## Division of Surgical Research

# Annual Report 2015

## Department of Surgery
## University Hospital Zurich
## Switzerland

University of Zurich[UZH]

UniversityHospital Zurich

# *Content*

# *Preface*

Dear Colleagues

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

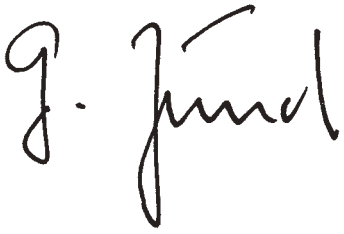
It is my pleasure to present the Annual Report 2015 of the Division of Surgical Research at the University Hospital Zurich.

In 2015, the purchase of major laboratory equipment included an Imager for Western Blot, an autosampler for a MicroCT, an ultra-low temperature freezer, a cell counter and three pressure sensors for the Bose bioreactor. Furthermore, we had to replace some defective equipment and acquired an X-Ray tube for the MicroCT and a mobile autoclave.

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

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

Yours sincerely



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

# 1. Organisation



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

Prof. Dr. med.
Pierre-Alain Clavien, PhD
Director Clinic of Visceral & Transpl. Surgery

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

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

Prof. Dr. med.
Francesco Maisano,
Director Clinic of Cardiovascular Surgery

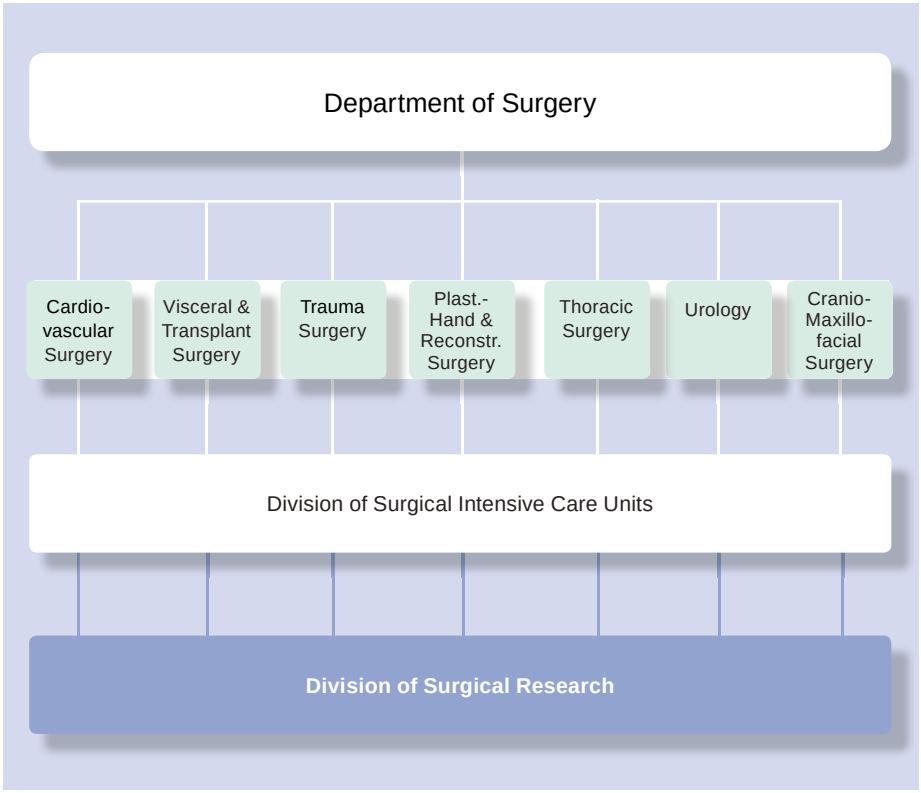
Prof. Dr. med.
Pietro Giovanoli,
Director Clinic of Plastic - Hand & Reconstr. Surgery

