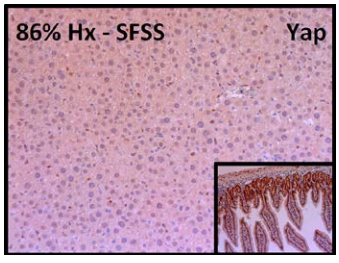


The miR-375-Yap pathway in liver regeneration and the Small-for-Size Syndrome

Ch. Tschuor, E. Kachaylo, A. Schlegel, P. Limani, A. Columbano, J.- H. Jang, D. A. Raptis, E. Melloul, M. Linecker, A. Vuck, Y. Tian, R. Graf, B. Humar, P.-A. Clavien

In our efforts to understand the molecular events that underlie the SFSS, we have observed an overinduction of miR-375 along with concomitant downregulation of its direct target Yap, a repressor of the Hippo pathway, which acts to limit organ size. Whether the miR-375-Yap axis has a crucial function during physiological liver regeneration is not known. Following siRNA knockdown and standard hepatectomy, liver regeneration was impaired, along with the development of SFSS-like symptoms. We now plan to stimulate regenerative Yap activity by suppressing its inihibitor miR-375 through antagomirs. These experiments will ask whether Yap is merely needed for normal regeneration to occur, or whether its promotion might be a means to expedite the speed or extent of regenerative processes following liver resection.





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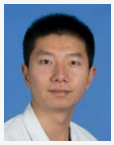

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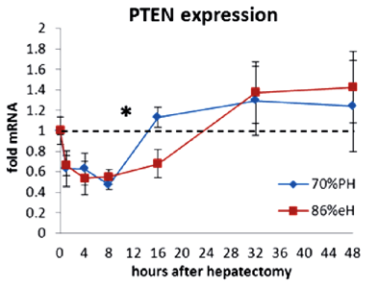
Pten function in liver regeneration

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

Pten, the well-known negative regulator of the growth-related PI3K-Akt-mTOR pathway, has many additional, emerging functions. In liver, Pten deficiency causes lipid accumulation, leading to steatohepatitis and cancer.

Given that liver regeneration features both tissue growth and transient hepatic steatosis, Pten regulation might be crucial after hepatectomy. Constitutive Pten knockouts feature high levels of pre-existing steatosis that interferes with normal regeneration. To study the role of Pten without steatotic confounders, we will use Cre-AlbERT2-Pten$^{fl/fl}$ mice. Preliminary results using pharmacological antagonissts suggest Pten suppression may be a requirement for efficient liver regeneration. We further will investigate whether Pten serves to orchestrate energy demands and growth pathways during tissue renewal.

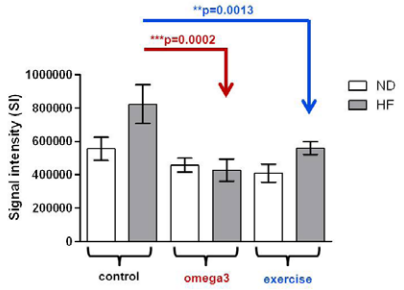


The impact of exercise and ω3-fatty acids on ischemia reperfusion injury in and regeneration of fatty liver

M. Linecker, M. Foti, A.-Ch. Piguet, J.-F. Dufour, E. Kachaylo, P. Limani, Ch. Tschuor, A. Schlegel, A. Vuck, D.A. Raptis, R. Graf, B. Humar, P.-A. Clavien

The current surge in obesity is the likely cause for the increasing number of patients that present with fatty liver (steatosis). Hepatic lipid accumulation increases the risk of liver cancer and hence contributes to an increased demand for liver surgery. However, fatty liver also is exquisitely sensitive towards ischemia reperfusion injury (IRI) and slows liver regeneration, thereby increasing postoperative complications. Exercise and ω3-fatty acids are known to counteract steatosis, but their effects on IRI and regeneration in fatty livers are less clear.Experimental steatosis was induced by feeding mice a high fat diet for 6w. Mice were then treated for 4w through calorie reduction (from 60 to 45kJ%) combined with either ω3-fatty acid supplementation (20% of the 45kJ%) or daily exercise (1h).

Both treatments markedly reduced steatosis and IRI (see fig), whilst their impact on regeneration needs further analysis. In a next step, we will investigate several key molecules governing fat metabolism to identify potential downstream mechanisms of the anti-steatotic ω3-fatty acid action. Any intervention that can safely reduce hepatic fat accumulation and mitigate IRI without negatively affecting the regenerative capacity would be most welcome in the clinic. Inasmuch ω3-fatty acids can substitute the beneficial effects of exercising is another point of interest, as regular exercise will always remain limited in its therapeutic potential due to matters of compliance.

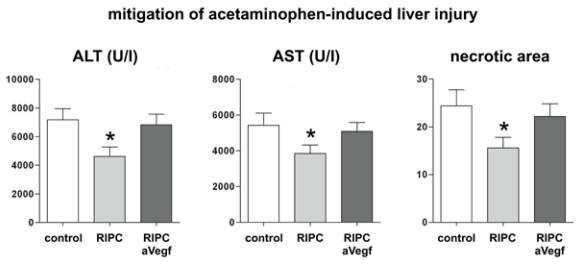


Remote ischemic preconditioning beyond protection from ischemia reperfusion injury

P. Limani, Ch. Oberkofler, Ch. Tschuor, A. Schlegel, E. Kachaylo, M. Linecker, R. Graf, B. Humar & P.-A. Clavien

We have recently identified a platelet-serotonin-Vegf-Mmp8/Il10 axis that mediates most of the protective effects remote ischemic preconditioning (RIPC) has on ischemia-reperfusion injury (IRI). Given that serotonin can have many beneficial effects such as promoting the regeneration of old liver, RIPC may serve as a safe and physiological way to elevate peripheral serotonin in patients, i.e. without causing unwanted neurological effects that can occur following the injection of serotonin or its analogues.

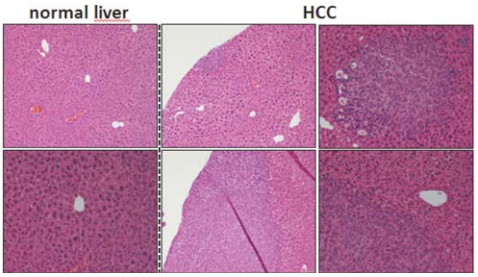
Preliminary data indicates RIPC is able to mitigate acute pancreatitis as well as paracetamol-induced liver toxicity (see fig). Our current findings suggest that RIPC can be used to boost the regeneration of SFSS liver. We will systematically assess the effects of RIPC on regeneration following extended hepatectomies, portal vein ligation, and other measures used to induce liver growth. Likewise, the impaired regenerative capacity of old liver will be investigated. Using proteomics approaches, we will search for additional molecule candidates that may mediate the beneficial effects of RIPC.



Endothelial contribution to the tumor microenvironment of hepatocellular carcinoma

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

Hepatocellular carcinoma (HCC) results from a complex interplay between environmental factors and genetic alterations, often in the background of pre-existing liver disease. The efficacy of existing therapies is modest, with alternative approaches being desperately sought. The tumor microenvironment (TME) may represent one alternative target, yet the interplay between HCC and its hepatic niche is ill-researched. Liver sinusoidal endothelial cells (LSECs) constitute the largest population of non-parenchymal liver cells, and their close association with hepatocytes is key to normal liver function. In this project, we will investigate how their highly differentiated features impact on HCC behaviour, and which molecular interactions contribute. To do so, we have developed a novel syngeneic mouse model of HCC (see fig), and are currently establishing LSEC-HCC co-culture systems. The characterization of LSEC-HCC interactions will provide hints as to whether LSECs may offer alternative targets for the treatment of HCC.

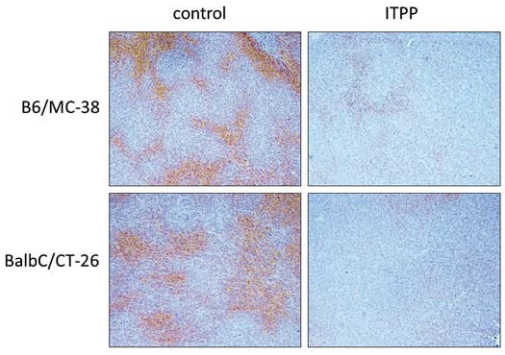


Antihypoxic therapy for colorectal cancer liver metastases

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

Hypoxia, a key feature of many solid tumours, predicts a bad outcome in colorectal cancer (CRC) liver metastases. Tumours respond to hypoxia by metabolic adaptation, an enhanced inflammatory state, an increased tumorigenic potential, pronounced invasiveness and a neoangiogenic switch. Current targeted therapies for CRC liver metastases such as Avastn specifically block the angiogenic response.

However, their impact on overall survival is marginal, likely because antiangiogenic therapy may promote hypoxic conditions and thereby an aggressive tumour phenotype. Inositol trispyrophosphate (ITPP) is the first non-toxic compound able to efficiently inhibit hypoxia. We have tested ITPP on two syngeneic mouse models of CRC liver metastasis. ITPP prevented several processes typically associated with hypoxia (see figure for hypoxia staining via piminidazole), promoted a mesenchymal-to-epithelial transition, and prolonged survival by 60%. A direct comparison of ITPP plus standard chemotherapy vs. Avastin plus chemotherpy will reveal whether ITPP can prevent the neoangiogenic switch without increasing tumour aggressiveness.

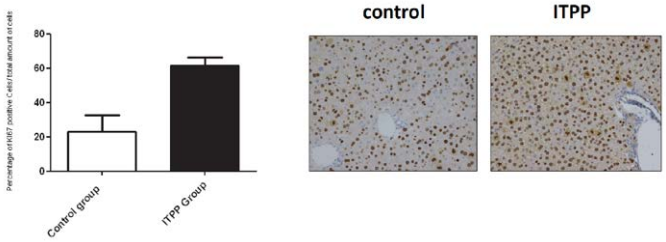


Oxygen for the promotion of liver regeneration

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

An efficient microperfusion is key to successful liver regeneration. Whilst the importance of microperfusion has been empirically recognized, circulation is required for the delivery of not only nutrients and essential growth factors, but also for the oxygen needed to generate sufficient energy for the consuming process of tissue renewal.

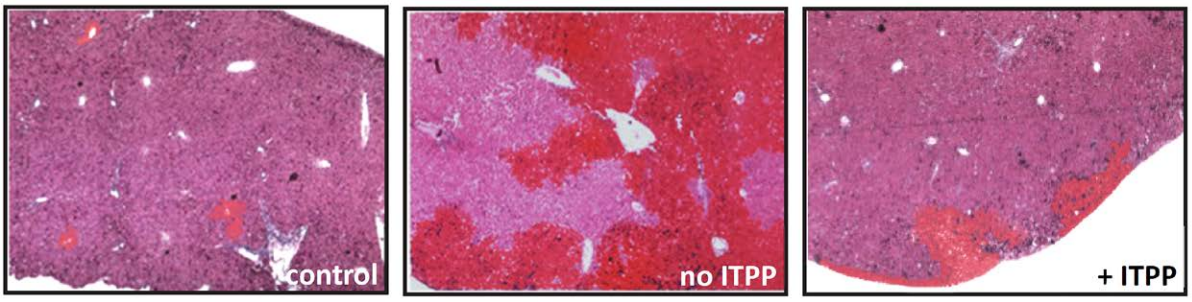
Following hepatectomy, tissue levels of oxygen are thought to drop due to the more prevalent flow of portal blood. Nevertheless, pretreatment with the antihypoxic compound ITPP promotes the regenerative process in hepatectmoized mice, indicating the importance of sufficient oxygen levels (see Ki-67 staining in below fig). In this study, we will define the hypoxic periods during liver regeneration and estimate their relevance through the tuning by ITPP. A detailed analysis should provide a basis to define the therapeutic utility of oxygen-modulating compounds in liver regeneration.



Counteracting ischemia during organ preservation

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

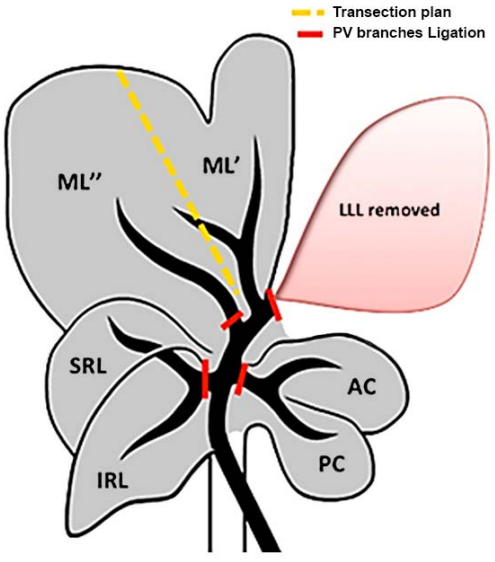
The time that elapses between organ harvest and transplantation is a critical period with profound impact on the viability of the graft. In order to improve the outcome of liver transplantations, graft storage prior to implantation needs optimization to minimise tissue injury. Given that graft storage essentially comprises an ischemic period followed by reperfusion, we reasoned that the antihypoxic molecule inositol trispyrophosphate (ITPP) may have beneficial effects on graft quality. A new model of isolated rat liver perfusion (IPRL) involving complete canulation was developed. To mimic the clinical situation, rat livers were harvested 45 minutes after induction of cardiac arrest. For graft preservation, livers were reperfused with an oxygenated solution consisting of full rat blood or isolated erythrocytes and Krebs–Henseleit–Buffer, both with or without ITPP. Antihypoxic treatment resulted in markedly reduced organ injury, increased bile flow and improved perfusion. ITPP-treated grafts used for rat transplantation resulted in a long-term survival of recipients, whereas a significant proportion of rats with untreated grafts died due to biliary cirrhosis. Therefore, ITPP has the potential to improve the outcome of liver transplantation.



A mouse model of ALPPS

A. Schlegel, E. Melloul, C. Tschuor, P. Limani, M. Lesurtel, R. Graf, B. Humar, P.-A. Clavien

ALPPS (for Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) is a surgical technique that has newly been introduced in the clinic to enable the resection of large parts of the liver. So far, usual approaches were based on portal vein ligation (PVL) of liver lobes to be removed (i.e. carrying a tumour). PVL induces hypertrophy of the contra-lateral liver lobes, enabling resection of the ligated lobe(s) a few months later even in situations, where the liver remnant would normally be too small to maintain vital function. In ALPPS, PVL is combined with lobe transsection, resulting in an unprecedented volume gain within a week. Therefore, ALPPS allows for a resection of even larger volumes than PVL within a drastically shorter time period. However, ALPPS is not established in the clinic, and its true advantages are a matter of controversial discussion. To demonstrate the utility of ALPPS, we have developed a mouse model of PVL combined with transsection. Indeed, following ALPPS, the liver remnant regains volume within a day, a process that usually takes a week in mice. The data from our model fully supports the boost in the regenerative speed following ALPPS. Our preliminary results indicate that the acceleration of liver regeneration is due to systemic factors that are released upon tissue injury such as transection.



Mechanisms underlying the unprecedented liver regeneration induced by ALPPS

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

ALPPS (for Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) induces liver regeneration at a speed unseen to date. Identification of the factors reponsible for the accelerated regeneration induced by ALPPS is of obvious therapeutic interest. Based on our preliminary data, the transection step during ALPPS causes the release of systemic factors that then push the regenerative capacity of liver beyond its usual limits. Injection of plasma from ALPPS mice is sufficient to accelerate liver regeneration after procedures such as portal vein ligation. Plasma treatment with protein depletion columns abolishes this effect, whilst re-addition of depleted proteins re-installs the regenerative response. Using a combination of proteomics and genomics approaches, we aim at identifying protein candidates that mediate this regenerative acceleration. Testing candidates in various mouse models of 'normal' or impaired regeneration will demonstrate their therapeutic potential.

Temporary Xenogeneic Transplantation for Successful Use of Small for Size Liver Grafts

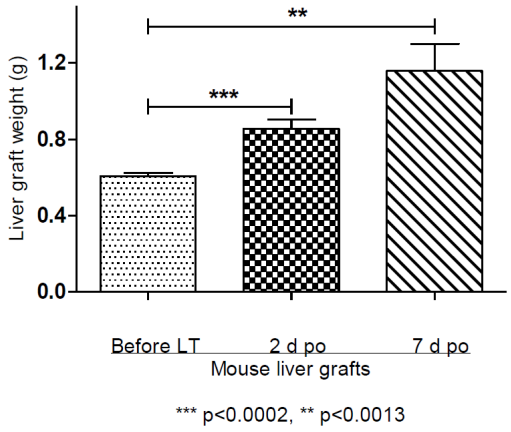
Y. Tian, B. Humar, R. Graf, T. Fehr, A. Weber, S. Segerer, Z. Song and P.-A. Clavien

Live donor liver transplantation (LDLT) is increasingly being used due to shortage in donor livers. Removing 30% of liver is safe for the donor, however 40% is needed for the recipient to ensure viability. Implanting a 30% graft provokes the Small-for-Size Syndrome (SFSS) in recipients, leading to liver failure and potentially death. To avoid the mismatch between available donor graft and the requirements of the recipient, we have developed the strategy of intermediate auxiliary partial liver xenotransplantation (IAPXLT). In IAPLXT, a 30% donor graft is first transplanted into a xenogeneic host.

Then, host liver is partially resected to induce the regeneration of both host liver and the donor graft. Once the donor graft has reached a sufficient volume (i.e. 50%), it is removed from the xenogeneic host and transplanted into the final recipient. In this way, SFSS can be prevented in the recipient without compromising the donor.

We have established a mouse-to-rat-to-mouse transplantation model to prove the feasibility of IAPLXT. Using our model, we could demonstrate that mouse donor 30% liver grafts actively regenerate in rat until 7 days after transplantation without acute rejection. In this period, they gain sufficient volume for recipient transplantation. We further could show that retransplantation of these grafts into mouse is possible. These experiments will now be repeated in larger animals.

The final step will be to demonstrate functionality of human grafts regenerated in xenogeneic hosts. If successful, IAPLXT will provide a novel strategy that may markedly increase the pool of organs from live donors.



Volume increase of mouse liver graft at day 2, & 7 after IAPLXT.

The Comprehensive Complication Index - A Novel Continuous Scale to Measure Surgical Morbidity

K. Slankamenac, R. Graf, J. Barkun, M. A. Puhan, P.-A. Clavien

The quality of surgical procedures has been often measured by the presence of postoperative complications but there is an incomplete reporting of all surgical complications. Furthermore, the severity of complications is often unclear. Alternatively, only the most severe complications are reported. Therefore, we developed a comprehensive complication index (CCI) which summarizes for the first time all postoperative complications and their respective severities in a single number ranging on continuous scale from 0 (none) to 100 (death). Four different validations showed that the CCI has a high validity and better responsiveness than previous reports of postoperative complications. The CCI has the potential to longitudinally measure the morbidity and to serve as a standardized endpoint in surgical trials and other interventional fields of medicine.

Collaborations/Sponsors:

- Prof. Dr. Adriano Fontana, MD, Experimentelle Immunologie (UniversityHospital Zurich, Switzerland)
- Prof. Dr. Bruno Stieger, PhD, (UniversityHospital Zurich, Switzerland)
- Prof. Dr. Achim Weber, MD, Institut für Pathologie (UniversityHospital Zurich, Switzerland)

2.2.2 Machine Liver Perfusion

A. Schlegel, R. Graf, P.-A. Clavien, P. Dutkowski

Our group previously showed the impact of an end-ischemic hypothermic oxygenated perfusion (HOPE) on reperfusion injury and biliary fibrosis in liver grafts.
Here, we aimed to investigate effects of HOPE on rejection after orthotopic liver transplantation (OLT). For this purpose, livers from Lewis rats were transplanted into Brown Norway rats to induce liver rejection in untreated recipients (allogeneic rat OLT model). Recipients were either treated with tacrolimus (1mg/kg), or liver grafts were machine perfused (HOPE) for 1h prior to implantation, but recipients received no immunosuppression. In a last step, low-dose tacrolimus treatment (0.3 mg/kg) was analyzed with and without HOPE. The results show, that allogeneic OLT without immunosuppression led to death within 3 weeks after OLT due to severe acute rejection. Full-dose tacrolimus prevented rejection, while low-dose tacrolimus led to graft fibrosis within four weeks. HOPE treatment without immunosuppression protected also from lethal rejection, as shown by survival and confirmed by T cell infiltration in the graft and activation in the blood (***Figure 1***). The combination of low-dose tacrolimus and 1h HOPE resulted in 100 % survival within 4 weeks without signs of rejection or fibrosis.
Based on this, we believe that allograft treatment by HOPE not only protects against preservation injury, but impressively down-regulates the immune-system blunting the allo-immune response. Therefore, HOPE may offer many beneficial effects, not only to rescue marginal grafts, but also by preventing rejection and the need for immunosuppression.

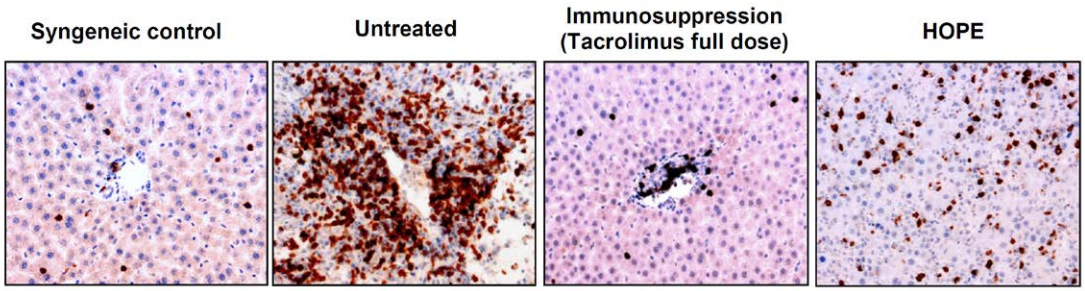
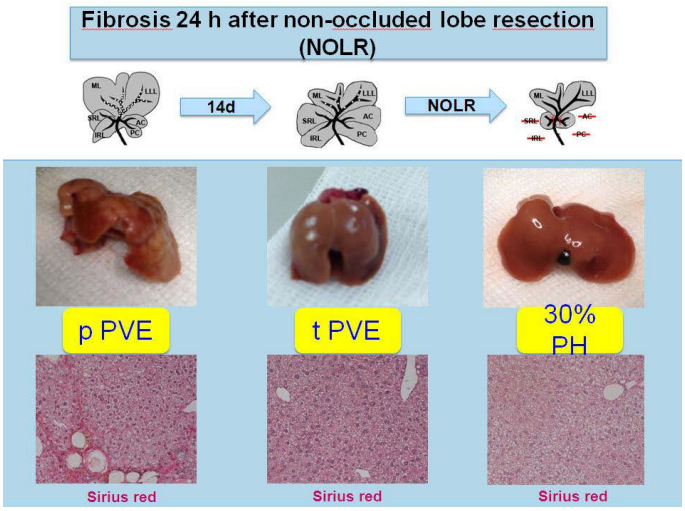


Figure 1: Infiltrating T Cells in liver tissue 2 weeks after transplantation.

2.2.3 Temporary Portal Vein Occlusion and Liver Regeneration

A. Vuck, N. Bain, M. Lesurtel

The aims of this project were (1) to assess the efficacy of temporary portal vein embolization (PVE) compared to permanent occlusion of the portal vein with embospheres or portal vein ligature (PVL) on hypertrophy of the non-embolized liver lobes; (2) to assess histological and functional recovery of embolized liver lobes after temporary and permanent PVE.
In a first set of experiments, we were able to show that temporary PVE is as efficient as permanent PVE or PVL to induce hypertrophy of the non-occluded lobes. In order to study embolized liver lobes, we resected the hypertrophic non-embolized liver lobes at day 14 following embolization (time point of complete revascularization after temporary PVE). We found that embolized lobes after temporary and permanent embolization were still able to hypertrophy and secure mouse survival. However, we found significantly less liver injury in the temporary PVE group than in the permanent PVE group.

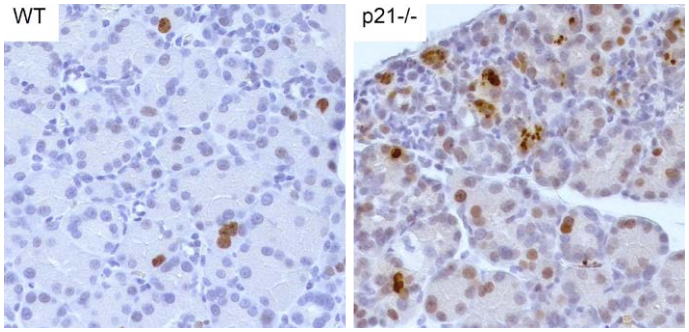


2.2.4 Pancreatitis Research Laboratory

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

K. Grabliauskaite, A. Hehl, 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 p21$^{WAF1/Cip1}$ 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.

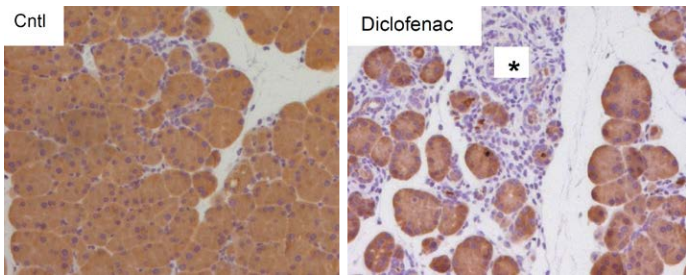


Expression of the DNA damage marker γH2AX increases in pancreatic acinar cells in absence of p21.

Inflammation contributes to the regression of acinar-to-ductal metaplasia during pancreatitis

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

A tight regulation of ADM regression is critical for the completion of regeneration of the injured pancreas and organ homeostasis. Our work revealed that ADM following pancreatitis or 60% pancreatectomy is associated with a strong inflammatory response, which is independent from the total level of inflammation in the pancreatic tissue. When mice with established ADM were treated with anti-inflammatory drugs, dissolution of ADM was prevented, suggesting that the immunity plays an active role in the regression of ADM.

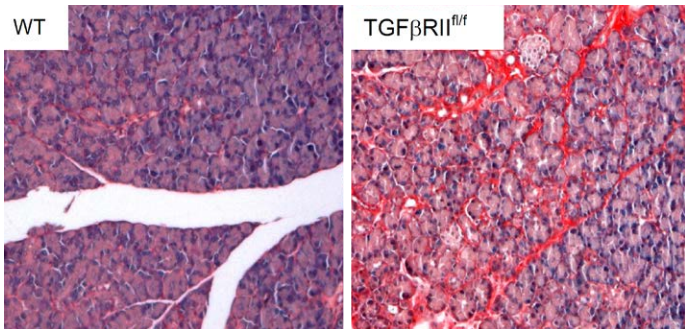


Anti-inflammatory treatment with diclofenac delays ADM (*) dissolution following pancreatitis.

Acinar specific TGF-β signalling regulates acinar cell regeneration

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

TGFβ signalling is implicated in many pathophysiological functions of pancreatic cells. However, the function of TGFβ signalling is strongly context-dependent and an acinar cell specific role of this molecule in modulating regeneration has not been completely investigated before. By using mice deficient in TGFβ receptor II (TGFβRII$^{fl/fl}$) exclusively in acinar cells, we showed that TGFβ signalling inhibited acinar cell cycle activation and prevented excessive ADM formation by limiting the activation of AKT. Additionally, loss of TGFβ signalling in acinar cells potentiated fibrogenic processes during pancreatitis, suggesting the existence of a regulatory feedback between acinar and stellate cells.

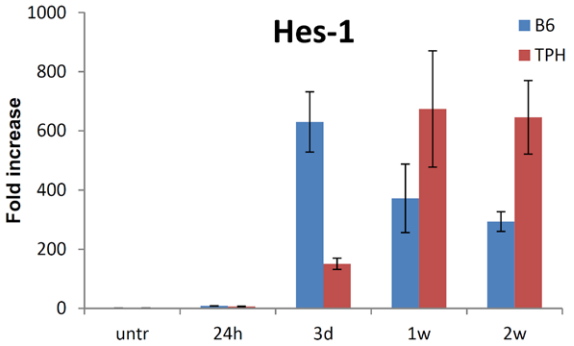


Collagen deposition increases following ablation of TGFβ signaling in pancreatic acinar cells.

Serotonin regulates progenitor cell-based regeneration in the adult pancreas

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

Regeneration of the pancreas appears to occur through two different programs, with the specific response being determined by the type and severity of the injury. Moderate kinds of pancreatic injuries, including 60% pancreatectomy, trigger a proliferation-based repair response, in which differentiated acinar cells divide to supply the additional cells necessary for tissue repair. In contrast, more significant injuries such as cerulein-induced pancreatitis, trigger a more powerful progenitor-cell based regenerative response. By using TPH1$^{-/-}$ mice with reduced peripheral levels of serotonin, we showed that this molecule is required for progenitor cell-based regeneration.

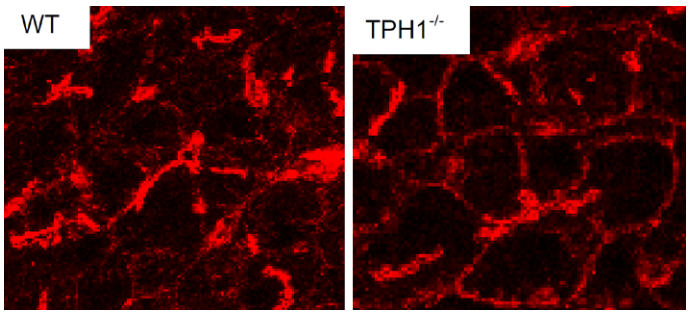


Lack of 5-HT in TPH1$^{-/-}$ mice delays the up-regulation of the progenitor cell marker Hes-1 following pancreatitis.

Serotonin mediates pancreatic acinar cell cytoskeletal remodeling in mice

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

In our previous study, we showed that serotonin is necessary for pancreatic acinar cell secretion in both physiological and pathological conditions. Since the secretory process is intrinsically dependent on cytoskeletal rearrangements, we now aim to study the effects of 5-HT on the regulation of cytoskeleton remodeling. Our data showed that serotonin modulates the dynamics of actin cytoskeleton and the localization of small GTPase proteins involved in cytoskeletal reorganization under both physiological and pathological conditions.

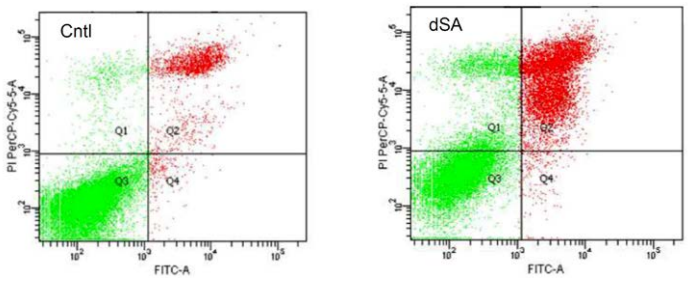


Basolateral localization of actin in acinar cells increases in mice deficient for 5-HT (TPH1$^{-/-}$).

Deoxysphingolipids, a novel biomarker for type 2 diabetes, are cytotoxic for insulin producing cells

R.A. Zuellig, T. Hornemann, O.O. Ogunshola, R. Graf and S. Sonda

Irreversible failure of pancreatic β-cells is the main culprit in the pathophysiology of diabetes mellitus, a disease that is now a major global epidemic. Recently, elevated plasma levels of deoxysphingolipids, including 1-deoxysphinganine, have been identified as novel biomarkers for the disease. We found that 1-deoxysphinganine induced dose-dependent cytotoxicity in β-cells with senescent, necrotic and apoptotic characteristics. In addition, 1-deoxysphinganine altered cytoskeleton dynamics, resulting in intracellular accumulation of filamentous actin, activation of the RhoGTPase Rac1 and compromised glucose-stimulated insulin secretion.

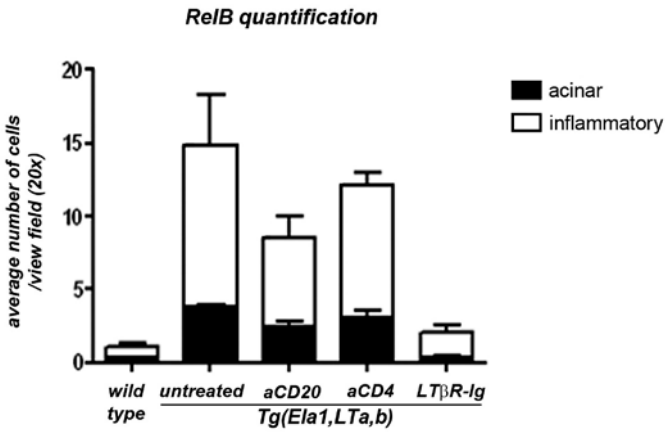


1-deoxysphinganine (dSA) triggers apoptosis and necrosis in β-cells.

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 long-term management of autoimmune pancreatitis (AIP) is still elusive. We previously demonstrated that acinar specific Lymphotoxin expression in mice Tg(Ela1-LTα,β) induces autoimmunity with features reminiscent of human AIP. In our unique genetic mouse model of AIP, we now demonstrate that inhibition of Lymphotoxin beta receptor (LTβR) signalling pathway with LTβR-Ig is therapeutically superior to CD4+ T-cell and B cell depletion in decreasing autoantibody production, acinar-to-ductal metaplasia formation and NF-kB signaling activation. Therefore, inhibition of the LTβR-signalling pathway could become an alternative or supplementary approach for AIP treatment.

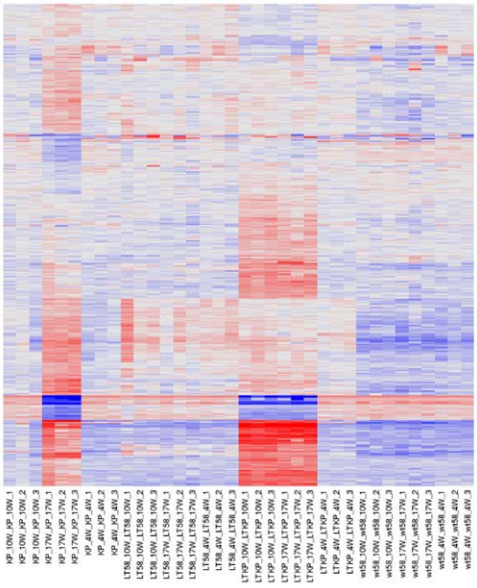


Treatment with LTβR-Ig efficiently prevents the activation of non-canonical NF-kb (RelB) signalling.

Lymphotoxin beta receptor signalling pathway promotes initiation of pancreatic cancer

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

Pancreatic inflammation is a well-known risk factor for pancreatic ductal adenocarcinoma (PDAC) development in humans, but the underlining molecular mechanisms remain elusive. Here we established a new genetic model by intercrossing the commonly used $p48^{+/Cre}$;$Kras^{+/G12D}$ (KP) model for pancreatic tumorigenesis, to a novel transgenic mouse expressing Lymphotoxin (LTαβ) in acinar cells and developing spontaneous pancreatic inflammation at an early age. Comparison of carcinogenesis progression and transcriptome analyses revealed that expression of Lymphotoxin in LTKP mice dramatically accelerates the development of premalignant PanIN lesions and highlight the involvement of LTβ receptor signalling in the initiation of pancreatic cancer.



Time-dependent regulation of gene expression in KP and LTKP murine models of pancreatic cancer.

Collaborations/Sponsors:

- Prof. Dr. Mathias Heikenwälder, PhD, (TUM Munich)
- Prof. Dr. Adrian Hehl, MD, (University of Zurich)
- Prof. Dr. Achim Weber, MD, (UniversityHospital Zurich)
- PD Dr. Thorsten Hornemann (UniversityHospital Zurich)

2.2.5 Bariatric Surgery

Hypertrophy dependent doubling of L-cells in Roux-en-Y gastric bypass operated rats

CF. Hansen, M. Bueter, N. Theis, T. Lutz, S. Paulsen, LS. Dalbøge, N. Vrang, J. Jelsing

L-cell derived gut hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) are thought to play a central role in the anti-diabetic effects of Roux-en-Y Gastric Bypass (RYGB). Therefore, an improved understanding of intestinal endocrine L-cell adaptability is considered pivotal.
We found that RYGB surgery induced hypertrophy of the gut mucosa in the food exposed regions of the small intestine coupled with a doubling in the total number of L-cells. The total gene expression capacity of the entire gut revealed a near 200% increase in both PYY and preproglucagon mRNA levels in RYGB rats associated with both increased L-cell number as well as region-specific increased transcription per cell (Figure 1). These findings indicate that RYGB in rats is associated with gut hypertrophy, an increase in L-cell number, but not density, and increased PYY and preproglucagon gene expression.

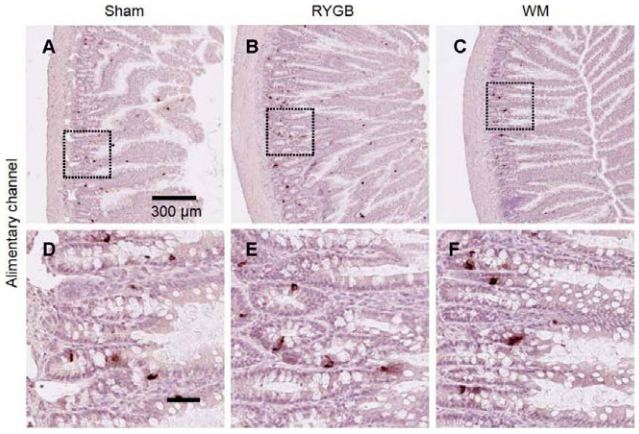


Figure 1: Representative micrographs of gut morphology (A-C) and GLP-2 immunohistochemistry (D-F) in the alimentary channel of SHAM, RYGB and SHAM WM animals.

Roux-en-Y gastric bypass surgery reduces bone mineral density and induces metabolic acidosis in rats.

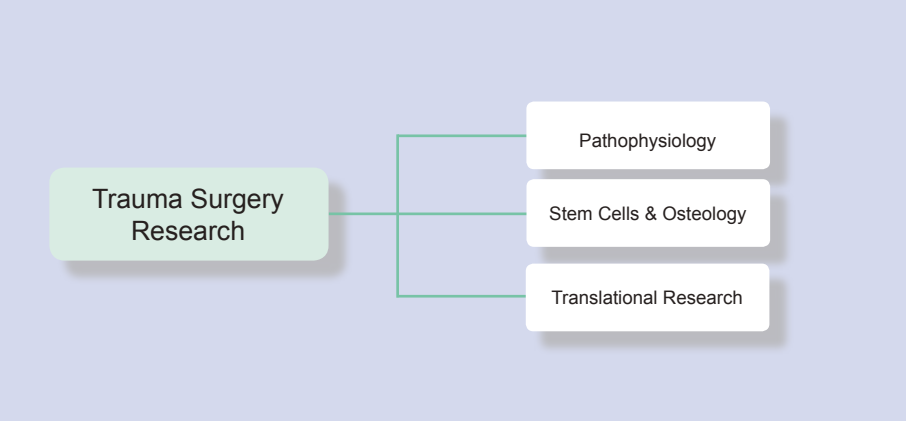
K. Abegg, N. Gehring, CA. Wagner, A. Liesegang, M. Schiesser, M. Bueter, TA. Lutz

Roux-en-Y gastric bypass (RYGB) surgery leads to bone loss in humans, but the primary causes remain unclear. To determine the contribution of calcium and vitamin D malabsorption bone mineral density, calcium and phosphorus balance, acid-base status, and markers of bone turnover were assessed at different time points for 14 wk after surgery in a rat RYGB model. Bone mineral density decreased for several weeks after RYGB. Intestinal calcium absorption was reduced early after surgery, but plasma calcium and parathyroid hormone levels were normal. 25-hydroxyvitamin D levels decreased, while levels of active 1,25-dihydroxyvitamin D increased after surgery. RYGB rats displayed metabolic acidosis due to increased plasma lactate levels and increased urinary calcium loss throughout the study. These results suggest that other factors than just calcium malabsorption contribute to insufficient bone restoration after RYGB.

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

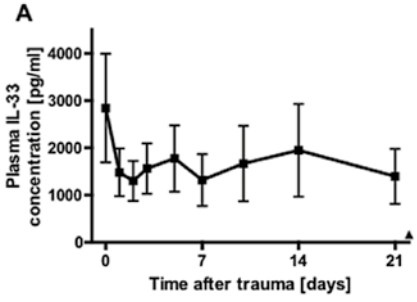

Prof. Dr. Clément Werner, MD

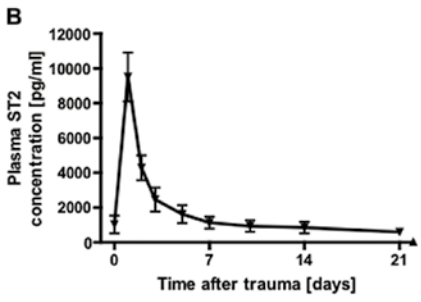
2.3.1 Pathophysiology

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

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. While IL-33 peaks within hours after trauma, the kinetics of sST2 release differ, with peak levels on d1. 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.





Time course (day 0 - 21) of interleukin-33 (IL-33) (A) and soluble ST2 (sST2) (B) in plasma from patients with multiple injury (injury severity score ISS ≥ 17 points, n=32).
▲= healthy volunteers (n=10).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Dr. Pavel Zwolak, MD


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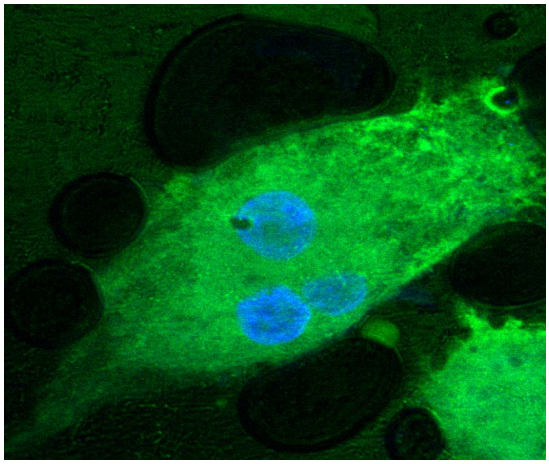
cand. med.

2.3.2 Stem Cells & Osteology

Adverse reactions to metal ions

D. Cadosch and H.-P. Simmen

Although many studies have investigated the role of metallic and non-metallic wear particles in osteoclastogenesis and aseptic loosening, very little is known about the effects of metal ions released by biocorrosion from the implant surface. At the bone metal interface, metal ions may directly interact with bone cells accelerating osteoclastic bone resorption and/or inhibiting the function of osteoblasts. Our projects aim to investigate the effects of the released metal ions on bone metabolism and their involvement in the pathophysiological mechanisms of increased osteolysis. Currently we are investigating the effects of vanadium 4+ and 5+ ions on the differentiation and activation of human osteoclasts *in vitro*. The results suggest that vanadium has an inhibitory effect on osteoclastic differentiation and activation without affecting cellular viability.

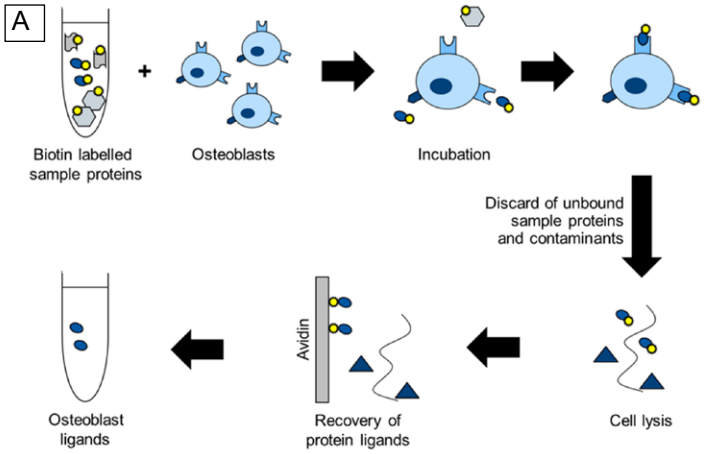


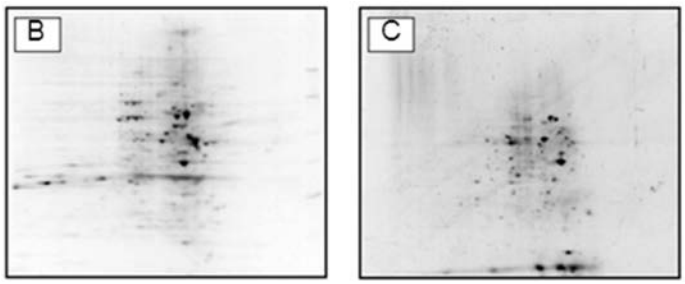
Multiphoton confocal fluorescence microscopy image (optical sections through the ''nuclear level'') showing human osteoclasts with intracellular metal ions complexes detected with Newport Green DCF diacetate ester (green color). Nuclei are stained in blue with DAPI.