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

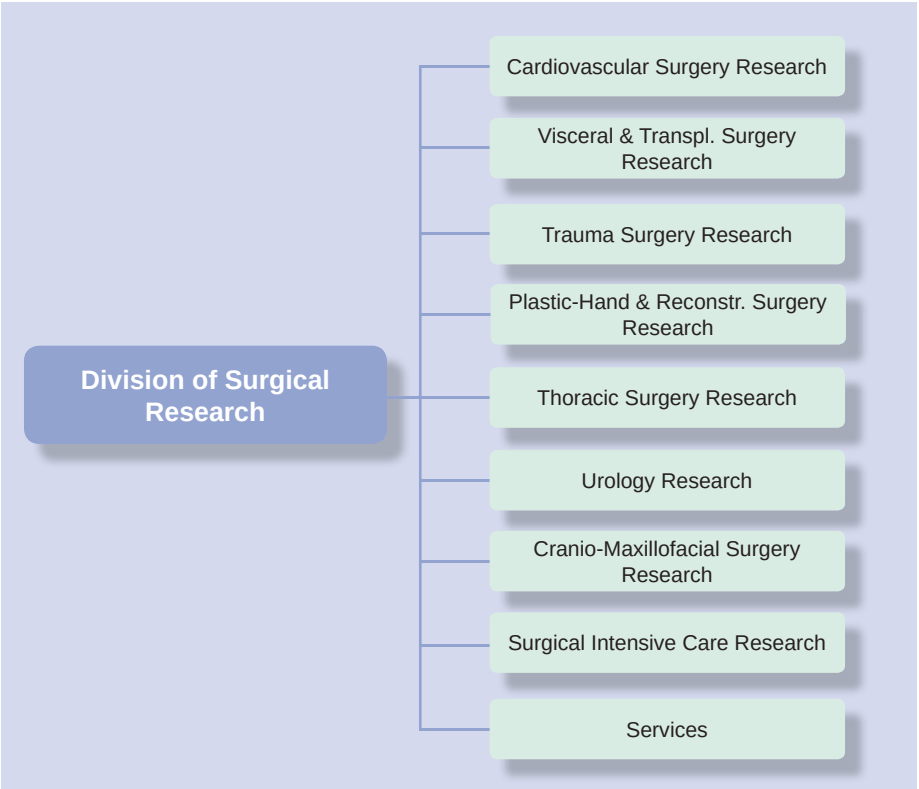
Prof. Dr. med. dent.
Martin Rücker, Director Clinic of Cranio-Maxillo-facial Surgery

Dr. med.
Peter Steiger,
Head of Intensive Care Unit

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



## 1.2 Structural Organisation of the Division of Surgical Research




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

Prof.
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. med. Simon Philipp Hoerstrup, PhD
Scientific Director

Prof. Dr. med. Francesco Maisano, Director

Prof. Dr. med. Mario Lachat

Silvia Born, Dipl.-Ing.