Identification of humoral factors responsible for an enhanced osteogenicity in patients with a severe traumatic brain injury

D. Cadosch, H.-P. Simmen, P. Cinelli and G. Wanner

It is nowadays well established that severe traumatic brain injury (TBI) are associated with an accelerated fracture healing with hypertrophic callus formation and an increased incidence of heterotopic ossification. It is suggested that osteoinductive factor(s) are released by the injured brain into the blood circulation and act peripherally on the affected soft tissue. We were previously able to demonstrate the *in vitro* osteogenic potential of cerebrospinal fluid and serum derived from patients with a severe TBI. Hence, since then our research aimed to identify the assumed osteogenic factors. Using a novel proteomic approach, we found clear-cut differences in the pattern of proteins in two-dimensional gels between TBI and control patients without TBI. The identification of these factors would enable a better understanding of the pathophysiological mechanisms of fracture healing. Foremost, it would offer the possibility of developing novel therapies, which would improve and enhance fracture healing.



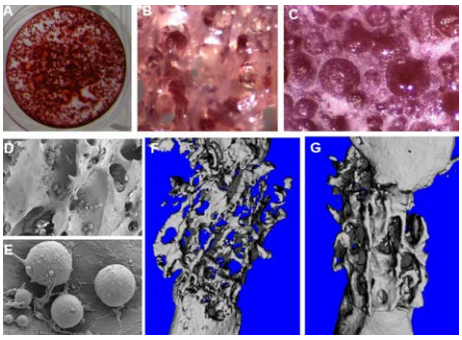


The figure shows the method of cell-based protein enrichment developed by our group. The method allows the isolation of all proteins that have a functional affinity for the surface receptors of a target cell line (e.g. human osteoblasts). Biotin is represented as yellow dot; structural osteoblastic proteins are represented as blue triangles. B.C.: 2D gel of serum (B) and CSF (C) proteins from TBI patients that have a selective affinity for human fetal osteoblastic 1.19 cell line.

Perivascular stem cells for bone tissue engineering

M. König, D. Cadosch, G. Wanner and P. Cinelli

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 using a magnetic-activated cell sorting (MACS) method. The osteogenic potential of the pericytes was then investigated *in vivo* using a robust “critical bone defect” mouse model.
A control group with collagenous bone scaffold but without cells was used. Eight weeks upon operation the bones were isolated and after removal of the plates the bone were analyzed by microCT. By 8 weeks in the animals which obtained a collagenous bone graft with perivascular stem cells an evident stronger mineralization was present as compared with the scaffold only controls, indicating that the CD146+NG2+CD45- population isolated from ASCs are able to contribute to bone regeneration and might represent a valuable alternative for improving bone healing in critical size bone injuries.



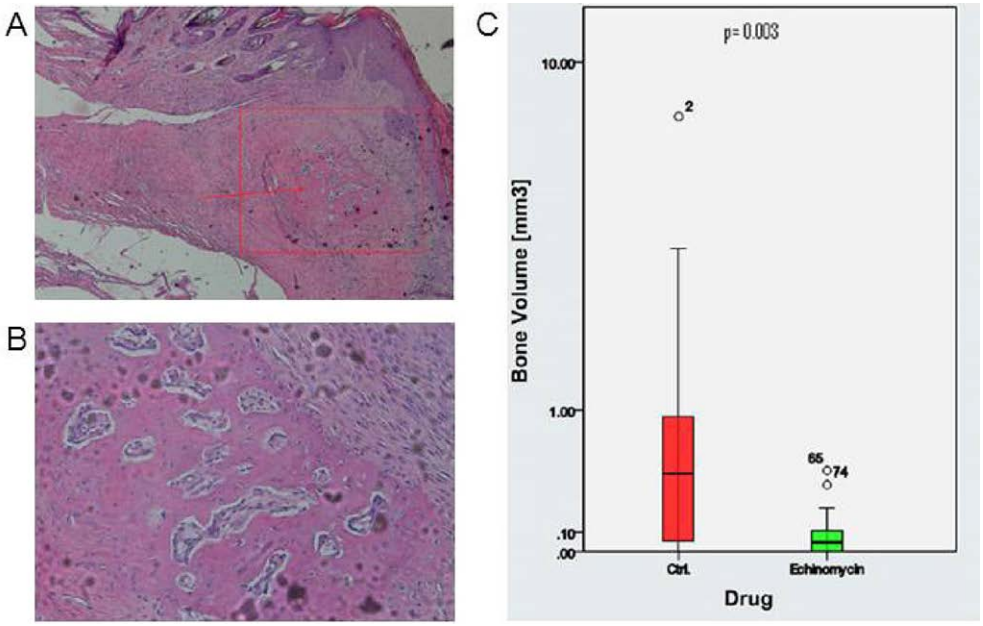
A. Differentiation potential of perivascular cells (PVC) towards osteoblasts. B. MTT staining of PVC seeded on collagenous bone. C MTT staining of PVC seeded on tricalciumphosphate scaffold. D,E. SEM pictures of PVC on collagenous bone. F,G. microCT 3D reconstructions of collagenous bone scaffold with (F) and without PVC (G) implanted in a femoral segmental critical-sized defect in mouse, 8 weeks upon implantation.

Heterotopic Ossification: New Approaches continued

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

Heterotopic ossification (HO) frequently causes complications following orthopedic and trauma surgery and may drastically reduce the postoperative outcome due to pain and joint contracture. HO may result in joint contracture, pain or even spasticity and neurovascular compression leading to significant disability. Patients with high-grade ossification frequently necessitate reoperation thereby largely increasing the costs of treatment.
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.

Hypoxia leads to numerous effects on a cellular level, one of which is the activation of the transcriptional complex hypoxia-inducible factor (HIF). Among several other actions, the HIF1-α signaling pathway in turn regulates angiogenesis through induction of the expression of vascular endothelial growth factor (VEGF).
We therefore hypothesized that by pharmacologically interfering with the HIF1-α signaling pathway, the amount of HO formation may be reduced. 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.
Mice were divided into two groups: The control group underwent Achilles tenotomy only. The Echinomycin group received Echinomycin subcutaneously. After 10 weeks the limbs were harvested and Micro CT was performed. We found a highly significant reduction in the bone volume following subcutaneous administration of Echinomycin compared to the control group. Nevertheless, it was not possible to completely prevent heterotopic ossification from forming. Further studies have yet to be conducted to optimize the results by altering the dosage and duration of administration as well as investigate the mechanism by which Echinomycin led to the reduction of HO formation.



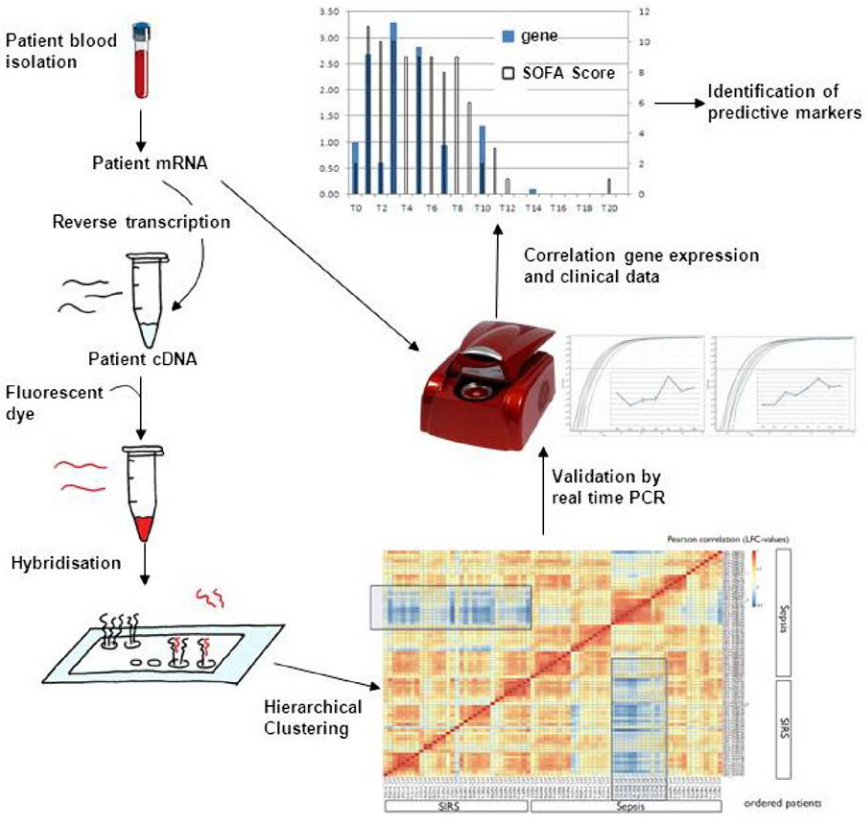
A. Islet of heterotopic bone within the soft tissue of a specimen's hind limb; B. Detailed image of islet of heterotopic bone; C. Bone volume in control and Echinomycin group.

2.3.3 Translational Research

Transcriptomic profiling in severely injured patients, opening "the window of opportunity"

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

Most Patients with multiple trauma develop post-traumatic complications such as a systemic inflammatory response syndrome (SIRS), sepsis and severe multiple organ dysfunction or -failure (MODS/MOF). Treatment of patients with severe trauma is performed by two alternative approaches: In "Early total care" all necessary operations are carried out immediately, whereas in the "Damage control" concept the patient is stabilized first and final operations, which might present a second stress/trauma for the patient, are performed some days (4-7 days) later during the "window of opportunity". However up to date no exact measures exist to precisely define this time point, which should be in an optimal way during a balanced phase of inflammatory and anti-inflammatory reaction. We performed a whole-genome gene expression analysis to get an insight into the complex mechanisms of the pro- and anti-inflammatory reaction followed by trauma. More than 100 severely injured patients with an injury severity score (ISS) >16 are enrolled in the study until today.
We identified a number of promising, not yet described genes which exhibit changes in expression and might play an important role in the inflammatory response. We validated the data by quantitative RT-PCR and we are currently designing a QRT-PCR based clinical diagnostic test for sepsis/SIRS for the evaluation of our patients.



Schematic representation of the project: Transcriptomic data upon validation and identification of candidate genes by quantitative real time PCR will be compared with clinical data and outcome allowing the identification of marker genes for the definition of the "window of opportunity".

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
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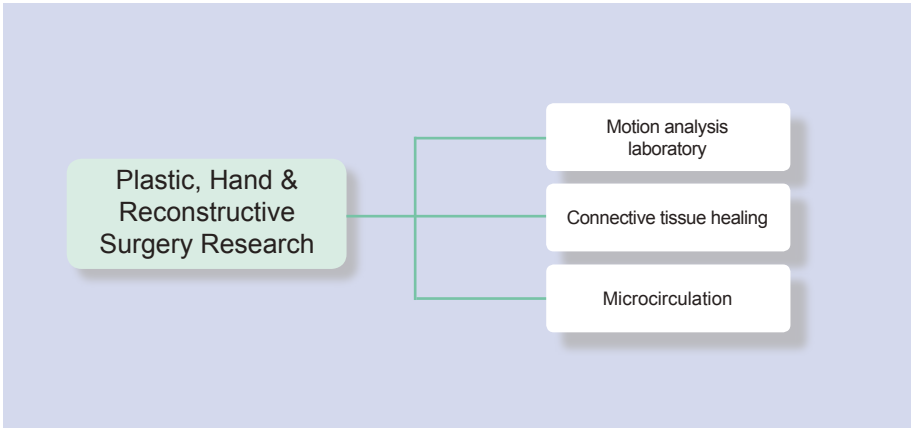

2.4.1 Tissue Engineering

In vivo high field MRI and histological analysis of artificial organs grown on the chorioallantoic membrane of the chick embryo: quantification of the perfusion capacity.

F. Kivrak-Pfiffner, C. Waschkies, Y. Tian, M. Calcagni, P. Giovanoli and J. Buschmann

Vascularization is essential for tissue regeneration and repair in tissue engineered artificial grafts. Current models do not allow easy analysis of vascularization of implants *in vivo*. Therefore *in vivo* visualization and analysis of vascularization in the biomaterials are desirable. A tool enabling to monitor non-invasively the perfusion capability of such artificial grafts in a cheap, established and reliable *in vivo* model would add great benefit to the research in this field.
We established an *in vivo* MRI method to quantify the perfusion capacity of DegraPol® foam scaffolds placed on the embryonic avian chorioallantoic membrane (CAM) *in ovo*. Perfusion capacity was assessed through changes in the relaxation rates R_1 before and after injection of a paramagnetic MRI contrast agent, Gd-DOTA (®Dotarem, Figure 1).

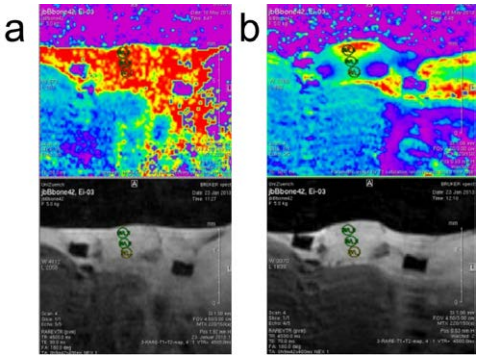

Figure 1 T_1-weighed images before (a), and after Gd-DOTA injection (b). ROIs were signed for each region of interest (interface, middle and surface).

Absolute R_1 relaxation rates were compared in different regions of the scaffold, i.e. at the interface to the CAM, in the middle and on the surface of the scaffold. The highest R_1 value was measured in the interface region, which attached to the CAM region, whereas the surface of the scaffold had the lowest R_1 value (Figure 2).

Significant positive correlation and agreement were observed between MR images and histologic analysis of capillary network density (R^2=0.983). Finally, we determined the contribution of the contrast agent in the biomaterial as a function of time (Figure 3). We thank *ab medica*, Italy, for providing the DegraPol® foams. This study has been funded by *Matching Fund 2011*.

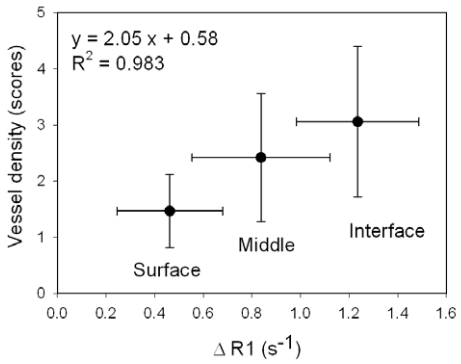

Figure 2 Relaxation rates (R_1) versus vessel density of three regions in scaffold-CAM complex.

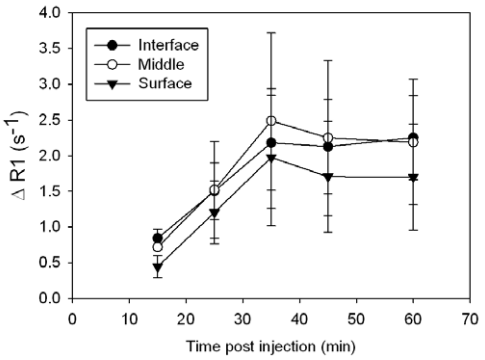

Figure 3 Differences of relaxation rates (R_1) and background relaxation rate (R_{10}) of scaffolds as a function of time.

Emulsion electrospinning of DegraPol® as a way of protein incorporation

O. Evrova, S. Nötzli, V. Milleret, J. Houska, M. Calcagni, E. Bonavoglia, P. Giovanoli, V. Vogel, J. Buschmann

Electrospun scaffolds from different polymers can act as carriers of growth factors and thus allow for different applications in the area of tissue engineering and regenerative medicine. For optimal use of these scaffolds and proper healing processes, appropriate release kinetics of the growth factors present on the scaffolds is necessary. Loading the scaffolds with growth factors can be realized by different immobilization techniques resulting either in covalent crosslinking, physical ab/adsorption, binding with the help of heparin or others.

In order to use electrospun DegraPol® meshes as growth factor carriers in tendon rupture repair, we chose emulsion electrospinning. As a model protein, FITC-labelled BSA was emulsion electrospun with DegraPol® (Figure 1).
Protein release kinetics are influenced by emulsion electrospinning conditions, which is a main part of this ongoing study. As a first model protein, we studied FITC-labelled BSA (Figure 2). We highly acknowledge the financial support by *ab medica*, Italy, and EMDO Stiftung, Zürich.

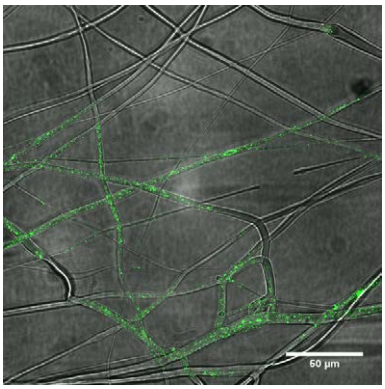

Figure 1 Water- in-oil emulsion electrospun DegraPol with FITC-labelled BSA. The incorporation of the model protein in the electrospun fibers can be clearly seen (green dots).

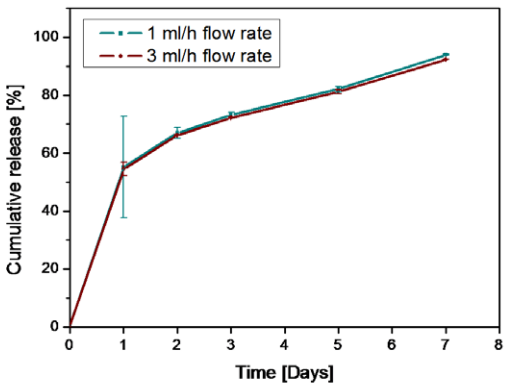

Figure 2 Cumulative release kinetics of FITC-BSA from electrospun DegraPol® fibers. Two different electrospinning conditions (1 and 3 ml/h flow rates were used) yielding different fiber diameters, however, not affecting the cumulative release kinetics.

2.4.2 Connective Tissue Healing

DegraPol® tube used as peritendinous anti-adhesive: a histological and biomechanical study in rabbits

G. Meier-Bürgisser, M. Calcagni, A. Müller, E. Bonavoglia, G. Fessel, J.G. Snedeker, P. Giovanoli and J. Buschmann

In (flexor) tendon rupture repair, there are still open problems up-to-date: adhesion and rupture in the early healing phase with a reoperation rate of 7 – 15 % leading to increased work disability and costs. On the one hand side, the repaired tendons should have high primary repair strength for early active post-operative motion, and on the other hand side, the repair site should be flat in order to allow the tendon to glide smoothly in the tendon sheath. According to Kuwata et al., optimum primary repair strength requires multi-strand locking loops and cross-stitch epitendinous sutures (Kuwata *et al.* 2007). However, such repair techniques lead to bulging at the repair site and thus to adhesion during the healing process (Khanna *et al.* 2009).

Considering these problems, a polymer device which bags the repaired tendon tightly and has a flat outer surface would probably help to reduce the adhesion caused by a rough and large primary cross-sectional area at the repair site. In addition, such a flattening tube may act as a potential carrier device and be supplemented with bioactive substances (Ehrbar *et al.* 2007) or stem cells (Yao *et al.* 2011) in order to stimulate the healing process *in situ*.

Here, an electrospun DegraPol® tube as an anti-adhesive was investigated. Therefore, the adhesion extent of lacerated rabbit Achilles tendons 6 weeks post-surgery either with or without the application of a DegraPol® tube was determined by macroscopic evaluation and by histology. In order to modulate the adhesion in the rabbit Achilles tendon model, we used two different immobilization protocols: The ankle angle of the cast was changed after 3 weeks from 180° to 150° (adhesion inhibiting immobilization protocol) or the cast had an ankle angle of 180° for the full 6-week period (adhesion provoking immobilization protocol). Biomechanical properties including load until failure, cross sectional area (CSA), stiffness and failure stress were determined. As results, (i) the application of a DegraPol® tube around the repaired tendon reduced successfully the adhesion formation without an inflammatory reaction in both post-operative treatment models (Figure 1 shows the anti-adhesive effect in the adhesion inhibiting immobilization protocol), and (ii) the biomechanical properties of the regenerated tendons were not adversely affected by the implantation of a DegraPol® tube (Figure 2).

The study is funded by the Fonds für Medizinische Forschung, the Wolfermann-Nägeli foundation and *ab medica*, Italy.

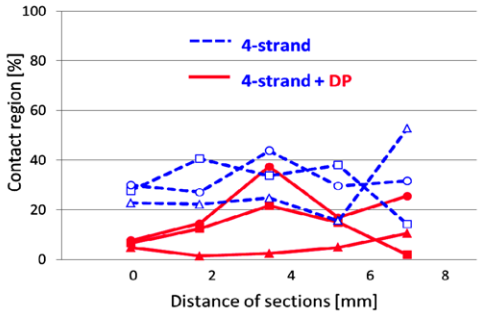

Figure 1 Adhesion extent at the repair site of conventionally sutured rabbit Achilles tendons (4-strand) and of 4-strand sutured tendons that received additionally a DegraPol tube (4-strand + DP) in the adhesion inhibiting immobilization protocol.While 4-strand sutured tendons exhibited on average 30% contact to the surrounding tissue over a distance of 7 mm at the repair site, the tendons that were 4-strand sutured and got a DegraPol tube showed a significantly lower contact region of on average 12% ($p < 0.001$).
(Method taken from Tan et al, Effects of Nonsteroidal Anti-Inflammatory Drugs on Flexor Tendon Adhesion, JHS 35A, June 2010).

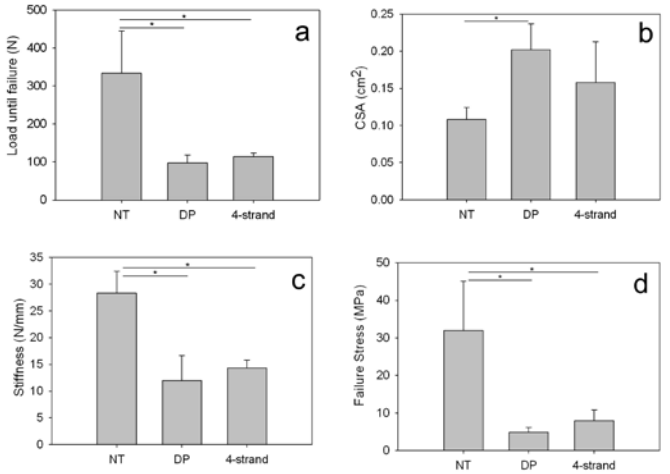

Figure 2 a-d Biomechanical properties of extracted Achilles tendons: Load until failure (a), cross-sectional area (b), stiffness (c) and failure stress (d). The application of a DegraPol tube does not have any adverse effect on the biomechanical properties of the regenerated tendons at 6 weeks post-surgery.

Collaborations:
- Department of Orthopedics, University Hospital Balgrist, Zurich

2.4.3 Microcirculation and Skin Tissue Engineering

N. Lindenblatt, A. Hegglin, M. Kijanska, M. McLuckie, K. Kornmann, N. Hegland, P. Giovanoli

Our group has developed a new model based on the original dorsal skinfold chamber, i.e. the modified dorsal skinfold chamber (MDSC), in which both the wound bed in the back and the tissue or material placed into the created skin defect in the front of the chamber simultaneously are accessible to repetitive intravital microscopy.