PD Dr. med. Dieter Mayer

PD Dr. med. Maximilian Emmert, PhD

Prof. Dr. med. Markus Wilhelm

PD Dr. med. Benedikt Weber, PhD

PD Dr. med. Zoran Rancic

PD Dr. med. André Plass

PD Dr. med. Christian Schmidt, PhD

Dr. med. Lyubov Chaykovska

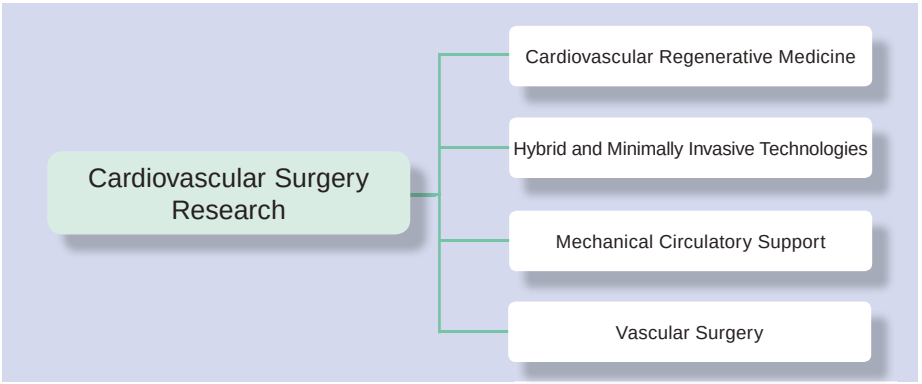
Dr. med. Herman Tolboom

Dr. med. Diana Reser

Steffen Zeisberger, PhD

Petra Dijkman, PhD

Laura Frese, PhD

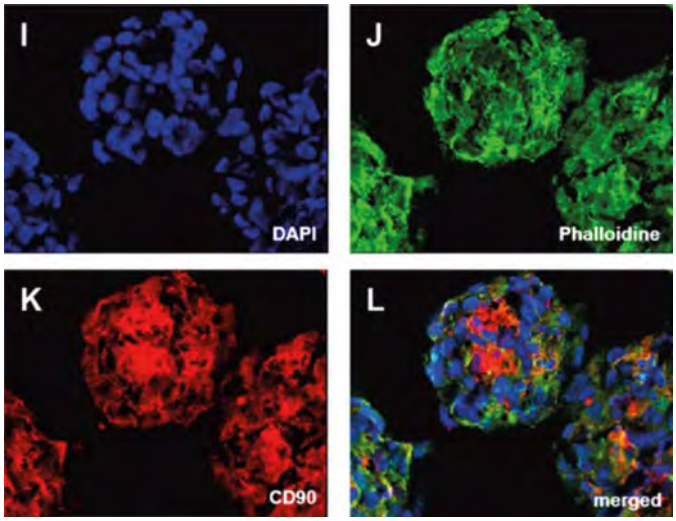



### 2.1.1 Cardiovascular Regenerative Medicine

#### 2.1.1.1 Stem cell based 3D microtissue technology platform for cardiac regeneration

*M. Emmert, S. P. Hoerstrup*

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




*Mesenchymal stem cell based 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.

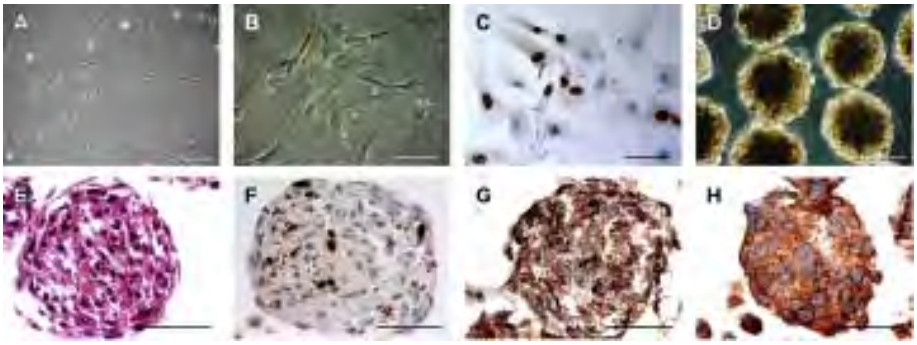



*Figure: Generation and characterization of human ATMSCs based three dimensional microtissues (3D-MTs). Human ATMSCs (A; magnification _20) were labeled with MPIOs (B; magnification _20) and tested for the proliferative capacity (C; Ki67; magnification _20) before 3D-MTs were generated within 72 hours. The cells within the 3D-MT displayed a homogenous distribution pattern and appeared to be well integrated and viable (D and E; Scale bar: 100 um and 50 um). The 3D-MTs were round-shaped with a homogenous uniformity and a predictable size according to the number of cells used for the 3D-MT generation (D and E; Scale bar: 100 um and 50 um). Positive staining for Ki67 was indicative for a continuing proliferation potential of human ATMSCs after cellular self-assembly into 3D-MTs (F; Scale bar: 50 um). The formation of extracellular matrix (ECM) within the 3DMTs was reflected via positive staining for Collagen IV and Laminin after hanging drop culture (G and H; Scale bar: 50 um) (Emmert et al. Biomaterials 2013.).*

## 2.1.1.2 Cardiovascular tissue engineering

*M. Emmert, S. P. Hoerstrup*

**The strategy of cardiovascular tissue engineering**

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

**Pre-clinical trials in sheep**

In recent years, research has demonstrated the principle feasibility of the autologous tissue engineering concept for cardiovascular applications in heart valves and blood vessels. Tissue-engineered large diameter vascular grafts have been successfully used in low and systemic pressure applications in sheep, and technology transfer to human cells has been shown. In a large animal study, we investigated the function and growth in tissue-engineered living main pulmonary arteries over a period of up to 240 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.

Michael Stader,
Study Coordination, Administration

Christine Lohmann,
Lab. Manager

Ursula Steckholzer,
Lab. Technician

Petra Wolint,
Lab. Technician

**Postdoctoral Fellows and Students**

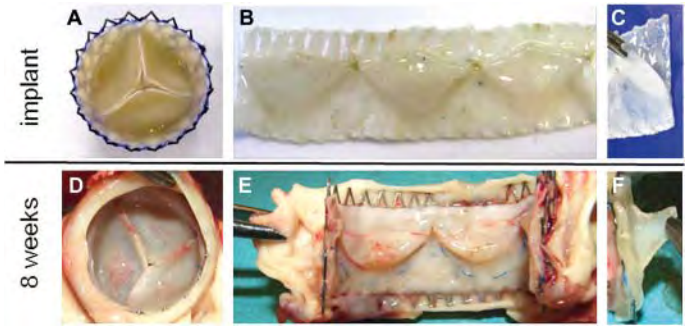
Debora Kehl,
PhD-Student

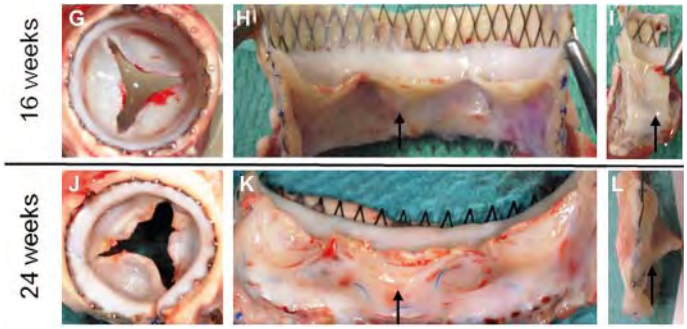
Dr. med.
Boris Jenni

Melanie Generali,
PhD-Student

Agnieszka Ksiazek,
Student vet. med.

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. In numerous studies we have also tested tissue engineered heart valves in the adult sheep and non-human primates. We have shown the principal feasibility of combining the concept of Heart Valve Tissue Engineering (HVTE) and trans-apical delivery into the pulmonary position of adult sheep, before we further pursued this concept in the systemic circulation of adult ovine models using several implantation devices. In particular, just recently, we demonstrated the feasibility to merge a bone marrow cell based heart valve tissue engineering approach with the state-of-the-art, anatomically orienting, commercially available transapical delivery system. Next, just lately we introduced the novel concept of off-the-shelf (decellularized) homologous TEHVs in an ovine model as a promising next step towards clinical application. In this study, functionality and importantly self-repair capacity of such off-the-shelf valves could be demonstrated in adult sheep for up to 6 months and long-term trials have been recently carried out in a FP7 European Initiative (LifeValve Program).




*Macroscopic appearance of the implanted (A to C) and explanted (D to L) decellularized in vitro grown TEHV in closed configuration (A,D,G,J), opened configuration (B,E,H,K), and as cross section (C,F,I,L). The implants and explants all revealed shiny and pliable leaflets. Complete closure was evident in the implant (A) and was maintained up to 8 weeks (D), while being incomplete thereafter (G,J). The line of attachment of leaflets to the wall moved upward in time (arrows), associated with a reduction in leaflet size (E,F,H,I,K,L). TEHV ¼ tissue-engineered heart valve.*

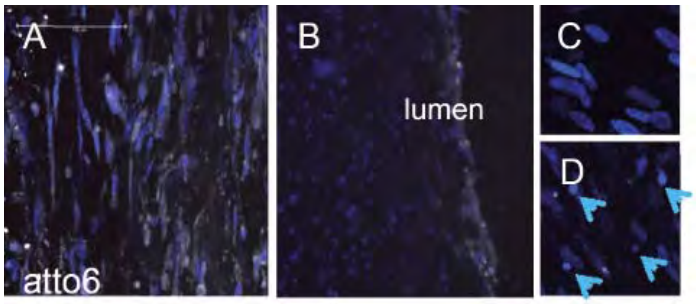
## 2.1.1.3 Disease modeling

*B. Weber*

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

**Tissue Engineered Atherosclerosis Modeling**

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




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

## 2.1.1.4 Novel targets for infarction prevention strategies

*C. Brokopp, C. Lohmann, M. Goeranson*

**The role of Fibroblast Activation Protein (FAP) in thrombosis**

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

**FAP diagnostics and therapeutic**

A first-in-class antibody (82C2) was discovered that inhibits the pre-thrombotic enzymatic activity of FAP (Figure A). 82C2 has been shown to lessen thrombosis in human blood *ex vivo* (Figure B), and shows potent anti-thrombotic behavior in thrombosis animal models (Figure C). Blood tests have been validated for patient selection, and future work seeks to complete GMP antibody production and toxicology evaluation of the antibody as a prerequisite to clinical testing.