1. Differential proteome analysis of skin graft taking

The aims of the differential proteome study were (i) to identify proteins that are involved in the revascularization and incorporation of a skin graft and (ii) to assign their expression changes in a time course manner. This approach enables to gain a deeper insight into molecular processes that so far have not been associated to skin graft healing and to the investigated pathological situation, respectively. The differential proteome analysis during skin graft taking revealed that most prominent protein expression changes affected proteins from the L-arginine-NO pathway and, for the first time, pointed towards Rho-GDI 2-connected signaling pathways (Fig. 1, 2). The project was performed in cooperation with Prof. M. Glocker and Prof. B. Vollmar, University of Rostock, Germany).

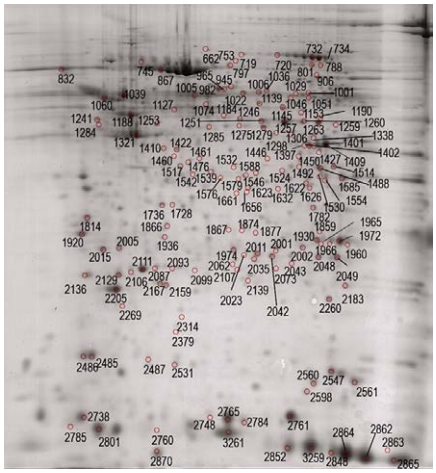

Fig. 1 Image of a reference 2D gel of a protein extract derived from a tissue sample pool consisting of 6 full-thickness skin grafts with underlying wound beds. For the first dimension (IEF) 400 µg protein were loaded on immobiline strips (pH 3-10 NL). SDS PAGE (12%) was applied for the second dimension and stained with Coomassie brilliant blue (CBB). About 1200 spots were separated and visualized. 101 non-redundant proteins were identified in 144 spots.

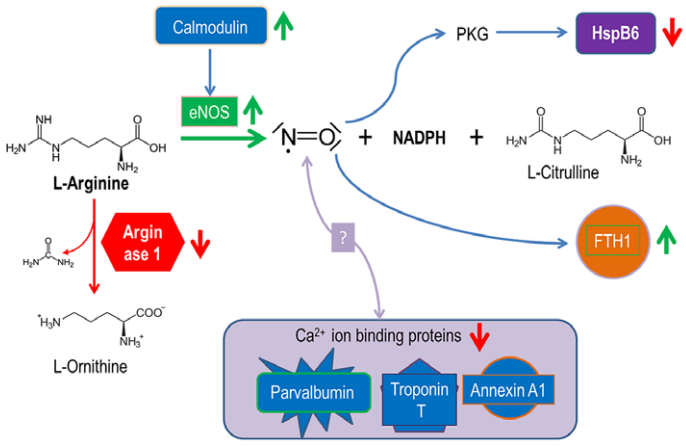

Fig. 2 Assignment of differentially expressed proteins to the nitric oxide pathway. Proteins marked with green arrows (overexpression) and red arrows (downregulation) were either positively identified as differentially regulated and their expression differences correspond with the nitric oxide pathway or their expression was complementarily tested in order to confirm the assignment of differentially expressed proteins to the NO pathway.

2. Evaluation of bacterial cellulose as wound dressing

First experimental studies in mice revealed that implanted bacterial cellulose is not vascularized. In addition an improved wound healing could be observed. It could serve as a wound dressing, as cells reject the dressing and close the wound created beneath it. Further studies are ongoing. (Fig 3). The project is a cooperation with Dr. Aldo Ferrari and Dr. Simone Bottan, ETH Zurich.

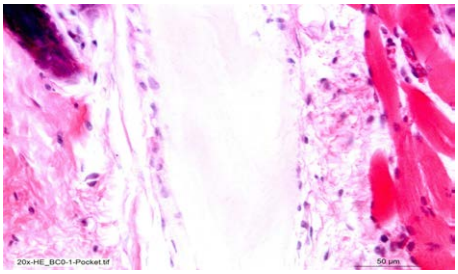

Fig. 3 HE staining of bacterial cellulose implanted into a skin pocket (A).

3. Vascularisation of polyurethane discs

We are studying the vascularization of polyurethane discs with a defined pore size of ~150 µm. After coating of the biomaterial with VEGF165 an increase in vascularization was observed compared to plain discs or discs coated only with Heparin (Fig. 4). This effect is dose-dependent. Further experiments are ongoing. The project is a cooperation with Prof. S. Hoerstrup and Dr. Christian A. Schmidt, UniversityHospital Zurich.

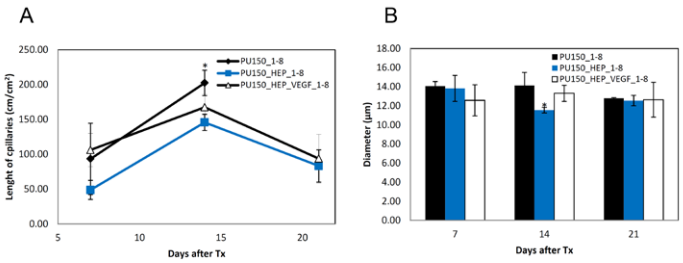

Fig. 4 Polyurethane disc revascularisation over 21 days after implantation in the DSC: (A) Length of perfused capillaries
*(B) Change of capillary diameter. *<0.05 vs. day 0.*

4. Analysis of the revascularization split-thickness skin grafts and the influence of storage time on graft performance

Storage of STSG is a common practice in burn surgery in Europe. Our study has proven the lack of detrimental effect of storage time up to 21 days on tissue collagen and elastic fibers. We assume that stored skin develops some hypoxia tolerance. Further research will be continuing to prove this hypothesis.

The direct comparison between the revascularization of FTSGs and STSGs exhibited a slightly different timing and strength in angiogenesis but maintained the same pattern of revascularization (Fig. 5).

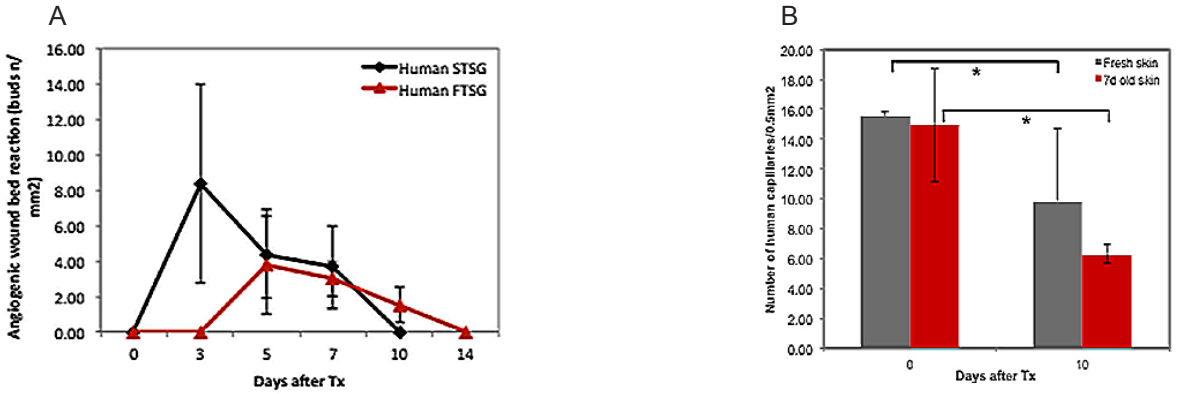

Fig. 5 : (A) Comparison of the wound bed reaction between STSGs and FTSGs transplanted into SCID mice. Angiogenic response of the host. Means ±SEM.
(B) Evaluation of capillary density in fresh and stored STSGs 10 days after transplantation.

Collaborations/Sponsors:

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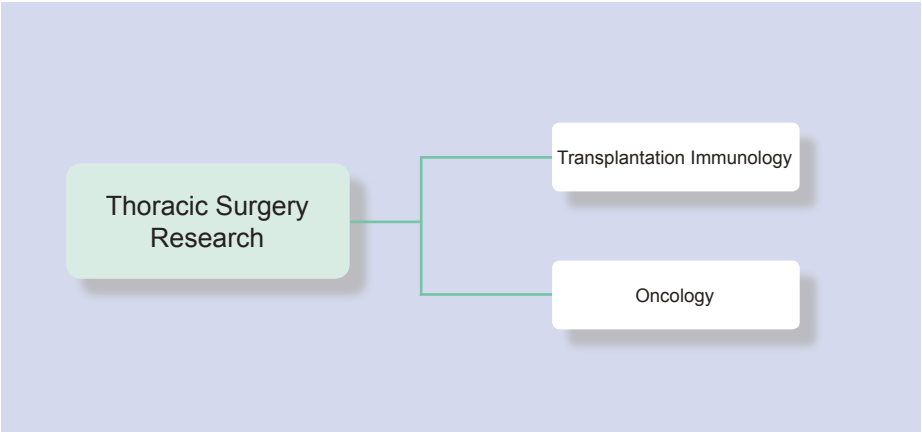
2.5 Thoracic Surgery Research



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2.5.1 Transplantation Immunology

The CD26-costimulatory pathway is critical for Th17-mediated lung allograft acceptance

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

The molecule CD26, a type II transmembrane glycoprotein, is expressed on activated T and B cells leading to classical T-cell co-stimulation and plays an important role in regulating $CD4^+$ T-cell activation in autoimmune diseases. Our *in vitro* experiments of mixed lymphocyte reaction (MLR) with a combination of sorted $CD4^+$ T-cells from C57BL/6 mice as targets (T) and splenocytes from BALB/c being effectors (E) upon CD26-inhibitor (Vildagliptin) showed that levels of IL-17A were significantly reduced when increasing the concentrations of Vildagliptin (p=0.003). Orthotopic mouse lung transplantation in a combination of MHC class I and II complete mismatch, BALB/c (donors) and C57BL/6 (lung Tx recipients) showed macroscopically, allografts from untreated mice (control) show severe AR, histologically A4, from Vildagliptin-inhibited mice show attenuated AR, histologically A1, and from CD26-/- mice show minimal AR, histologically A2. These findings identify CD26 as an important, yet underestimated co-stimulatory molecule in Th17-mediated lung allograft rejection.

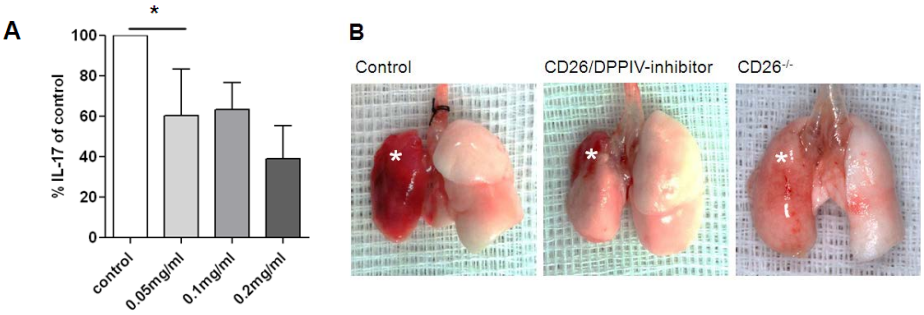

*Figure **1A**: Mixed lymphocyte reaction (from 4 independent experiments) between sorted $CD4^+$ T-cells from C57BL/6 mice being targets and splenocytes from BALB/c being effectors in a E:T ratio of 1:2. Levels of IL-17, as determined by ELISA, were significantly reduced by increasing the concentrations of CD26/DPP4 inhibitor (p=0.003);*
***B**: Allogeneic mouse single lung transplantation (n=11) between BALB/c (donors) and C57BL/6 (recipient) mice. Allografts (*) from non-treated mice (control) show robust acute rejection (AR), from CD26/DPPIV-inhibited mice (CD26/DPPIV-inhibitor) show attenuated AR, and from CD26 knock-out mice (CD26-/-) show minimal AR.*

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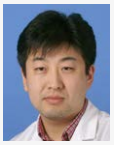

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Intragraft but not long term systemic CD26/DPPIV-inhibition protects from late pulmonary ischemia-reperfusion injury

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

The transmembrane molecule CD26/DPPIV has a catalytic activity which cleaves and thus degrades a wide range of peptides. An important substrate for CD26/DPPIV is SDF-1, a chemokine that has key functions in the recruitment of stem cells to ischemic injured organs for regeneration. We here aimed to increase the bioavailability of SDF-1 by inhibition of CD26/DPPIV with the specific inhibitor Vildagliptin to recover from ischemia-reperfusion (I/R) injury and to improve the outcome of lung transplantation (Tx) at a late time point after I/R injury, a time point which is generally underinvestigated in I/R injury research.
When determining SDF-1 in plasma after Tx, we surprisingly observed significantly more SDF-1 to be detectable in the abdominal aorta than in the inferior vena cava **(Fig. 1A)**. We could show that SDF-1 remained at high levels up to day 7 **(Fig. 1B)**, however, neither a reduction of immune cells that are infiltrating the transplant, nor an increase of beneficial stem cells could be observed at this late time point. In contrast, when preconditioning the donor lung with a CD26/DPPIV inhibitor, we found a macroscopic Tx amelioration **(Fig. 2A)** and a substantial reduction of immune cells that are infiltrating the transplanted lung **(Fig. 2B)**.

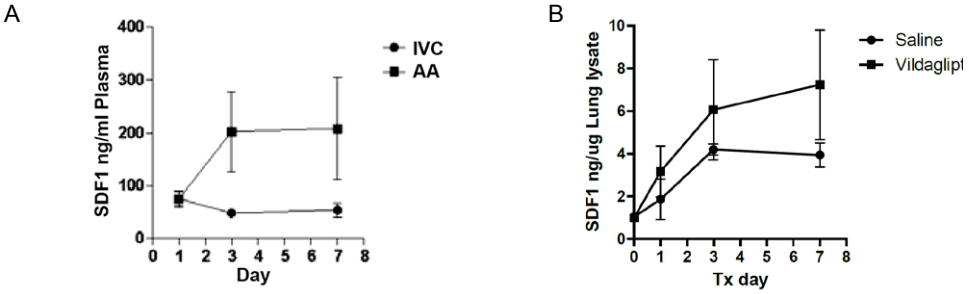

Figure 1: Difference of circulating SDF1 levels between inferior vena cava (IVC) and abdominal artery (AA) after orthotopic mouse lung Tx (n=4) (A) and the increase of lung transplant SDF-1 by Vildagliptin treatment (n=4) (B).

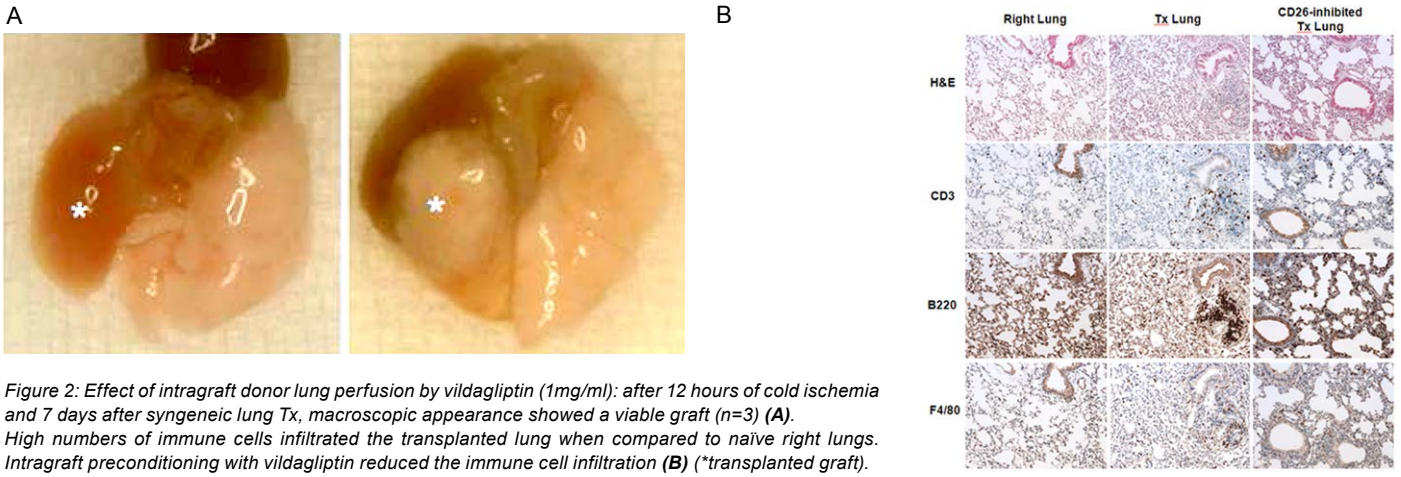

*Figure 2: Effect of intragraft donor lung perfusion by vildagliptin (1mg/ml): after 12 hours of cold ischemia and 7 days after syngeneic lung Tx, macroscopic appearance showed a viable graft (n=3) **(A)**.*
*High numbers of immune cells infiltrated the transplanted lung when compared to naïve right lungs. Intragraft preconditioning with vildagliptin reduced the immune cell infiltration **(B)** (*transplanted graft).*

CD26/DPPIV inhibition reduces lung tumor growth

J. H. Jang, W. Jungraithmayr

Recent work from our group revealed a correlation between lung cancer and CD26/DPPIV activity in patients particularly in early tumor stages (Fig. 1A). We therefore developed a model of tumor development in mice (inferior vena cava injection of syngeneic cell lines, LLC, MC38) and tested various cell lines for a potential anti-tumor effect upon CD26/DPPIV inhibition. After 3 weeks, tumor nodules could be observed within the lung without metastasis to the secondary organ (Fig 1 B, C).

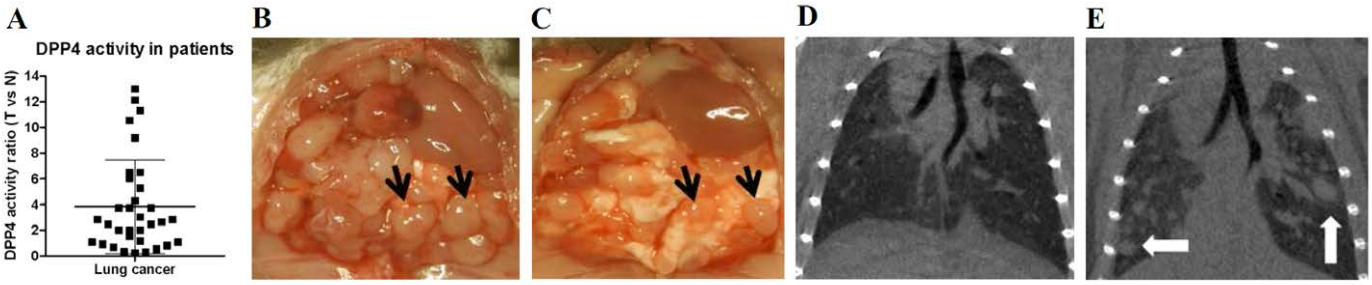

*Figure 1: CD26/DPPIV activity ratio between tumor and normal tissues in lung adenocarcinoma patients (**A**). Macroscopy of tumor manifestation from MC38 (**B**) and LLC (**C**) cell lines within the lung (arrows). Depiction of normal mouse lung by micro CT and (**D**) and 3 weeks after tumor cell injection, tumor nodules can be visualized within in the mouse lung (**E**, white arrows).*

Before testing the specific CD26/DPPIV inhibitor (Vildagliptin) *in vivo*, we tested different cell lines *in vitro* which are of various origins including mouse colon (MC38, CT26), human colon (HT29), mouse lung (LLC), and human lung (Ekvx, H460).
A single treatment of Vildagliptin (3.2mg/ml) reduced viability of cell lines within 3 days (Figure 2).

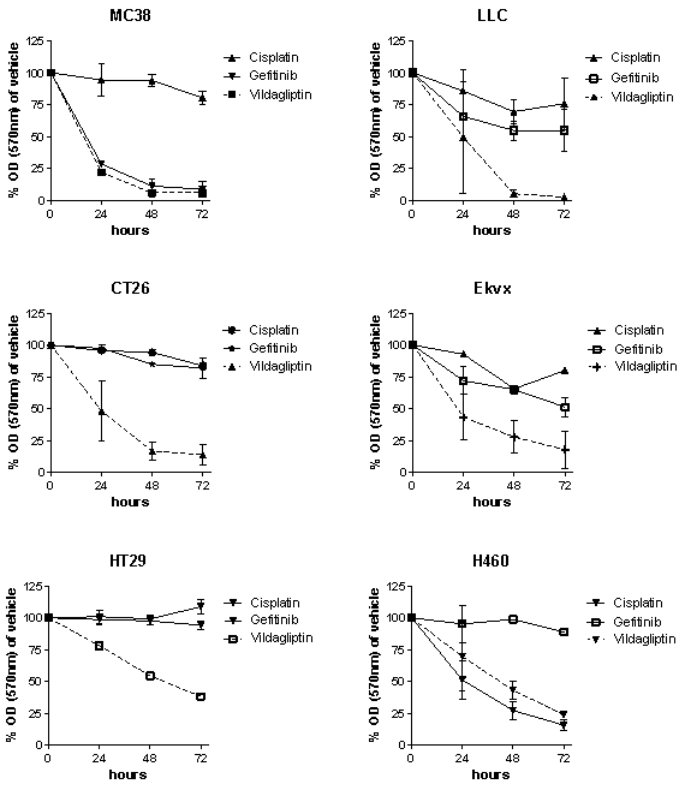

Figure 2: The effect of CD26/DPPIV inhibitor, Vildagliptin against different cancer cell lines in vitro.

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- Dr. Markus Weiger, ETH Zurich, Institut für Biomedizinische Technik, Zürich
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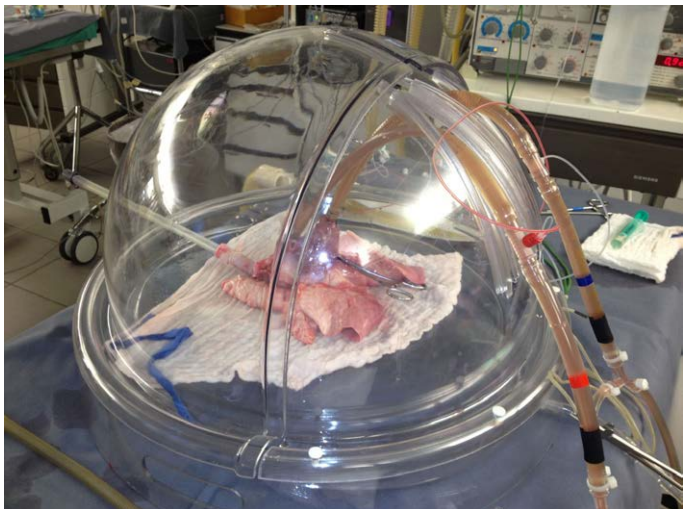
Ex vivo reconditioning of donor lungs with inhaled N-Acetyl cysteine after prolonged cold ischemia

I. Inci, S. Hillinger, S. Arni

N-Acetyl cysteine (NAC) is a precursor of the most important physiological antioxidant glutathione and a sulfhydryl containing substance. Sulfhydryl-containing compounds, especially glutathione, are important in the protection of cells against hydroperoxide damage. This important reducing agent and antioxidant is involved in maintaining the cellular oxidation-reduction balance, and has been shown to protect cells from a wide variety of endogenous and exogenous insults.

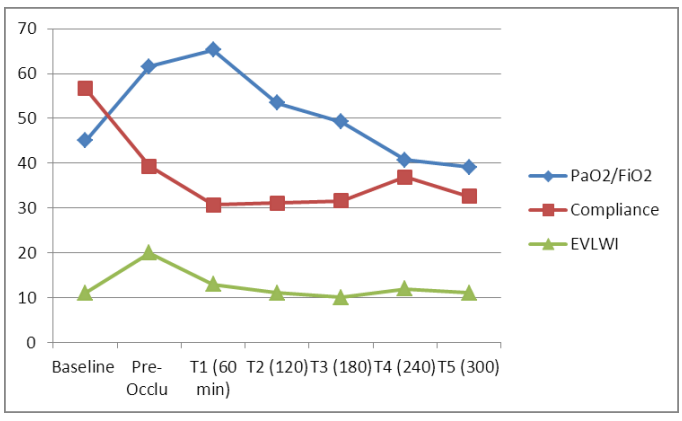
The *ex vivo* lung perfusion (EVLP) is as a method, not only to evaluate lungs before transplantation, but also recondition lungs of inferior quality outside the body.

In order to reduce primary graft dysfunction following lung transplantation, we will evaluate 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 will use 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 will allow to better document the beneficial role of reconditioning damaged lungs with both EVLP and inhaled NAC after a prolonged cold ischemic storage.

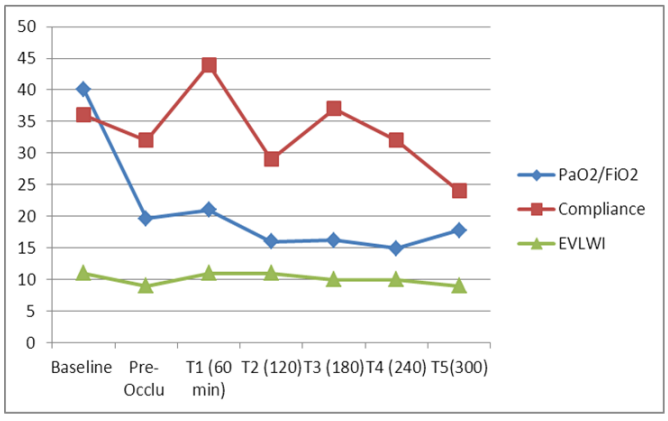


Preliminary work

The graphs shown below are the 2 representative experiments completed in the present project either with inhaled N-acetylcysteine during EVLP for a treated animal or inhaled saline for the control over the 6 hours survival experiment. When the damaged lungs were nebulized with NAC the treated animal has a better graft function as measured by oxygenation (PaO2/FiO2 ratio), lung compliance and low lung water index which shows decreased lung edema compared to control animal (Graphs 1 and 2). These promising pilot experiments are documenting, *in vivo*, the physiological improvement of the damaged lung by a pre-treatment of the grafts with the reducing and anti-oxidant reageant NAC.



Graph1. Treated group: animal transplanted with donor lung reconditioned with inhaled NAC during EVLP



Graph2. Control group animal: Saline inhalation of donor lung during EVLP

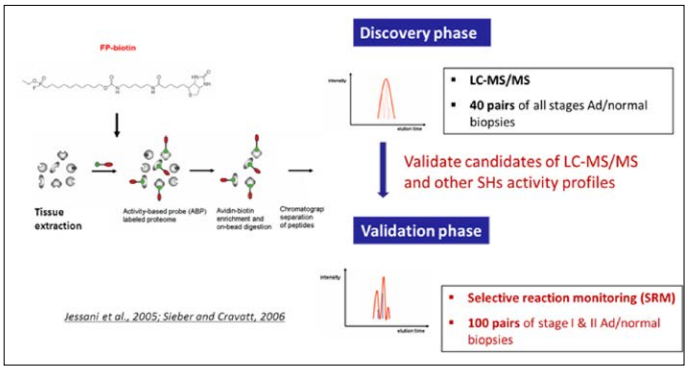
2.5.2 Oncology

2.5.2.1 Lung cancer

Selective reaction monitoring for activity-based proteomics in human lung cancer biopsies

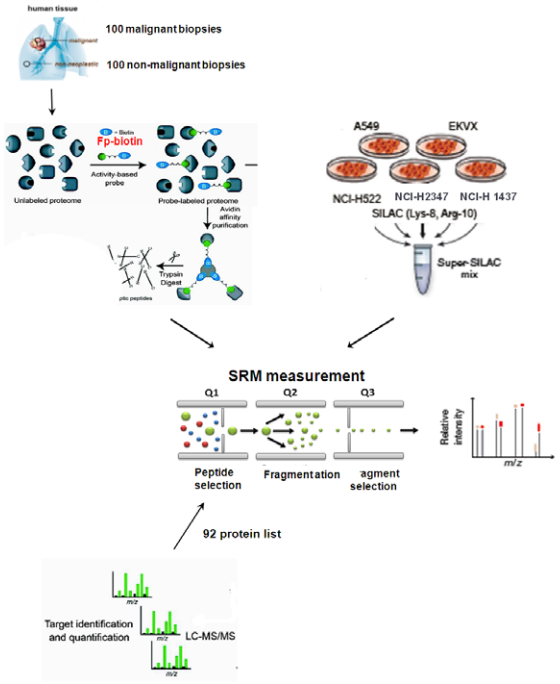
N. Le, M. Matondo, S. Hillinger, T. Wiedl, W. Weder, R. Aebersold, S. Arni

Our long-term goal is the use of the activity profile of the serine hydrolase (SH) enzyme superfamily as potential biomarker candidates in human lung adenocarcinoma (LA). In the discovery phase, we could demonstrate that the SH activities of ESD and ABHD11 as potential biomarker candidates for LA, both in a statistically significant model. Now we validate ABHD11, ESD and other SHs activity profiles with a larger cohort of patient tissues and with the selected reaction monitoring (SRM) methodology.



The discovery phase and validation phase of our studies

In this study, a set of 100 adenocarcinomas stage I and II biopsies with 100 matching non-neoplastic biopsies will be analyzed by using quantitative proteomics approach, selected reaction monitoring (SRM). The lysates from 200 biopsies will be labelled with FP-probe to target functional members of the SH superfamily before measuring collected peptides by SRM.



Workflow of SRM-based proteomic experiments for the validation phase

From the list of 121 serine hydrolase enzymes defined by our previous LC-MS/MS, other publications and databases, we detected 92 SH enzymes by SRM experiments, including our 2 candidates ESD and ABDH11. In the next step, assays for measuring 92 proteins will be applied to 200 SH-probe labeled samples. The final goal is to validate the activity changes of ESD and ABDH 11, even other SHs. We anticipate that ESD and / or ABHD11 activities have the potential to develop into molecular predictors with a reliable clinical significance. The implemented activity-based proteomics platform represents a powerful tool in the search for novel disease biomarkers.

Collaborations:

- Prof. Dr. Ruedi Aebersold, Dr. Mariette Matondo (Institute of Molecular Systems Biology, Swiss Institute of Technology, Zurich)
- Dr. Rik de Wijn, Dr. Martjin Dankers (PamGene International, 's-Hertogenbosch, The Netherlands)
- Prof. H. Moch and Dr. A. Soltermann, Department of Pathology, UniversityHospital Zurich

Multiplex profiling of protein tyrosine kinase substrates in early stages human lung adenocarcinoma

S. Arni, T. Hong, N. Le, W. Weder, S. Hillinger

Biomarkers with reliable prognostic significance are of utmost importance but due to a lack of immediate correlation between levels of protein and their corresponding mRNA, a screen based on the kinase activity becomes a promising option to circumvent this limitation with the tremendeous advantage of focusing on therapeutically targetable enzymatic activities. The aim of this study is to clarify the following hypothesis: Is the *in vitro* multiplexed tyrosine phosphorylation of substrates a possible approach to molecularly classify the kinome of early stage lung adenocarcinoma biopsies and obtain a prognostic signature correlating with the survival of patients?

We incubated TNM stage 1 and 2 lung adenocarcinoma kinomes on PamChip®4microarrays and followed the kinetics of the multiplexed tyrosine phosphorylation for 144 peptides substrates. Based on a 76-point 'response-signature' we obtained 73 % of correct prediction with a 10 fold cross validation PLS-DA analysis in 74 early stage lung adenocarcinoma biopsies. Moreover, we detected 26 peptides substrates significantly more inhibited in kinomes of long-term survivors than in kinomes of the short-term survivors (Fig1).

In frozen biopsies of TNM stage I adenocarcinoma and with a PLS-DA analysis applied to a 76-point 'response-signature' we present the feasibility to discriminate between long-term and short-term survivors (Fig.2). Furthermore, the found differences in enzymatic activities in lung biopsies may result in the identification of new targets in future anti lung cancer therapy efforts.

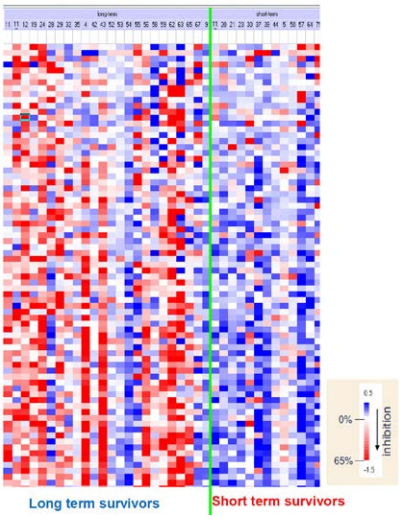


Figure 1
Heatmap showing fold change of peptide tyrosine phosphorylations for TNM stage 1 lung adenocarcinoma patients sorted according to survival . The Log2-transformed ratio of phosphorylation for the biopsies of malignant versus malignant treated with the PTKI gefitinib of the 76 selected peptides used for the signature are sorted according to correlation with patient survival. Inhibition is scaled per peptide and the red color indicate higher inhibition of phosphorylation. The vertical green bar indicates the separation of the long-term survivors on the left side from the short-term survivors on the right side.

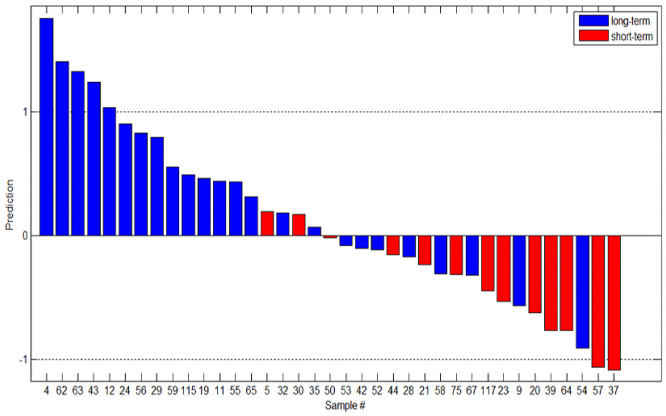


Figure 2
TNM stage 1 lung adenocarcinoma PLS-DA class prediction result performed with the 76 selected peptides. Prediction performance was tested using 10-fold cross-validation for 37 samples tested to obtain here 73% correct prediction. With prediction performance greater than zero, the samples are allocated to the long-term survivor group and to the short-term survivor group when prediction performance are smaller than zero. Prediction performance which is further away from the decision boundary set at 0 is less likely to really belong to the opposite group.

Collaborations:

- Prof. Dr. Ruedi Aebersold, Dr. Mariette Matondo (Institute of Molecular Systems Biology, Swiss Institute of Technology, Zurich)
- Dr. Rik de Wijn, Dr. Martjin Dankers (PamGene International, 's-Hertogenbosch, The Netherlands)
- Prof. H. Moch and Dr. A. Soltermann, Department of Pathology, UniversityHospital Zurich

2.5.2.2 Malignant pleural mesothelioma

Clinical relevant prognostic markers for Malignant Pleural Mesothelioma (MPM):

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

A Aberrant dysregulation of signaling pathways such as Hippo and Phosphatidylinositol 3-Kinase (PI3K)/ mammalian Target of Rapamycin (mTOR) pathways has been reported in a wide variety of cancers including MPM and can represent the major cause of therapeutic resistance [1]. Loss of the tumor suppressor Neurofibromatosis type II (NF2), major upstream regulator of the Hippo and mTOR pathways, has been reported in nearly half of MPM patients [1]. We previously detected expression loss of phosphatase and tensin homologue (PTEN), a tumor suppressor gene of the PI3K/mTOR pathway, in 62% of MPM patients [2]. We first sorted out the prognostic significance of the PI3K/mTOR pathway employing tissue microarrays composed of paired samples from patients with MPM (*n* = 153) collected prior- and post-induction-chemotherapy. We observed that high p-S6 expression, the downstream effector of mTOR/PI3K pathway, and high Ki-67 expression (proliferation index) in samples of untreated patients was associated with shorter progression free survival. Paired comparison of samples prior and post induction chemotherapy revealed that decreased cytoplasmic PTEN as well as increased p-mTOR expression was associated with a worse overall survival. Employing fluorescent *in situ* hybridization probing genomic region of PTEN, we further confirmed that the reduced expression of PTEN tumor suppressor gene is not due to the gene deletion. These data were recently published [3]. If confirmed, these data suggest PI3K/mTOR pathway to be a target for selected MPM patients.

B NF2 takes part in Hippo pathway by inducing phosphorylation and cytoplasmic retention of Yes-associated protein (YAP). YAP works as a transcriptional co-activator, in the absence of NF2, it translocates to the nucleus and enhances transcription of target genes such as survivin, connective tissue growth factor (CTGF) to induce tumor growth and suppress apoptosis [1,4]. In this regard, we aimed to investigate the prognostic value of Hippo pathway major constituents (NF2, YAP, survivin and CTGF) in both cytoplasmic and nuclear fractions. Kaplan-Meier survival curves revealed an association of nuclear survivin labeling index assessed in pre-chemotherapy tissues with PFS months (p=0.051; figure 1). Nuclear YAP score and nuclear survivin labeling index was significantly reduced in post-chemotherapy compared to pre-chemotherapy tissue. We also observed strong correlation between proliferation index (Ki-67) and nuclear survivin (p<0.0005).

We will confirm the trend observed of nuclear survivin in an independent MPM cohort. However, NF2 and CTGF assessment is still ongoing. Thus, the correlation and stimulation mechanism between NF2 and Hippo pathway will be investigated in the near future. If confirmed, a strategy to normalize the dysregulation of NF2- Hippo pathway might be the rationale for developing a novel therapy against MPM.

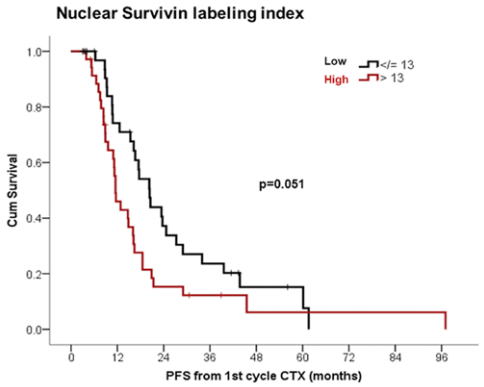


Figure 1: Kaplan-Meier survival curves revealing association between Ki-67 and nuclear survivin labeling index assessed in pre-chemotherapy tissues with clinical outcome. Median PFS months (95% CI): 20 (16-24) vs 12 (9-14).

Collaborations:

- Toronto General Hospital, University of Toronto (Dr. Ghassan Allo, Dr. Ming Tsao, Prof. Marc de Perrot)
- Biostatistics Unit, University of Zurich (Dr. Burkhardt Seifert)
- Laboratory of Molecular Oncology, USZ (Prof. Rolf Stahel, Dr. Emanuela Felley-Bosco)
- Department of Pathology, UniversityHospital Zurich (Prof. Holger Moch, Dr. Alex Soltermann, Dr. Bart Vrugt)
- Brigham and Women's Hospital, Boston (Prof. Raphael Bueno)

Localized intracavitary treatment with hedgehog antagonist in an orthotopic Malignant Pleural Mesothelioma rat model of recurrence:

M. Meerang and I. Opitz

Tumor recurrence remains a challenge in MPM even after complete resection of the tumor. Stem cell activation by the hedgehog pathway was recently reported in MPM patient tissues [5]. Thus we hypothesized that the presence of tumor stem cells in MPM could contribute to chemo-resistant phenotype and tumor recurrence. Here we aim to use an orthotopic MPM rat model of recurrence by using *in vivo* bioluminescence imaging [6] to test the efficacy of hedgehog antagonism in the prevention of MPM recurrence.

A potent and selective hedgehog antagonist, Vismodegib, targets and inhibits the cell surface activator of hedgehog signaling, smoothened (SMO) thus antagonizes the hedgehog signaling pathway [7,8]. We specifically aim to prove whether the localized intracavitary treatment with Vismodegib could efficiently inhibit MPM recurrence. Intracavitary administration of chemotherapy was proven to be effective in the improvement of tissue drug concentration [9]. This treatment approach is currently under phase I of clinical trials in a study being conducted by our group. The inoculation of MPM cells expressing luciferase (IL-45-luc) into immunocompetent rats produced a single tumor nodule at day 6 after inoculation in all rats. The nodule was resected and by visualizing the relapse on a daily basis, we observed tumor relapse with continuous growth at day 1 after resection. Six days later, the tumor was resected and we could detect the expression of a hedgehog ligand (desert hedgehog) while it was nearly undetectable *in vitro* (see figure 2) suggesting a role of the hedgehog pathway in this rat MPM model.

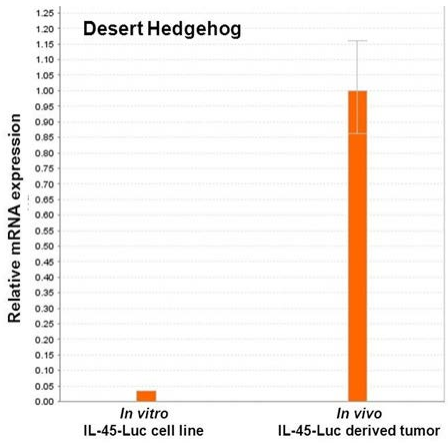


Figure 2: Quantitative real time PCR analysis showing the comparison of desert hedgehog expression (mRNA) in IL-45-Luc cell line versus IL-45-Luc derived tumor.

Collaborations:

- Division of Thoracic Surgery, USZ (Prof. Walter Weder, Karima Bérard)
- Laboratory of Molecular Oncology, UniversityHospital Zurich (Prof. Rolf Stahel, Dr. Emanuela Felley-Bosco)
- Laboratory for Molecular Radiobiology, UniversityHospital Zurich (Prof. Martin Pruschy, Dr. Angela Broggini-Tenzer)

Evaluation of tumor imaging techniques for Malignant Pleural Mesothelioma orthotopic rat model:

M. Meerang, I. Opitz

An orthotopic rat tumor model for MPM is useful for several applications such as drug testing and surgical intervention [10]. For non-invasive and repetitive visualization of tumor burden, a reliable imaging method is required. Here, we compared 2 techniques namely bioluminescence *in vivo* imaging (Bli) [6] and magnetic resonance (MR) imaging. Tumor burden quantified from MRI correlated significantly with macroscopic tumor volume measured ($p<0.0001$; $r=0.99$). However, signal intensity of Bli did not correspond with tumor volume measured neither by the macroscopic observation ($p=0.50$; $r=-0.41$) nor by MRI ($p=0.50$; $r=-40$; see figure 3). Our results showed that MRI allowed reliable assessment of MPM tumor burden in the present model. This non-invasive imaging technique could also be performed repetitively. Bli has been shown to be a sensitive detection method; however reliable quantitation could be influenced by several factors such as the expression level of luciferase in cells or the variable absorption of its substrate D-luciferin.

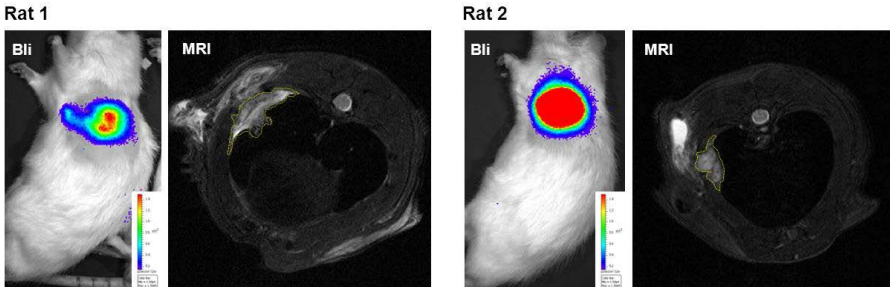


Figure 3: The figure shows discrepancy between tumor volume visualized by MRI and Bli signal. Rat 2 shows strong Bli signal (red) although the tumor size measured by MRI is smaller contrarily to Rat1 which exhibits lower Bli signal but big tumor volume can be visualized by MRI.

Collaborations:

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- Laboratory of Molecular Oncology, UniversityHospital Zurich (Prof. Rolf Stahel, Dr. Emanuela Felley-Bosco)
- Department of Radiology, UniversityHospital Zurich (Dr. Andreas Boss, Dr. David Kenkel)
- Laboratory of Molecular Radiobiology, UniversityHospital Zurich (Prof. Martin Pruschy, Dr. Angela Broggini-Tenzer)

Clinical staging for Malignant Pleural Mesothelioma

I. Opitz, W. Weder

In this project, we aim to assess the value of different modalities for a better clinical staging and assessment of therapy response of malignant pleural mesothelioma (MPM) including computed tomography (CT)-scan, positron emission tomography-CT (PET-CT), PET-magnetic resonance (MR) (Frauenfelder et al. 2011). Patients with proven MPM will undergo chest CT scan and PET-CT before and after chemotherapy. Tumour response will be measured and classified with modified RECIST criteria and compared to tumour volumetric approach in CT-scans, the metabolic response will be defined in PET-CT. Clinical staging will be obtained using TNM classification and IMIG-stages with the help of CT- and PET-CT. In a separate project, patients will be staged retrospectively based on CT and PET-CT by 2 independent observers (2 radiologists and 1 thoracic surgeon) and inter-observer correlation in clinical staging will be assessed. Outlook: Improvement of the diagnostic tools would help to select patients for treatment of MPM. PET-MR is currently assessed as a new staging tool for malignant pleural mesothelioma.