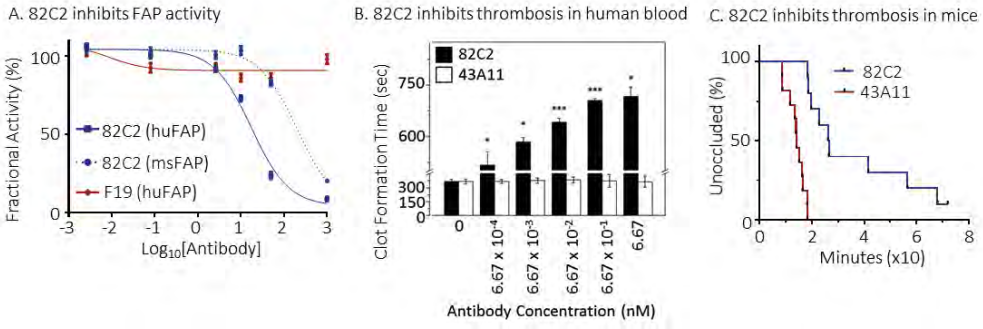



*Figure: (A) 82C2 is a novel FAP-inhibiting antibody that lessens thrombosis. 82C2 inhibits the enzymatic activity on human (huFAP) and murine FAP (muFAP), compared to non-inhibitory anti-FAP antibody F19. (B) 82C2 lessens the thrombosis of human blood in a dose-dependent manner compared to 43A11. (C) 82C2 inhibits thrombosis in mice compared to biologically inactive isotype-matched control antibody 43A11.*

**Collaborations:**

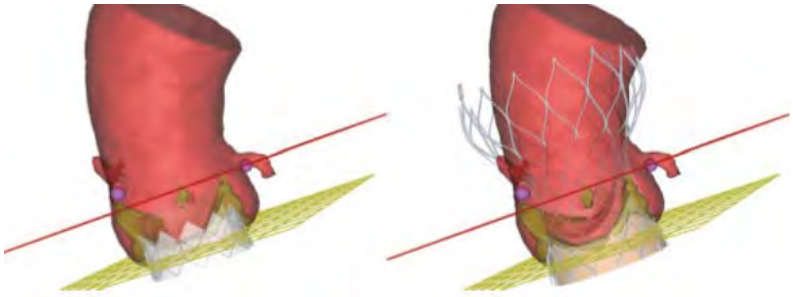
- Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, USA
- Department of Biomedical Engineering, Technical University Eindhoven, The Netherlands
- Center for Integrative Human Physiology, University of Zurich, Switzerland
- Department of Materials, Federal Institute of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

## 2.1.2 Hybrid and Minimally Invasive Technologies

### 2.1.2.1 The advanced role of imaging in transcatheter cardiac valve treatment

*S. Born*

Interventional, catheter based treatment of heart valve disease has become a widely accepted alternative option for the treatment of aortic and mitral valve pathologies in patients at high risk for surgery. Pre-, intra-, and postoperative imaging is crucial because -unlike to open surgery- no direct visual assessment of the pathology or the treatment result is possible.
Preoperatively, computertomography (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 necessary to decide which surgical or interventional treatment option offers the optimal trade-off between outcome quality and perioperative risk. Our interdisciplinary team of cardiac surgeons, cardiologists, radiologists, and engineers is constantly developing and validating new image analysis methods and tools to increase the reliability of clinical decisions.
The hybrid operating room (Hybrid OR) opened in 2011 at USZ contains state-of-the-art imaging equipment and was designed to allow for an optimal integration of the different imaging modalities in order to help surgeons and interventionists in creating a virtual image of the beating heart, the catheters, and the devices at the tip of the catheters.
Together with engineers at the ETH Zürich and Philips Healthcare in Best (Netherlands) we are exploring the capabilities offered by the new infrastructure and software available in this facility. Softwaretools for preoperative planning of TAVI procedures (Heart Navigator) as well as a navigation tool (EchoNavigator) used in MitraClip procedures are assessed in clinical studies and further developed together with Philips Healthcare. The EchoNavigator was used in 21 patients in 2012 and the results were compared to those of 21 patients treated without this software immediately before the installation of the software. The results indicate that it might facilitate the procedure, decrease the length of the procedure and the radiation dose.
The HeartNavigator was used in all TAVI patients to plan the procedures. Additionally, its ability to perform intraoperative rotational computertomography scans was assessed and further developed.
An own software tool was developed and validated for preoperative TAVI planning. 85 patients were retrospectively planned by clinicians involved in the heart team. The results indicate that this 3D-template tool might be an alternative tool to prevent adverse events like paravalvular leakage or atrioventricular block after TAVI implantation.