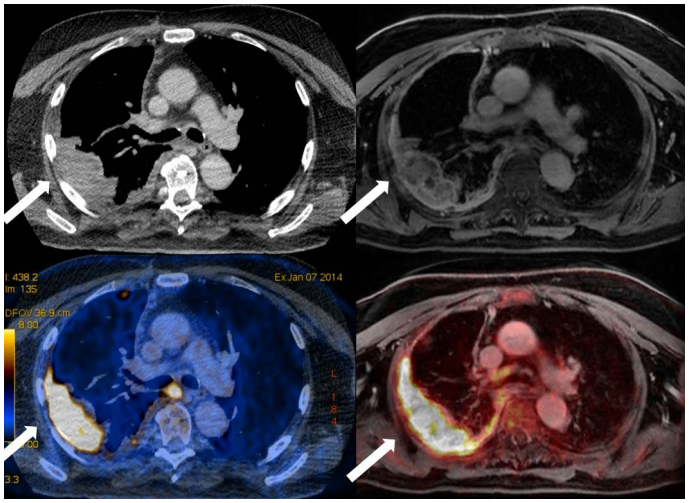


Figure 4: upper row CT with iv contrast and MR with iv contrast and lower row PET-CT and PET-MR. It is apparent, that with MR-analysis the layers of the thoracic wall are better illustrated than with CT.

Collaborations:

- Division of Thoracic Surgery, USZ (Dr. Martina Friess, Dr. Peter Kestenholz)
- Laboratory of Molecular Oncology, UniversityHospital Zurich (Prof. Rolf Stahel)
- Institute of Biostatistics, UniversityHospital Zurich (Prof. Burkhard Seifert)
- Institute of Radiology, UniversityHospital Zurich (Dr. Thomas Frauenfelder, Dr. Roger Hunziker, Dr. Thi Dan Linh Nguyen-Kim)
- Division of Nuclear Medicine, USZ (PD Dr. Patrick Veit-Haibach, PD Dr. Lars Husmann)

Localized intracavitary therapy for MPM – from bench to bedside

I. Opitz, W. Weder

Our newly developed intracavitary chemotherapy with cisplatin loaded in to a fibrin carrier for MPM will be applied into clinical application (Lardinois, Jung et al. 2006; Opitz, Lardinois et al. 2007; Opitz, Erne et al. 2011). Safety and tolerability, and later efficacy will be assessed in mesothelioma patients who underwent prior surgery. This study comprises of Phase I-dose-escalation trial and Phase II trial for the confirmation of safety and tolerability of intracavitary cisplatin-fibrin after Pleurectomy/Decortication (P/D) (Phase I Dose-Escalation and Phase IIa Monocentric Open Trial for the Evaluation of the Safety of ***In***tracavitary Cisplatin-***F***ibrin ***L***ocalized ***C***hemotherapy after Pleurectomy/Decortication for the Treatment of Patients with Malignant Pleural ***Meso***thelioma, ***INFLuenCe*** – ***Meso***).
The primary objective of the phase I is to determine the maximally tolerated dose (MTD) of intracavitary cisplatin-fibrin in patients with MPM. The secondary objectives of the phase I are the safety and tolerability of intracavitary cisplatin-fibrin. Furthermore, the recommended dose of intracavitary cisplatin-fibrin for exploration in a phase II study will be assessed. Patients' outcome will be measured by assessment of overall (OAS) - and progression free survival (PFS) in order to determine the efficacy of the treatment. Moreover, the pharmacokinetics for the use of intracavitary cisplatin-fibrin in humans will be studied.
In order to gain more information about the intracavitary application of cisplatin-fibrin at the MTD, a phase II study with 20 more patients will be conducted. Primary endpoint will be to study the safety and tolerability of intracavitary cisplatin-fibrin after radical P/D at the MTD in 20 patients. Secondary endpoint will be to study the efficacy of intracavitary cisplatin-fibrin by assessment of OAS and PFS. Further studies of the pharmacokinetics of intracavitary cisplatin-fibrin in humans will be performed. The effect of cisplatin-fibrin on mechanisms of resistance to cisplatin will be assessed by determination of marker for senescence and apoptosis.
So far we included patients in the first and second dose level and we observed no dose limiting toxicity. Preliminary pharmacokinetic analyses are very promising with very high and cytotoxic cisplatin concentrations in the chest wall and very low systemic concentrations.
Outlook: With this study, we expect to transfer local tumor control for predominantly locally recurring MPM by introduction of intracavitary application of cisplatin-fibrin after radical surgery into clinic.

Collaborations:
- Division of Thoracic Surgery, USZ (Dr. Martina Friess, Dr. Olivia Lauk, Dr. Arthur Kostron, Dr. Mayura Meerang, MSc. Cordelia Bommeli)
- Division of Pharmacology and Toxicology, UniversityHospital Zurich (Dr. Alexander Jetter)
- Laboratory of Organic Chemistry, Swiss Federal Institute of Technology (Prof. Detlef Günther)
- Laboratory of Molecular Oncology, UniversityHospital Zurich (Prof. Rolf Stahel, Dr. Emanuela Felley-Bosco)
- Guillaume Wuilleret (Dissertation)
- Biostatistic Unit, ISPM, University of Zurich (Prof. Burkhardt Seifert)

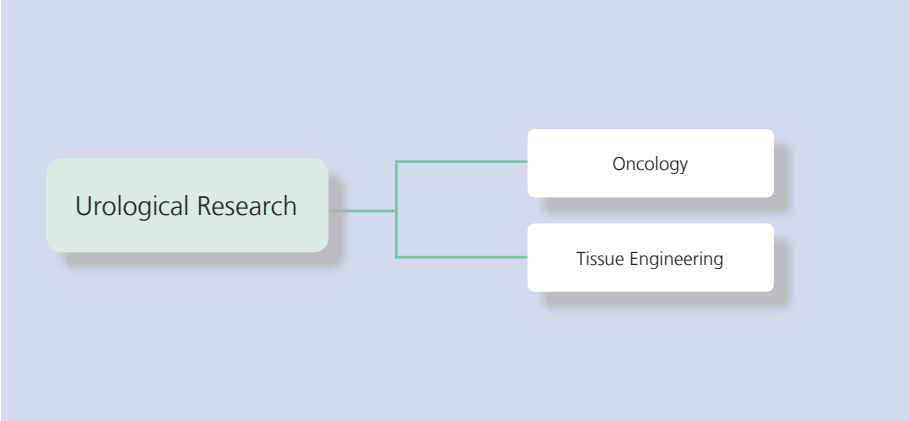
Multimodality benefit score for improved patient selection for patients with malignant pleural mesothelioma undergoing extrapleural pneumonectomy after induction chemotherapy - A review of 12 years' experience

I. Opitz, W. Weder

To identify selection factors for multimodal therapy of patients with malignant pleural mesothelioma (MPM) based on survival data from 12 years of experience we analyzed by multivariate analysis 186 MPM patients (intended to be treated with induction chemotherapy followed by extrapleural pneumonectomy (EPP) from May 1999 to August 2011). Hematologic toxicity was significantly less frequent after cis/pem in comparison to cis/gem. There were no differences in response or survival outcome between the regimens. 128 patients underwent EPP with a 30-day mortality of 4.7%. The median OAS of patients undergoing EPP was significantly longer with 22 months (95% CI: 20-24) as compared to 11 months (95%CI: 9-12) for patients treated without EPP. A prognostic score was defined considering tumor volume, histology, CRP and response after chemotherapy, to which identify patient groups who benefit most from multimodality treatment.
Induction chemotherapy with cis/gem or cis/pem followed by EPP for MPM of all histological subtypes and irrespective of nodal status results in a median survival of 22 months. If confirmed in an independent cohort, our multimodality benefit score may allow to better council MPM-patients since it identifies patients with a poor prognosis not improved by multimodality treatment.
Outlook: Validation of the second cohort.

Collaborations:
- Division of Thoracic Surgery, USZ (Dr. Martina Friess, Dr. Peter Kestenholz, Dr. Didier Schneiter)
- Laboratory of Molecular Oncology, UniversityHospital Zurich (Prof. Rolf Stahel)
- Department of Diagnostic Radiology, UniversityHospital Zurich (PD Dr. Thomas Frauenfelder, Dan Linh Nguyen-Kim)
- Biostatistics Unit, University of Zürich (Dr. Burkhardt Seifert)
- Division of Thoracic Surgery, Medical University Vienna (Prof. Walter Klepetko)

2.6 Urological Research

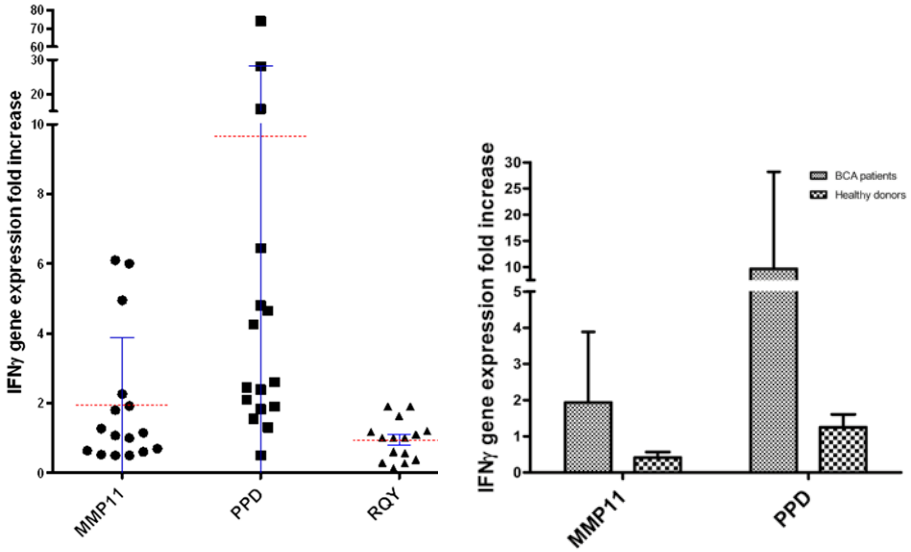


2.6.1 Oncology

Matrix Metalloproteinase 11 as a potential new target for cancer immunotherapy in bladder cancer

L. Luberto, C. Poyet, D. Aquino-Delmo, T. Sulser, M. Provenzano

Matrix Metalloproteinase-11 (MMP11, Stromelysin-3) has been proposed to play an important role in cancer. It is expressed during embryogenesis, tissue involution and wound healing, but also in most invasive primary carcinomas (breast, colon, pancreas, lung, skin and gastric cancer) and preclinical studies showed its role in promoting cancer progression by remodeling extracellular matrix, anti-apoptotic and anti-necrotic effect on tumor cells. In bladder cancer its expression (shown by IHC) correlates with a more aggressive phenotype (lymphatic vessel invasion, infiltrative pattern of invasion). We are currently investigating the specific *ex vivo* immune response of HLA-A*0201 bladder cancer patients against a HLA-A*0201 MMP11 immunogenic peptide and characterizing the peptide-induced T-cell immune response.



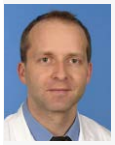
Ex vivo stimulation of PBMCs from 16 MIBCs patients compared to healthy donors. 38% of our patients were responsive to MMP11 stimulation.


PD Dr. Maurizio Provenzano, MD, PhD


Prof. Dr. Tullio Sulser, MD, Director


PD Dr. Daniel Eberli , MD, PhD


Damina Balmer, Scientific Coordination


Dr. Cédric Poyet, MD


Dr. Laura Luberto, PhD

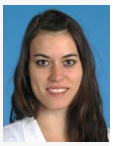

Dr. Souzan Salemi, PhD


Sarah Nötzli, M.Sc.

Postdoctoral Fellows and Students


Dr. Ashkan Mortezavi, MD


Deana Haralampieva, PhD Student


Ria Tauscher, M.Sc.


Dr. Markus Rottmar, PhD


Daniel Keller, Master Student

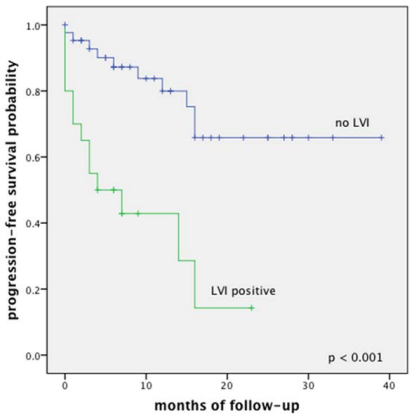

Pract. med. Etienne Xavier Keller


David Aquino Delmo, MSc

The prognostic impact of lymphovascular invasion (LVI) in bladder cancer and the detection of lymph-specific markers in a LVI+ patient

C. Poyet, T. Benoit, M.S. Günthart, T. Sulser, M. Provenzano

Approximately 25% of patients undergoing surgery for bladder cancer show lymph nodal metastases (LnM+). A positive lymph node status is generally associated with aggressive tumors and lymphovascular invasion (LVI) implies poor prognosis. In our study, LVI was found in 31.7% of patients (tot n=63). Both, the correlation with tumor progression (p=0.002) and the association with shorter Progression Free Survival (log rank p<0.001) were significant. In one LVI+ patient (LnM+) we found an elevated expression of lymph-specific markers (VEGF-A, C, D) and their receptors (VEGFR-2, 3), as compared to LVI- LnM- patients.



Kaplan-Meier curve for progression-free survival (PFS) for LVI+ vs. LVI- patients

A link between BKV expression and PCa cancer risk supports future investigations

S. Delbue, P. Ferrante, M. Provenzano

The Polyomavirus BK (BKV) has been proposed to be one of the possible co-factors in the genesis of prostate cancer (PCa) but, so far, the only convincing explanation is the hypothesis of a “hit and run” carcinogenic mechanism induced by the virus at early stages of this disease. To support this hypothesis we conducted a meta-analysis on previous studies regarding the association between BKV and PCa, in order to interpret the contrasting results and to explore whether there might be a significant virus-disease link. This updated analysis provides evidence for a significant link between BKV expression and PCa development, particularly between the BKV infection and the cancer risk.

Antibody response against the BK virus large tumor antigen as an independent predictor of biochemical recurrence after radical prostatectomy

E.X. Keller, P. Kardas, C. Acevedo, C. Poyet, I. Banzola, A. Mortezavi, B. Seifert, T. Sulser, H.H. Hirsch, M .Provenzano

In this study, we aimed at defining the role of Polyomavirus BK (BKV) in PCa by testing a humoral immune response against BKV proteins VP1 and L-Tag in patients with PCa undergoing radical prostatectomy at first diagnosis (n=264). Antibody titers were correlated to 5-year follow-up clinical data focusing on evidence of biochemical recurrence (BR) after surgery. Patients with a modest L-Tag-IgG titer showed a significantly lower Recurrence Free Survival rate (RFS), as compared to patients with higher L-Tag-IgG titers (5-year RFS 65% vs. 75%, p=0.021). In the multivariate analysis, a weak anti-L-Tag IgG response independently predicted BR (HR 2.58, 95% CI 1.38-4.83, p=0.003).

Collaborations:

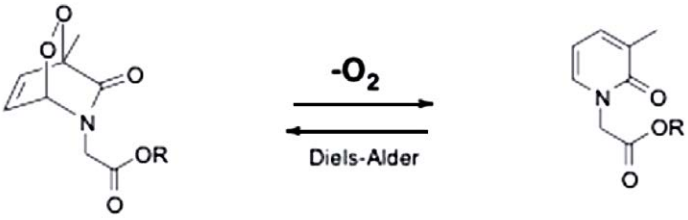
- Institute for Medical Microbiology and Division of Infectious Diseases, University of Basel
- Institute for Surgical Research and Hospital Management, Oncology section, University Hospital of Basel
- Department of Biomedical, Surgical and Dental Sciences, University of Milan, Italy
- Institute of Pharmaceutical Sciences, ETH, Zürich

2.6.2 Tissue Engineering for Urologic Tissue

Controlled oxygen release from pyridone endoperoxides promotes cell survival under anoxic conditions

S. Nötzli, H. J. Jessen, D. Eberli

In tissue engineering, survival of larger constructs remains challenging due to limited supply with oxygen caused by a lack of early vascularization. Controlled release of oxygen from small organic molecules represents a possible strategy to prevent cell death under anoxic conditions. A comprehensive study of methylated pyridone-derived endoperoxides has led to the development of water-soluble molecules that undergo retro Diels-Alder reactions in aqueous environment releasing oxygen in high yield and with half-lives of up to 13 hours. These molecules in combination with vitamin C as singlet oxygen quencher significantly improved survival of 3T3 fibroblasts and rat smooth muscle cells challenged with oxygen-depleted conditions.



TOC. Retro Diels-Alder reaction generating oxygen from pyridone endoperoxides

Non-invasive tracking of muscle precursor cells for muscle tissue engineering

D. Haralampieva, D. Eberli

Organ transplantation is the gold standard for the treatment of terminally damaged organs. This method has significant drawbacks including the shortage of available donor organs and the high morbidity of immunosuppressive therapy. Regenerative medicine offers an alternative using autologous stem cell therapy for skeletal muscle diseases. In this study we investigated the possibility of using a mutated dopamine D2-receptor and PET Imaging for precise localization and long-term *in vivo* tracking of the implanted cells. The engineered human muscle precursor cells (hMPCs) were injected subcutaneously in nude mice and could later be tracked by accumulation of the radiotracer 18F-Fallypride. Therefore, PET Imaging may offer a novel method for non-invasive visualization and detection of autologous stem cells after injection for treatment of muscle diseases.

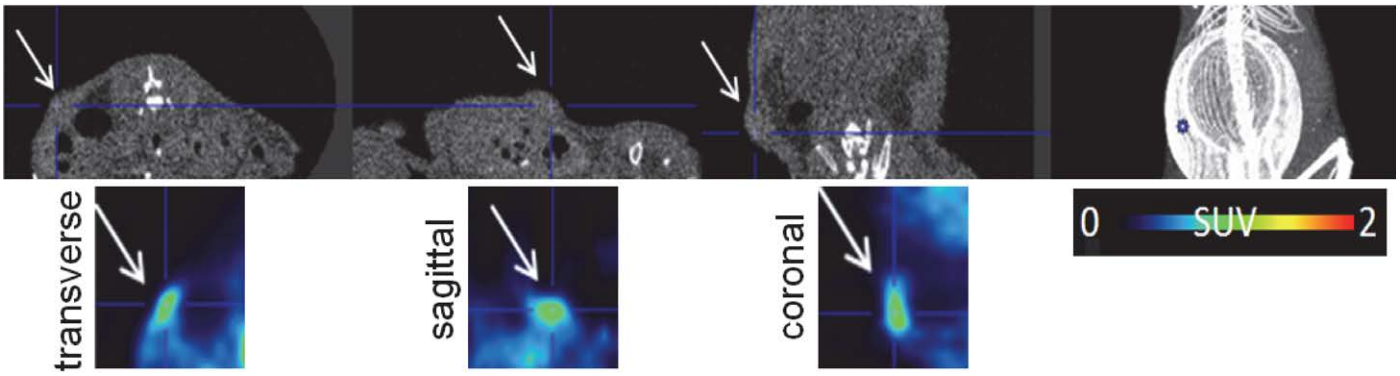


Fig.1 PET Imaging of engineered hMPCs in vivo after 2 weeks.
D2R-transduced hMPCs were s.c. injected in nude mice and visualized by PET/CT Imaging after 2 weeks using [18F]-Fallypride.
The results show successful tracking of the location of the engineered muscle tissue.

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

M. Rottmar, A. Boss, D. Eberli

Recent advances in cell therapy approaches to treat urinary incontinence are promising; however, evaluating the success of such treatments is difficult, mainly relying on indirect measures. Changes in magnetic resonance (MR) relaxation properties have recently been found to enable monitoring of myogenic *in vivo* differentiation of adult muscle precursor cells (MPCs). The quality of the regenerated tissue is of crucial importance for its proper function and thus, reliable markers reflecting the cellular composition and maturation state of the developing tissue are of paramount importance for clinical application of such a cell therapy approach. In this project, magnetization transfer (MT) imaging is employed to directly assess muscle fiber formation as a possible measure of repair tissue quality. Initial results are promising, demonstrating increasing MT during myogenic *in vivo* differentiation of MPCs.

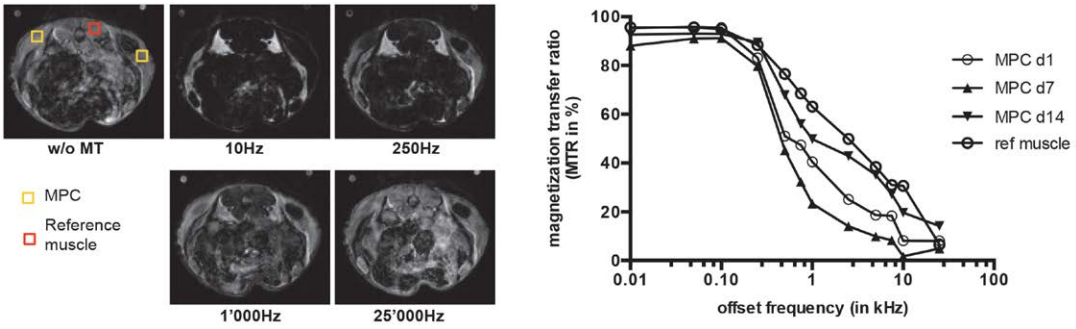


Figure. MT during myogenic in vivo differentiation. MR-images without and with MT-pulse at increasing offset frequencies and development of MT for a range of offset frequencies during 2 weeks post-injection of MPCs.

Differentiated Adipose Derived Stem Cells for functional Smooth Muscle bioengineering

S. Salemi, D. Keller, A. Boss, D. Eberli

The loss or failure of a tissue or an entire organ is one of the most frequent, troubling, and pricy issues in contemporary health care. Tissue engineering may provide novel treatments for many diseases including smooth muscle pathology. Adipose derived stem cells (ADSC) might be a key instrument to bioengineer contractile bladder tissue when differentiated to smooth muscle cells (SMC). It is our aim to evaluate the success of *in vivo* differentiation of ADSC to SMC and observe tissue formation ability of injected cultured cells.