### 2.1.2.2 Computational models in cardiac surgery

*S. Born*

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

**Biomechanics of Transcatheter Aortic Valve Implantation**

In an SNF funded project run together with the groups of Professor Mazza and Professor Székely at ETH Zurich, the biomechanical impact of stented transcatheter aortic valve implants onto the aortic root and left ventricular outflow tract and its influence on the outcome after transcatheter aortic valve implantation (TAVI) have been investigated.
In this project, we developed an advanced system for the selection of the most appropriate implant and its optimal placement for a particular patient.
In 2015, analysis of the mechanical situation of TAVI stents after implantation was finalized based on clinical data of more than 100 patients. A software, which was developed by the group, was used to extract the shape and estimate the contact forces. This information was then mapped to charts, which allowed to identify typical patterns for different groups of patients (Figure 1).

Further, we trained self-learning algorithms to automatically predict the occurrence of adverse events for a specific intervention. Finally, we continued to work on the validation of our simulation tool by simulating TAVI cases prospectively and compare our results with the actual intervention outcome.

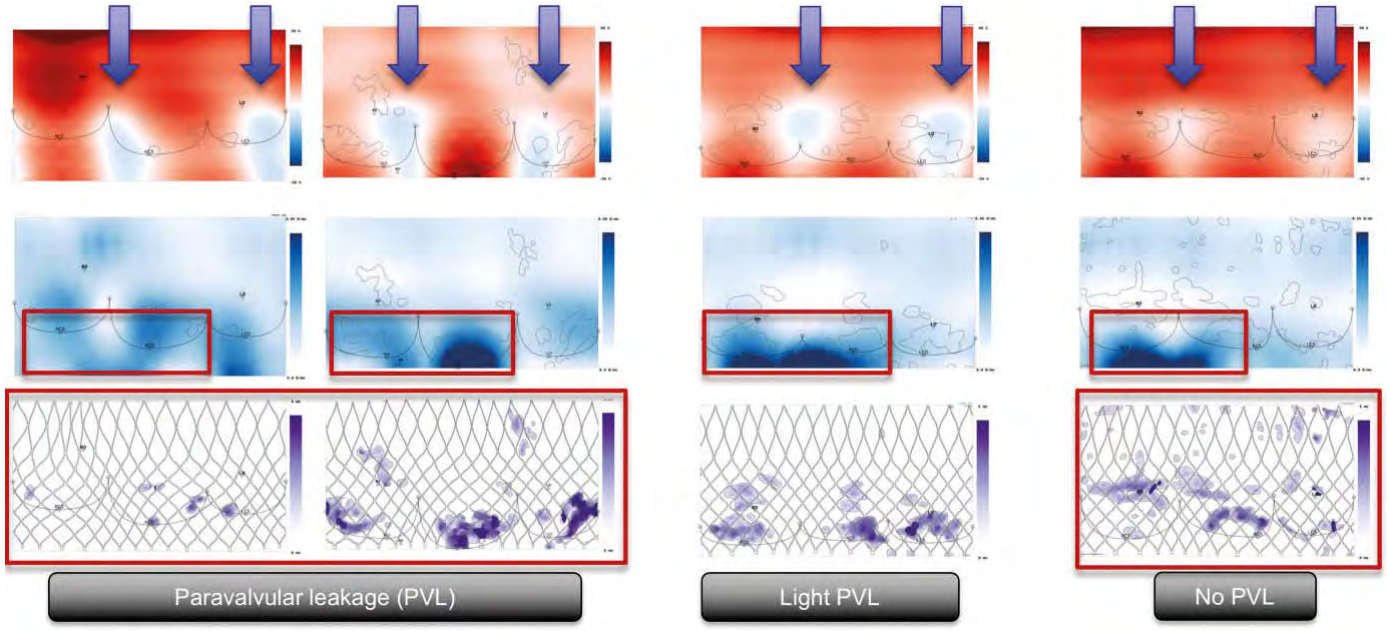



*Figure: Patterns of calcification, radial forces, and stent deformation for different TAVI outcomes.*