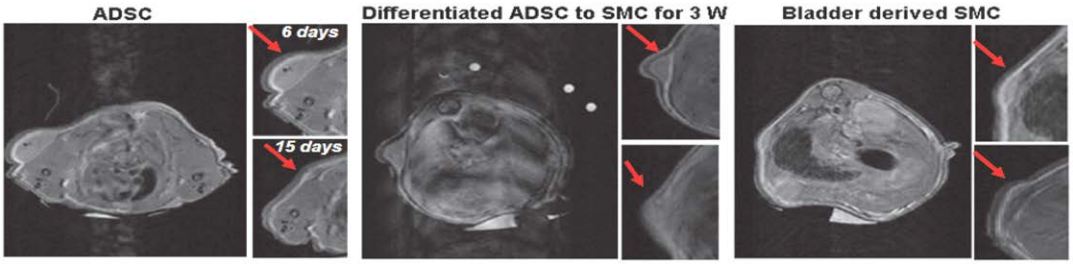
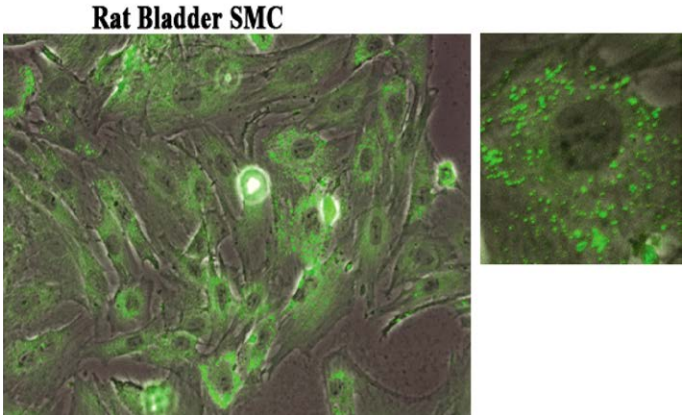


Figure. MRI scanning of injected rat ADSCs, engineered cells in vivo. ADSC differentiated for 3 weeks and bladder derived SMCs. The cells were tracked by MRI after 5 and 15 days of injection. The arrow indicates cellular bulge under the skin of nude mice.

The role of autophagy during the differentiation of Adipose Derived Stem Cells to Smooth Muscle

S. Salemi, D. Eberli

Tissue engineering utilizing smooth muscle regeneration may provide substitute for diseases with smooth muscle pathology such as bladder dysfunction, urinary incontinence, and erectile dysfunction. 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*.
Rat ADSC were characterized by immunocytochemistry and FACS. ADSC were induced towards SMC using induction medium for 1 to 6 weeks. The changes in gene and protein expression level for SMC specific markers and autophagy genes were investigated by ICC and WB.

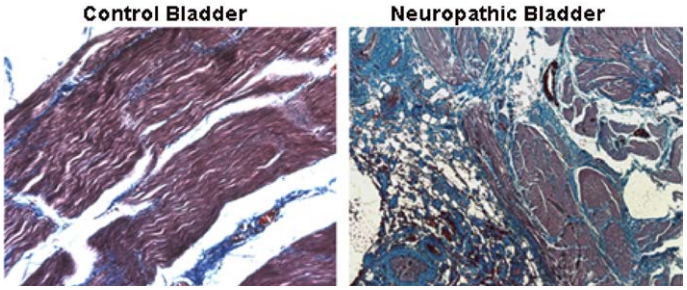


The SMC were stained with autodot dye specific for autophagy. The green punctuated staining indicates autophagosome formation

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. In muscular disorders increased autophagy is known to protect cells by compensating for defects in lysosome function, but the negative effect is increased or defects in completing autophagy result in accumulation of autophagosomes that impair cell function. We hypothesise autophagy may play an important role in remodeling of bladder SMC in children with neuropathic bladder. Bladder biopsies were taken from children with neuropathic disorder. A piece of bladder tissue was snap frozen for genetic analysis and another piece was fixed for immunostaining. Samples were stained with SMC lineage associated markers and autophagy related proteins.



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

Retrospective analysis of urinary tract infections, resistance patterns and effectiveness of antimicrobial perioperative prophylaxis for transurethral procedures

F. Maryna, A. Mortezavi, D. Eberli

Drug-resistant bacteria are an increasing clinical problem and thus the selection of the correct antimicrobial perioperative prophylaxis (APP) for urological transurethral procedures has become more challenging. To evaluate if an individualized APP based on preoperative urine culture (PUC) would lower the infection rate we analyzed consecutive clinical charts from patients undergoing transurethral procedures. This retrospective investigation was performed in our department including all 1033 patients undergoing transurethral procedures between 11/2011 and 12/2012.

Collaborations:

- Prof. Benjamin Harrison, PhD, Wake Forest University School of Medicine, Winston-Salem
- Prof. Rita Gobet, Division of Pediatric Urology, University Children's Hospital Zurich
- Prof. Christoph Handschin, Biozentrum, Focal Area Growth and Development, University of Basel
- Prof. Hans Uwe Simon, Pharmacology Institute; Bern
- Prof. Simon Ametamey, Federal Institute of Technology, Zurich, Switzerland
- Prof. Markus Rudin, Inst. f. Biomedizinische Technik, Universität und ETH Zürich, Schweiz
- Prof. Janos Vörös, Institut f. Biomedizinische Technik, Federal Institute of Technology, Zurich, Switzerland

2.7 Cranio-Maxillofacial Surgery Research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PhD


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dent.
Klaus W. Grätz,
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Prof. Dr. Dr.
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Joachim
Obwegeser,
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PD Dr. Dr. dent.
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PD Dr. Dr. dent.
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Dr. Dr. dent.
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Lindsay Sulzer,
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Barbara
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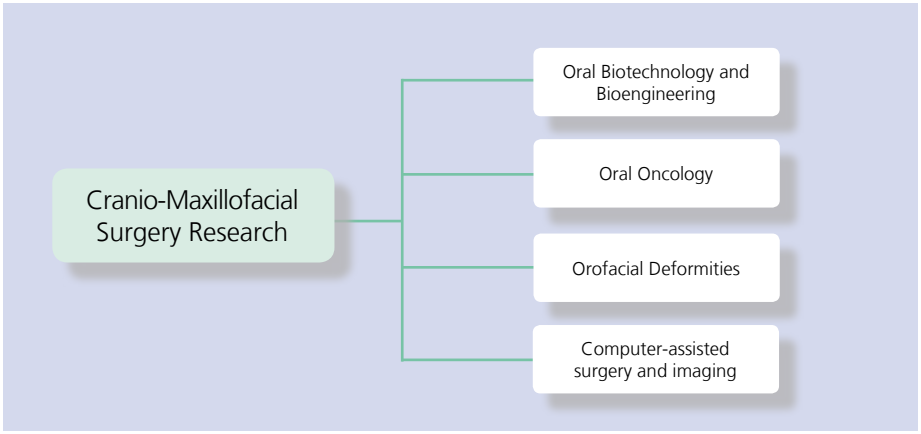


2.7.1 Oral Biotechnology and Bioengineering

Bone, cartilage and tooth regeneration

F. Weber, Ch. Ghayor, L. Karfeld-Sulzer, N. Roungsawasdi, B. Gjoksi, B. Siegenthaler, D. Waldvogel, O. Schätti, A. Tchouboukov, Y. Bloemhard

Growth factor mediated bone regeneration and their enhancers

The small chemical N-methyl pyrrolidone (NMP) was identified by us to be an enhancer of bone regeneration by increasing the kinase activity of the BMP/BMP receptor complex for key signalling molecules for bone formation. Meanwhile we saw that NMP 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 double delivery of BMP and NMP *in vivo*.

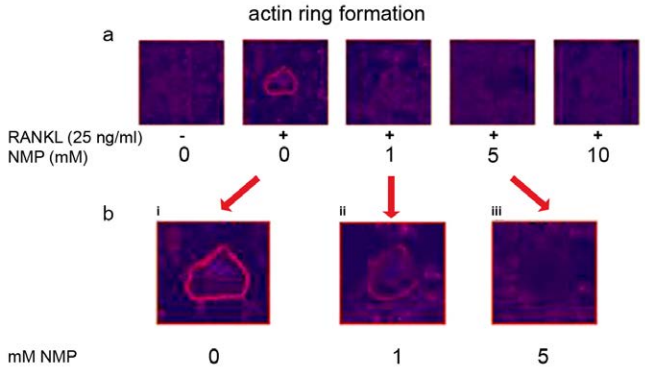


Fig. 1: NMP inhibits bone resorption. Bone resorption demands for a compartment formed by the osteoclast which can be acidified. Such a compartment is formed underneath the osteoclast by an acting ring. Preosteoclasts are matured to osteoclasts by RANKL and form acting rings. In the presence of 1 mM NMP actin ring formation is disturbed and totally absent at NMP concentrations of 5 mM.

Bone substitute materials

Partial or full resection of the jaw due to cancer treatment still poses a great challenge. The applied bone substitutes will have to withstand high mechanical forces. Therefore we work on the development of 3D titanium based scaffolds manufactured by selective laser melting, which allows the realization of diverse designs and mechanical resistance.

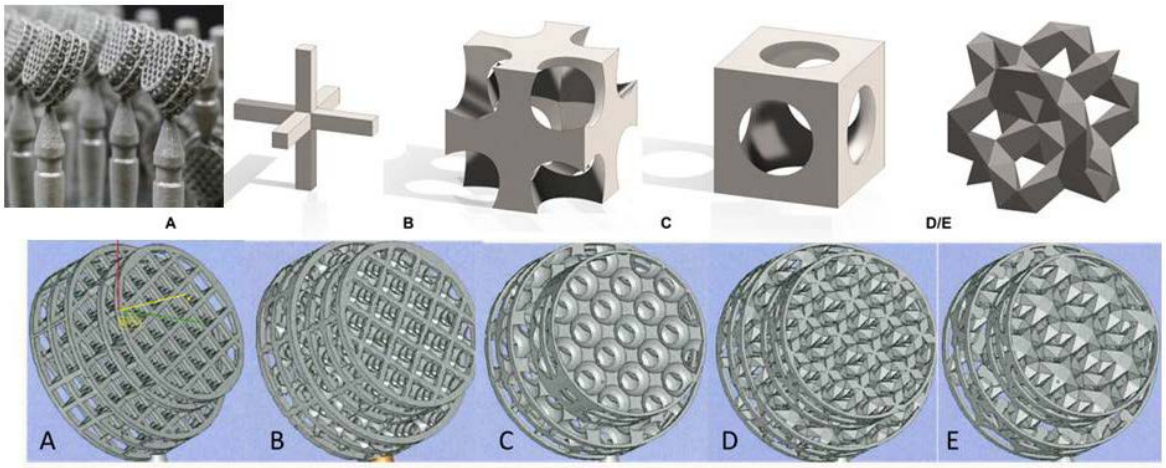


Fig. 2: 3D titanium scaffolds and a variety of designs to test for osteoconductivity and mechanics.

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

Due to changes in our life-style and at the work place more and more people suffer from back pain due to degeneration of discs. NPmimetic is an EU-funded project with the goal to find solutions for bone regeneration and disc substitution. To that end, electrospinning technology is exploited to develop a nano-fiber based, biocompatible, biodegradable, synthetic scaffold mimicking the mechanical properties of the native Nucleus Pulposus for immediate and short term treatment.

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. The unique expertise of our partners at the ZZM (Prof. Luigi Gallo) to calculate stress-field areas and to monitor contraction patterns of masticatory muscles, e.g. how long and how often TMJs are loaded, allows us to program a machine which can stress the cartilage explants in a more realistic way than it is normally done in similar experiments.

Pulp regeneration

Tissue regeneration strategies have gained substantial attention in the dental literature over the recent years. 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 procedure is deemed to be especially helpful in children with teeth with incomplete root formation that lost pulp vitality due to caries or trauma. The goal of this project is to establish a new soft tissue in the pulp space that is capable of continuing hard tissue formation, thus rendering the tooth less prone to fracture and consequent loss.

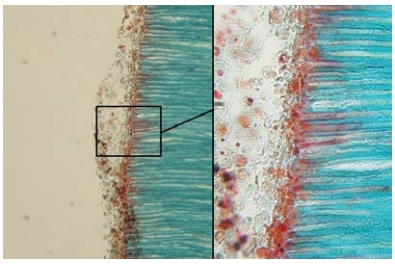


Figure 3: Pulp space treated with EDTA allowed the extension of cells into dentin

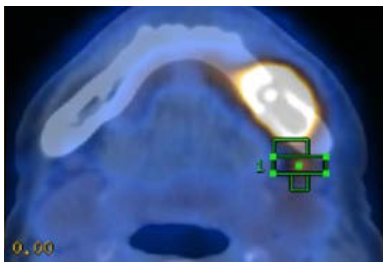
2.7.2 Oral Oncology

M. Bredell, A. Kruse

KFSP project on tumor oxygenation

Patients with hypoxic tumors have shown to have a poorer prognosis than those with an aerobic metabolism and that change to an anaerobic metabolism occurs even despite of an apparent well vascularised and oxygenated tumor. This poorer prognosis is relevant for patients undergoing surgery, radiotherapy as well as chemotherapy. One of medicines great challenges is to predict in a non-invasive way which tumors follow the anaerobic metabolic pathway and be defined as a hypoxic tumor. In this multidisciplinary

study we strive to establish a non-invasive diagnostic pathway of tumor hypoxia with the intent to predict oxygen related metabolism behaviour of tumors before and during therapy. Apart from using established tumor biomarkers, new biomarkers are being tested and will later be correlated to examinations like arterial spin labelling MRI and oxygen PET in a prospective study. Serum, urine as well as saliva biomarkers will be used to further look for a non-invasive way of predicting the oxygen related metabolism of tumors. The relationship of the inflammatory process and local immunological factors are in the process of investigation.



Metabolic activity based on FDG PET is representative of metabolic activity, but not of tumor hypoxia.

2.7.3 Oral Deformities

J. Obwegeser, Ch. Jacobsen

Until today, several standardized therapy methods for the surgical correction of craniofacial deformities were developed. In some severe cases, surgical distraction of syndromic craniofacial deformities is the method of choice to achieve the best possible functional and aesthetic result. During the last decade different devices for surgical distraction in the facial area were developed, but for all of them it remains difficult to determine the correct vectors. Additionally some devices show early loosening and unaesthetic scarring, especially in small children. For this a new external distraction device for distraction in Le Fort III level was developed in collaboration with KLS Martin Group. This device was successfully applied in a child with syndromic craniosynostosis.

2.7.4 Computer-assisted Surgery and Imaging

T. Lübbers

“Conditio sine qua non” for successful treatment is the knowledge about the patient’s anatomy. Over centuries this knowledge was based on anatomical studies only and not matching the patients’ particular details. The specific situation of a patient was not revealed until it became obvious during e.g. surgery.

The Nobel prize appraised discovery of x-rays by Wilhelm Conrad Röntgen in 1895 and the clinical implementation of Computed Tomography by Ambrose and Hounsfield in 1972 opened wide windows giving a view into patients individual anatomy.

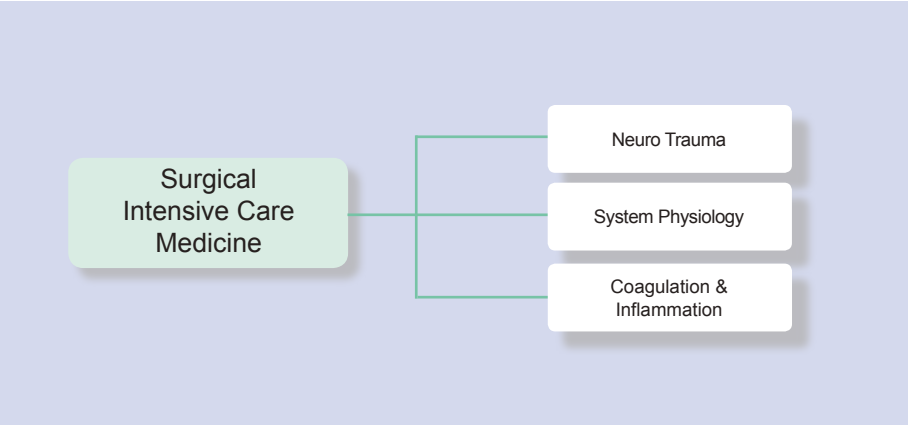
Today, in the times of Cone Beam Computed Tomography, three-dimensional imaging is almost routine in modern dentistry. However, the whole benefit of this technique can only be derived in a fully digital environment.

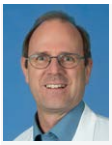
Fig.4 Target registration error map-ped onto the 3D surface model. Registration via rapid splint. The error increases with distance from the reference markers.

Collaborations:

- Department of Fixed and Removable Prothodontics and Dental Material Science, University of Zurich, Switzerland (Prof. Dr. Ch. Hämmerle, PD Dr. Ronald Jung, PD Dr. Daniel Thoma)
- Disney Research, Zurich (Prof. Dr. M. Gross)
- Division of Preventive Dentistry, Periodontology and Cariology, University of Zurich
- Center of Dental Medicine, Zurich, Switzerland (Prof. Dr. T. Attin, PD Dr. M. Zehnder, Prof. Dr. P. Schmidlin)
- Department of Masticatory Disorders, University of Zurich, Switzerland (Prof. Dr. Luigi Gallo)
- Division of Obstetrics (Prof. Dr. Roland Zimmermann, Dr. Martin Ehrbar)
- EPFL Institute of Bioengineering (Prof. Dr. Matthias Lütolf)
- ETH Zürich, Department of Chemistry and Applied Biosciences (Prof. Dr. Wendelin Stark)
- ETH Zürich, Department of Computer Science, Institute for Visual Computing, Computer Graphics Laboratory (Prof. Dr. M. Gross)
- University of Hongkong, Prof. Dr. Roger Zwahlen.
- AO Research Institute, Davos, Switzerland (Prof. Dr. 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. Dr. Th. Smit)
- University of Sheffield, UK (Prof. Dr. Ch. Sammon)

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:
Transcranial Color-Coded Duplex sonography (TCCD) is a non-invasive bedside tool and has a broad diagnostic potential in the intensive care setting. Implementation of TCCD requires repeated reliable measurements of flow velocities in the middle cerebral artery MCA (as illustrated in Figure 1). Since data acquisition is accomplished by various operators with a wide range of experience it is essential to establish the learning curve of TCCD which is the aim of the proposed study.

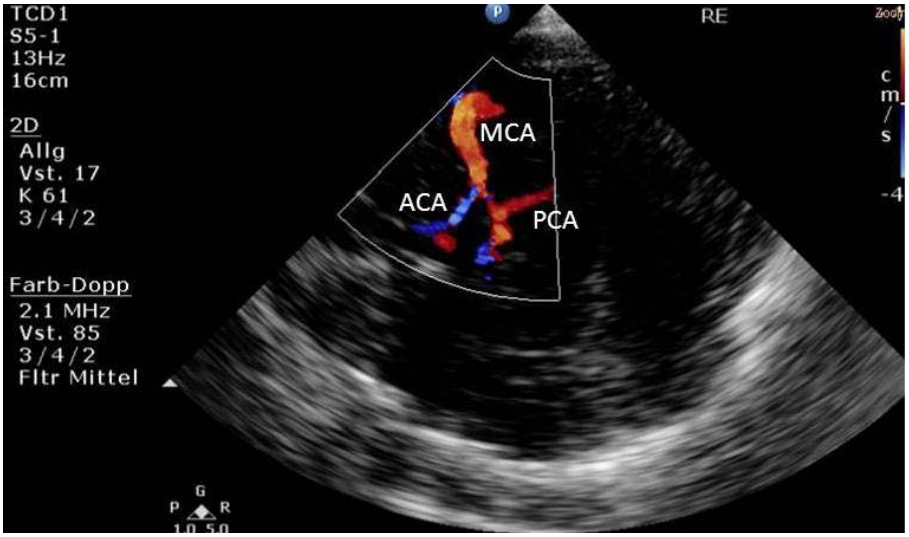


Figure 1: TCCD image of the circle of Willis. MCA middle cerebral artery; ACA anterior cerebral artery, PCA posterior cerebral artery.

Dr.
Miriam Ender,
PhD

Dr.
Jerzy Madon

Dr.
Stephanie
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Dr.
Fabio Ugolini
PhD,
Lab. Technician

Renato Lenherr

Mario Fasshauer

Postdoctoral Fellows and Students

Dr.
Alessandro
Franchini,
PhD

Dorothea
Heuberger,
PhD Student

Laura
Vazquez Rojo,
MS Student

Project 2:
Carbon dioxide is a potent modulator of small brain vessel tonus. Carbon dioxide is regulated by ventilation. We plan to investigate the physiologic reaction to hyper- and hypoventilation in terms of flow velocities in the MCA obtained by Transcranial color-coded duplex sonography (TCCD) in sedated and mechanically ventilated patients. Data are compared to the physiologic response to deliberately induced hyper- and hypoventilation (Table 1) in spontaneously breathing volunteers.

	Normoventilation	Hyperventilation	Hypoventilation
Et CO2 5.3 (5.0-5.5)	4.1 (3.9- 4.3)	6.0 (5.9-6.1)	
Blood flow velocity	55 (46-60)	46 (38-51)	62 (54-69)

Table 1: Effect on blood flow velocity in the A. cerebri media obtained by TCCD to deliberately induced hyper- and hypoventilation in spontaneously breathing volunteers. $EtCO_2$: end-tidal carbon dioxide. Data are given as median (IQR).

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).

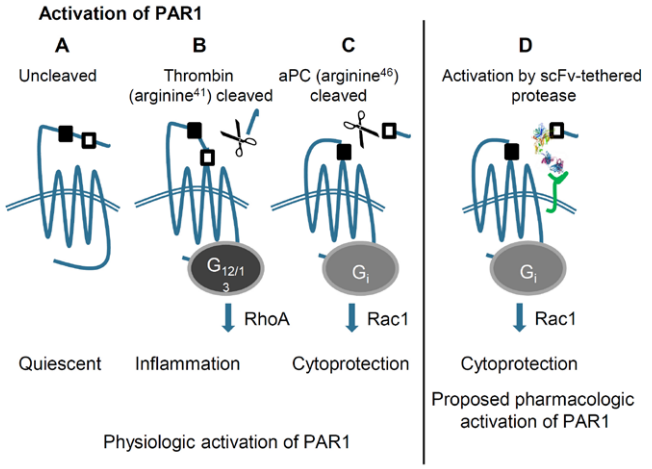
Outcome	HES (n = 23)	Lactated Ringer's (n = 22)	Difference
Primary outcome			
Total volume at days 1–3, mL			−1,213 (95% CI −3,975 to 1,549)
Secondary outcomes			
Creatinine at day 1, μmol/L	77 (66, 99)	74 (55, 90)	
Creatinine at days 1–3, μmol/L			0.4 (95% CI −18.7 to 19.5)
Urinary output at day 1, 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, M. Ender, A. Franchini, J. Madon, F. Ugolini, D. Heuberger, L. Vazquez Rojo

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.