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

## 2.1.2.3 Hybrid revascularization

*D. Reser*

Hybrid coronary artery revascularization has come to the focus of attention due to the excellent long-term patency of the left internal mammary artery (LIMA) to the left anterior descending artery (LAD). It combines the advantages of percutaneous coronary intervention (PCI) and minimally invasive direct coronary bypass (MIDCAB), providing the benefits of proven long-term patency of a LIMA-to-LAD graft. Between January 2009 and December 2015 revascularization of the LAD was performed in 49 patients with MIDCAB through a left anterior mini-thoracotomy followed by PCI of non-LAD vessels in one single procedure in our surgical hybrid suite with good results. Angiography confirmed patency of all LIMA grafts. Three of the patients died of cancer. Major adverse cardiac and cerebrovascular event free survival was 100% after 6 years.

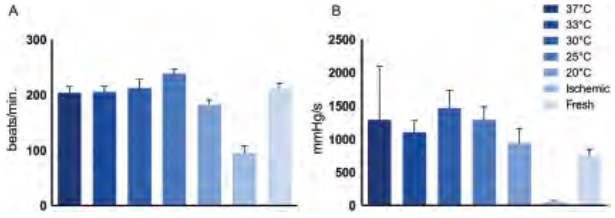
## 2.1.3 Transplantation and Mechanical Circulatory Support

### 2.1.3.1 Transplantation research

*H. Tolboom, M. Wilhelm*

**Moderate hypothermia during *ex vivo* machine perfusion promotes recovery of hearts donated after cardiocirculatory 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.



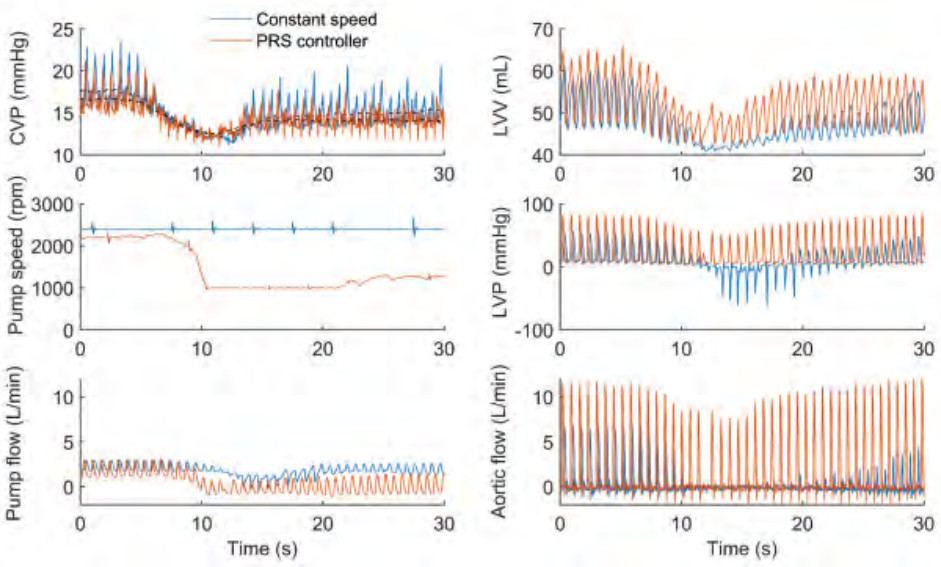

*Mean heart rate heart (A) and dP/dt (B) of reconditioned, ischaemic and fresh hearts during Langendorff reperfusion following cold storage.*

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.
The goal of the project is to establish the optimal machine perfusion temperature for recovery of hearts in a rodent model of donation after declaration of cardiocirculatory death (DCD).
The most important findings of this study are as follows:
(i) Functional recovery of the hearts subjected to 25 min of global ischaemia can take place during 60 min of reperfusion at temperatures between 20 and 37°C.
(ii) Temperatures in 25–30°C range appear to best stimulate functional recovery.
(iii) Replenishment of ATP levels occurred at an equal rate in all reconditioned groups.

### 2.1.3.2 Mechanical circulatory support research

*M. Wilhelm*

***In vivo* evaluation of the preload responsive speed controller and systolic pressure controller for automatic flow adaptation of ventricular assist devices**




The goal of the study which is part of the project “Zurich Heart” was to show the feasibility of automatic and instantaneous adaption of the pump speed to variable preload and afterload conditions in a large animal model.
The concept could be proven. Both the preload responsive speed (PRS) controller and the systolic pressure (SP) controller adjusted blood propulsion following changes of pre- and afterload.