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).*

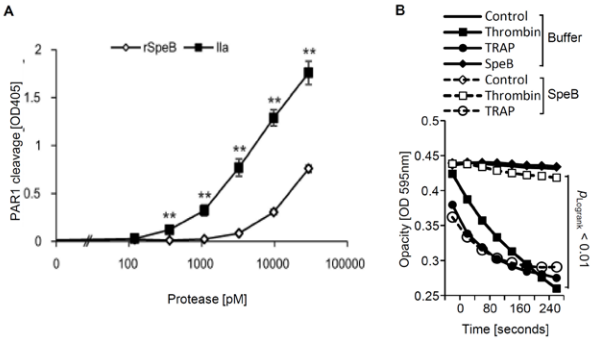


Figure 1: *Group A Streptococcus secrets SpeB to interfere with PAR1 induced cellular responses:* ***(A)*** *Cleavage efficiency of PAR1 reporter constructs by thrombin and rSpeB.* ***(B)*** *Turbimetric quantification of platelet aggregation (lower OD means more aggregates). Washed platelets were incubated with either buffer alone (closed symbols) or recombinant SpeB (open symbols) before given agonists were added and aggregation was quantified. (PLoS One. 2013 Nov 22;8(11):e81298)*

Supported by the Swiss National Science Foundation we synthetized a chimeric clotting protease that efficiently binds to a protein co-localized to PAR1 and that activates PAR1 at the desired arginine 46 cleavage site (Scheme 1d). We linked a single chain variable fragment (scFv) to activated protein C's protease domain. Studies on whether this chimeric protease carries a therapeutic potential are currently under investigation.

We recently found that not only human but also pathogen derived proteases cleave PAR1. Group A *Streptococcus* secretes the potent cysteine protease SpeB that cleaves PAR1 at lysine 43. Thereby Group A *Streptococcus* blunts platelet responses to the prototypical pro-coagulant protease thrombin. (Figure 2). [Figure 2]. Similarly we found *Staphylococcus aureus*, an important human pathogen, to efficiently cleave protease activated receptor 2 (PAR2). We are currently investigating whether PAR2 activation would allow to attenuate bacterial virulence by interfering with bacterial adherence to mammalian cells.

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

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DVM

Dr.
Nikola
Cesarovic,
DVM, PhD

Flora Nicholls,
Dipl. biol.

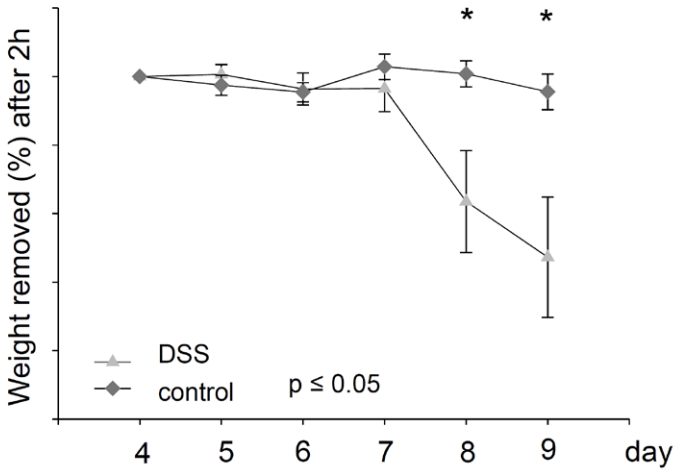
Andreas Rettich,
Dipl. biol.

Dr.
Miriam Lipiski,
DVM

Dr.
Paulin Jirkof,
PhD

Dr.
Thea Fleischmann,
DVM

The assessment of pain and distress, as well as the evaluation of the efficacy of stress-reduction strategies, is crucial in animal experimentation but can be challenging in laboratory mice. In our studies we develop physiological and non-invasive behavioural parameters, easily recorded in the animal`s home cage, to assess pain, distress and general condition in laboratory mice. Scoring of nest complexity and monitoring of burrowing performance for example have been proposed in more realistic and clinically relevant preclinical models of disease, and reduction of these behaviors seems to be especially useful as an early sign of dysfunction and to monitor disease progression. These tools allow us also to optimize anaesthesia and pain relief, provide effective postoperative care and the optimal housing conditions after invasive procedures and may help provide a global picture of a mouse`s state, and thus ensure well-being in animal experimentation.

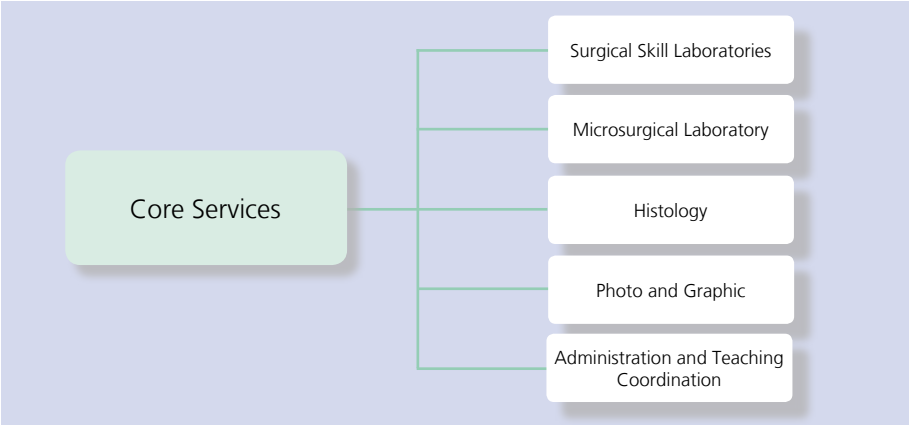


Burrowing performance for monitoring during murine DSS colitis: Percental weight of pellets removed out of test apparatus. Mice received DSS (triangles, n = 6) or water (diamonds, n = 5). Burrowing was tested for 2 h. Induction of colitis was followed by a significant reduction of the weight of removed pellets. p ≤ 0.05 (*).

Collaborations:

- Knut Husmann, Orthopädische Universitätsklinik Balgrist und Schweizerisches Paraplegikerzentrum, University of Zurich
- Thomas Weber, Institute of Microbiology, ETH Zurich
- Martin Hausmann, Department of Gastroenterology and Hepatology, University Hospital, Zurich
- Andreas Rettich, Institute of Laboratory Animal Science, University Zurich
- Alain Rudiger, Department of Anesthesiology, UniversityHospital Zurich
- Daniel Konrad, Stephan Wüest, Department of Endocrinology, University Children's Hospital Zurich
- Johannes Vogel, Institute of Veterinary Physiology, Vetsuisse Faculty, University of Zurich
- Katja Nuss, Brigitte von Rechenberg, Musculoskeletal Research Unit, Vetsuisse Faculty, University Zurich
- Arnaud Tourvieille, Humanvet, Lausanne

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.


PD Dr.
Margarete Arras,
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Dr.
Nikola
Cesarovic,
DVM, PhD


Nico Wick,
Photographer


Lea Schütz,
Photographer


Carol De Simio,
Scientific
Illustrator


Stefan Schwyter,
Scientific
Illustrator


Pia Fuchs,
Lab. Technician


Donata Gröflin,
Teaching
Coordination
Division of
Surgical
Research


Corinne Renold,
Teaching
Coordination
Division of
Surgical
Research

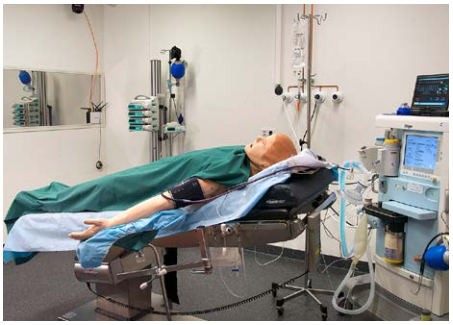

Susanne
Frehner,
Administration
Division of
Surgical
Research

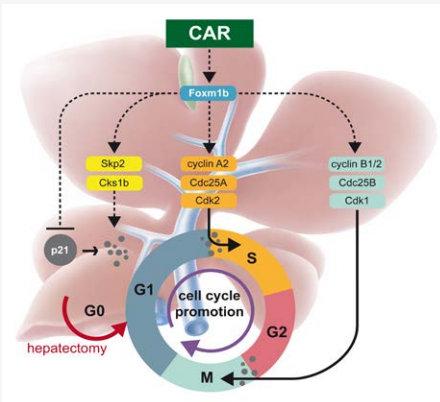
3.6 Photo and Graphic Services

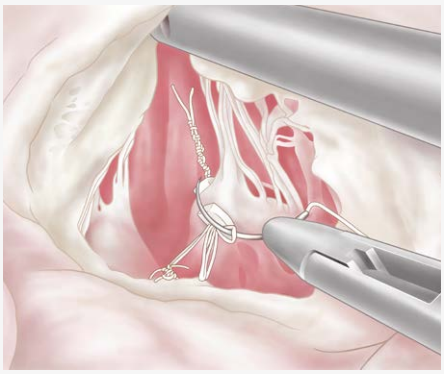
A quick, flexible, versatile and professional service.

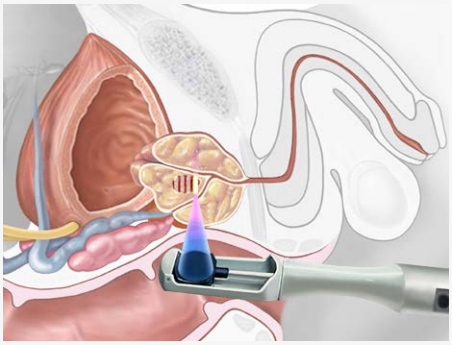
We offer

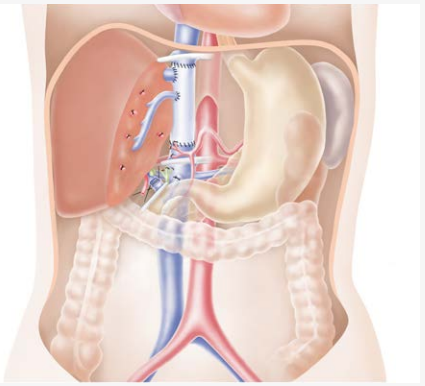
- photographic documentation of patients and events
- technical photography, on location or in our studio
- graphic and design of illustrations for papers and books
- reproduction and digitalization of any original
- layout of printing matters
- preparation of files for external printing
- print service
- 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 2013

12th Day of Clinical Research, April 4

Surgical Suture Skills Course, May 5

Talk "Moving forward", May 21

45th Annual Meeting of the European Pancreatic Club, June 26-29

Delivery of the Zyklotron September 6

CTC Symposium November 7

Christmas Party, December 20

5. Publications 2013

Cardiovascular Surgery

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  Livedoid vasculopathy: an in-depth analysis using a modified Delphi approach.
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- Cabrera, M S; Oomens, C W J; Bouten, C V C; Bogers, A J J C; Hoerstrup, S P; Baaijens, F P T (2013).
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  Transcatheter implantation of homologous “off-the-shelf” tissue engineered heart valves with self-repair capacity: long term functionality and rapid *in vivo* remodeling in sheep.
  J Am Coll Cardiol. 2013 Dec 9. pii: S0735-1097(13)06374-2. [Epub ahead of print]
- Emmert, M Y; Weber, B; Wolint, P; Frauenfelder, T; Zeisberger, S M; Behr, L; Sammut, S; Scherman, J; Brokopp, C E; Schwartländer, R; Vogel, V; Vogt, P; Grünenfelder, J; Alkadhi, H; Falk, V; Boss, A; Hoerstrup, S P (2013).
  Intramyocardial transplantation and tracking of human mesenchymal stem cells in a novel intrauterine pre-immune fetal sheep myocardial infarction model: a proof of concept study.
  PLoS ONE 8(3), e57759
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  Human stem cell-based three-dimensional microtissues for advanced cardiac cell therapies.
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- Emmert MY, Hitchcock RW, Hoerstrup SP. Cell therapy, 3D culture systems and tissue engineering for cardiac regeneration.
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  Expert Rev Med Devices. 2013 Nov 26. [Epub ahead of print]
- Emmert, M Y; Wolint, P; Winklhofer, S; Stolzmann, P; Cesarovic, N; Fleischmann, T; Nguyen, T D L; Frauenfelder, T; Böni, R; Scherman, J; Bettex, D; Grünenfelder, J; Schwartlander, R; Vogel, V; Gyöngyösi, M; Alkadhi, H; Falk, V; Hoerstrup, S P (2013).
  Transcatheter based electromechanical mapping guided intramyocardial transplantation and *in vivo* tracking of human stem cell based three dimensional microtissues in the porcine heart.
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- Lachat M, Mayer D, Pfammatter T, Criado FJ, Rancic Z, Larzon T, et al.
  Periscope endograft technique to revascularize the left subclavian artery during thoracic endovascular aortic repair.
  J Endovasc Ther 2013; 20(6):728-34.
- Mauri, A; Zeisberger, S M; Hoerstrup, S P; Mazza, E (2013).
  Analysis of the uniaxial and multiaxial mechanical response of a tissue-engineered vascular graft.
  Tissue Engineering. Part A 19(5-6), 583-592
- Ochsner G, Amacher R, Amstutz A, Plass A, Schmid Daners M, Tevaearai H, Vandenberghe S, Wilhelm MJ, Guzzella L.
  A Novel Interface for Hybrid Mock Circulations to Evaluate Ventricular Assist Devices. IEEE Trans Biomed Eng 2013;60:507-16
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  Toward a rational design of surface textures promoting endothelialization.
  Nano Lett. 2014 Feb 12;14(2):1069-79.
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  Interact Cardiovasc Thorac Surg. 2014 Jan;18(1):13-6.
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- Winnik, S; Lohmann, C; Siciliani, G; von Lukowicz, T; Kuschnerus, K; Kraenkel, N; Brokopp, C E; Enseleit, F; Michels, S; Ruschitzka, F; Luscher, T F; Matter, C M (2013).
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Visceral and Transplant Surgery

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  Sewed revascularization for arterialized liver transplantation in mice.
  Journal of Surgical Research 184(2), e1-7
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Trauma Surgery

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Veterinary Services

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6. Grants 2013

Cardiovascular Surgery

Source	Title of Project	Project Leader
Commission of the European Communities	Living autologous heart valves for minimally invasive implantable procedures	S. Hoerstrup
Swiss National Science Foundation	Advanced Cell Therapies for Cardiac Repair-SPUM	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	S. Hoerstrup
Schweizerische Herzstiftung, Bern	Living Heart Valves for the few	S. Hoerstrup
Schweizerische Herzstiftung, Bern	Assessment of human amniotic fluid stem cell-based engineered heart valves in a mouse model: Establishment of a SCID/bg model for the investigation of in situ remodeling and cell fate.	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
Novartis Stiftung für Biologisch-Medizinische Forschung	miRNA manipulations to improve the regenerative potential of bone-marrow derived MSCs	S. Hoerstrup
SCIEX-NMSch Fellowship	SCIEX Fellowship Jaro Slamecka	S. Hoerstrup
Unitectra Technologietransferfonds	Targeting Fibroblast Activation Protein to prevent Infarction	S. Hoerstrup
Schweiz. Gesellschaft für Kardiologie	Cardiovascular Biology Prize of the Swiss Society for Cardiology	S. Hoerstrup
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
EMDO Stiftung, Zürich	Establishment of a novel SCID/g heterotopic working heart transplantation model for *in vivo* investigation of tissue engineered heart valve remodelling mechanisms and cell fate	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	Hoerstrup SuiValveuBioMedical Materials	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
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
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 biocamptibility comparison of two commercially available coated oxygenators and circuits	M. Wilhelm
Schweizerische Herzstiftung, Bern	Mitral Valve Annuloplasty: from diagnostic tools to predictive simulation	S. Jacobs
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

Cardiovascular Surgery

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 Bio-prostheses	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
Medtronic Ventor Technologies / NL	Medtronic Engager Feasibility and Pivotal Trial	V. Falk
Schweizerische Herzstiftung	CAST (Comprehensive ASsessment of frailty Test) and FORE-CAST (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

Visceral & Transplant Surgery

Source	Title of Project	Project Leader
Hepatobiliary Laboratory		
Swiss National Science Foundation	Serotonin and regeneration in the normal, old and diseased liver	P.-A. Clavien
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
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
Kurt und Senta Herrmann Stiftung, Vaduz, FL	Targeting Reactive Oxygen Levels	K. Lehmann

Visceral & Transplant Surgery

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
Pancreatitis Laboratory		
Swiss National Science Foundation	Role of serotonin in inflammation, repair and regeneration of the pancreas	R. Graf & S. Sonda
Gebert Rüf Stiftung, Basel	PSP and Sepsis	R. Graf
Amélie Waring Stiftung	Pathophysiology of chronic pancreatitis	R. Graf
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 in the injured pancreas	K. Grabliauskaite & S. Sonda
Universität Zürich, Fonds für medizinische Forschung	The role of Lymphotoxin in the initiation of pancreatic carcinogenesis	G. Seleznik

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
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 antispetic 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, Schraubenosteosynthese 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 severly open fractures using othogonal 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	Characterization of the vascularization of skin grafts, skin substitutes and biomaterials *in vivo* and identification of the vascular mechanisms	N. Lindenblatt
Swiss National Science Foundation	Breast tissue reconstruction: Potential and therapeutic implications of mesenchymal stem cells	J. Plock
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 Hartmann-Müller 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 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 nerv	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
Claude Verdan Grant, Swiss Handsurgery Society	Reconstructive Transplantation	Plock JA

Thoracic Surgery

Source	Title of Project	Project Leader
Swiss National Science Foundation Förderungsprofessuren	Malignant Pleural Mesothelioma - an integral approach for better outcome	I. Schmitt-Opitz
Swiss National Science Foundation	Immunotherapy for lung cancer	S. Hillinger
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	In-Vivo Bioreactor for the reepithelialization of tissue engineered trachea	W. Weder
Swiss National Science Foundation	Micro Computer-Tomographie für in-vivo Bildgebung	W. Jungraithmayr (Co-Applicant) Applicant: PD Dr. A. Boss
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

Thoracic Surgery

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
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
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
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
Matching Fund UZH 2011	Tolerance induction via NK cell mediated elimination of donor antigen presenting cells in mouse lung transplants	W. Jungraithmayr
EMDO-Stiftung 2013, Zurich, Switzerland	Impact of sevoflurane anesthesia on primary graft dysfunction after experimental mouse lung transplantation	W. Jungraithmayr
BECON AG Foundation	Prognostische Marker für das Maligne Pleuramesotheliom	W. Weder, I. Schmitt-Opitz

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	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

Urology

Research Grant Innovations-Fond University Zürich for the clinical research project	Focal Therapy for Prostate Cancer	D. Eberli
Research Grant form 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 potenetial of N-methylpyrrolidone to prevent osteoporosis and to enhance bone regeneration	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
Swiss National Science Foundation	Artificial mesenchymal progenitor cell niches for bone tissue engineering	F. Weber from USZ, M. Lütolf from EPFL

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
Olga Mayenfisch Stiftung Zürich	Activated Clotting Factor X Enhances Cancer Growth by PECR Dependent Activation of the Protease Activated Receptor 1	R. Schüpbach
Matching Fund UZH 2012	Cytoprotection through non Anticoagulant Engineered Chimeric Activated Protein C	R. Schüpbach
Fresenius Kabi (Schweiz) AG Stans	Early fluid resuscitation with balanced HES 130/0.4 (6%) in severe burn injury	M. Béchir
Diverse	Gerinnung	R. Schüpbach
Matching Fund UZH 2011	Regulation of the Endothelial Barrier by the Protease Activated Receptor 1	R. Schüpbach

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
BVET Bern (Bundesamt für Veterinärwesen)	Etablierung von effizienten Schmerzbehandlungsmethoden für die Labormaus	M. Arras

7. Awards 2013

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

- Paulin Jirkof
  Prix Jean-Pierre Miévielle
  in Anerkennung des hervorragenden wissenschaftlichen Beitrages der Veterinärmedizin zum Wohle des Tieres
  Universität Bern, Vetsuisse-Fakultät

- Gitta Seleznik
  UEG National Scholar Award; best abstract submitted from Switzerland:
  "Comparative effectiveness of immune-cell depletion in the treatment of autoimmune pancreatitis".
  United European Gastroenterology Week (UEGW), Berlin, 12th-16th October 2013

- Enrica Saponara
  Poster award at the 12th Day of Clinical Research, UniversityHospital Zurich, 4th April 2013.

- Jan Plock
  Basic Science Award
  Local and Regional Immunomodulation with Mesenchymal Stem Cells in Rat Hindlimb Vascularized Composite Allotransplantation
  Federation of European Societies for Surgery of the Hand (FESSH)

- Përparim Limani
  Association of Research in Surgery Preis
  "Inositol trispyrophosphate (ITPP) and its anti-hypoxic potential in colorectal metastases of the liver"

- P Kamat, R Schweizer, P Kaenel, S Salemi, D Eberli, M Calcagni, P GIovanoli, A Andres, JA Plock
  Best Paper, Human adipose derived MSCs can promote breast cancer progression and metastasis
  IFATS, New York

- Andrea Schlegel
  Rising Star award
  International Liver Transplantation Society, Sydney, Australia

- Gormasz A, Giovanoli P, Plock JA
  Best Presentation
  Is Fat Grafting to the Breast Safe? - Recommendations for Patient Selection Based on Experimental and Clinical Data
  Swiss Society of Plastic Reconstructive and Aesthetic Surgery

- Malina -Altzinger, J; Ghayor, C; Grätz, K W; Weber, F E
  Poster award
  N -Methyl Pyrrolidone Promotes Osteoblast Differentiation Impaired by Tumor Necrosis Factor-alpha
  IPJ Die Deutsche Gesellschaft für Zahn-, Mund- und Kieferheilkunde und die Quintessenz Verlags-GmbH

- Reto Schüpbach
  Award for the best non clinical publication 2013
  Protease-Activated Receptor1 Cleaved at R46 Mediates Cytoprotective Effects
  Society of Intensive Care Medicine, Jahrestagung 2013, Genève, 05.09.2013

- Reto Schüpbach
  Walter und Gertrud Siegenthaler Wissenschaftspreis 2013
  Dies Academicus 2013, Zürich, 27.04.2013

- Horst M, Milleret V, Nötzli S, Madduri S, Sulser T, Gobet R, Eberli D
  1st Basic Research Prize of the Swiss Urological Association
  Increased Porosity of electrospun hybrid Scaffolds improve Bladder Tissue Regeneration
  Annual Meeting of the Swiss Urological Association, Geneva 2013

- Maurizio Provenzano
  Expert speaker at the 5th International Conference on Polyomaviruses and Human Diseases:
  Basic and Clinical Perspective" 2013, Stresa, Italy

- W. Jungraithmayr
  Award for the Best Oral Presentation (from 2200 submitted abstracts)
  Natural killer cells improve allogeneic lung transplants via depletion of donor dentritic cells
  European Society of Organ Transplantation (ESOT) congress, Vienna, September, 2013

- W. Jungraithmayr
  Award for the Best Experimental Presentation 2013
  Natural killer cells improve allogeneic lung transplants via depletion of donor dendritic cells
  Swiss Society of Thoracic Surgery

- W. Jungraithmayr
  Award for the Best Experimental Publication 2013
  The depletion of donor macrophages reduces ischemia-reperfusion injury in mouse lung transplants
  Swiss Society of Thoracic Surgery

Editorial
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