*Figure: Full scale perfusion system*

**Collaborations:**

- pd|z Product Development Group Zurich, Department of Mechanical and Process Engineering, ETH Zürich (Prof. M. Meboldt)
- Wyss Translational Center Zurich, Swiss Federal Institute of Technology (ETH) Zurich, Center for Mechanics (Zürich)
- Institute for Dynamic Systems and Control, Department of Mechanical and Process Engineering, ETH Zürich (Prof. C. Onder, Prof. L. Guzzella)
- Micro- and Nanosystems, Department of Mechanical and Process Engineering, ETH Zürich (Prof. C. Hierold)

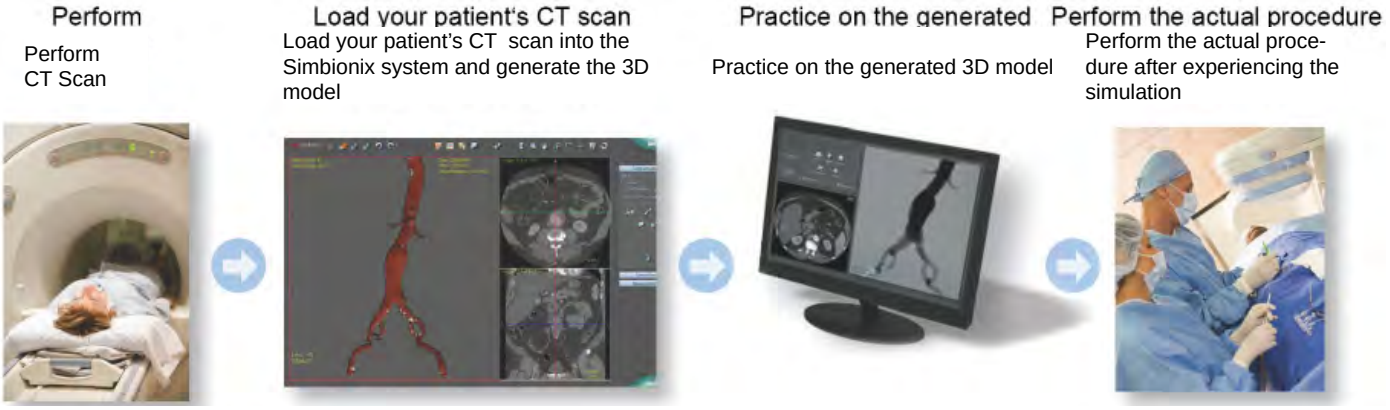
## 2.1.4 Vascular Surgery

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

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

Ongoing technological advances, especially in the field of image processing, have refined medical simulations to offer life-like replications of medical and surgical procedures in a variety of specialties. Patient-specific image data are incorporated into these simulations, and transformed into a 3D model.

This enables the practitioner and his/her team to perform and practice 'real' cases on a virtual patient prior to performing the real procedure on the actual patient. This new technology has been referred to as 'patient-specific' rehearsal, also 'mission' or 'procedure' rehearsal.




### 2.1.4.2 Evaluation of the impact of DoseAware in a clinical setting

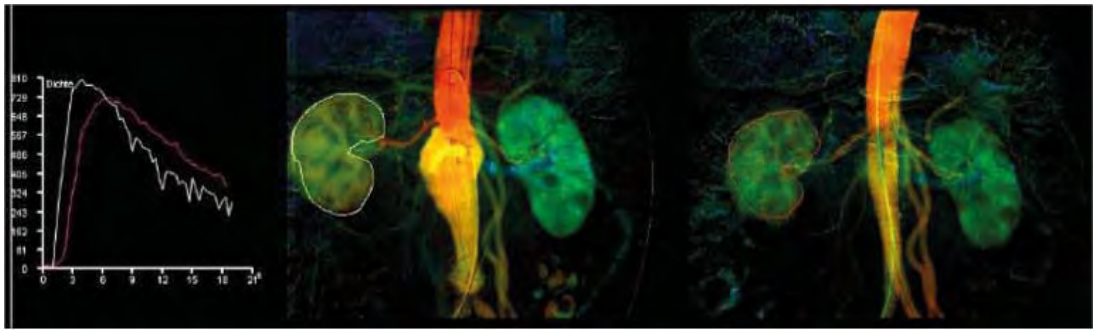
*L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat*

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


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

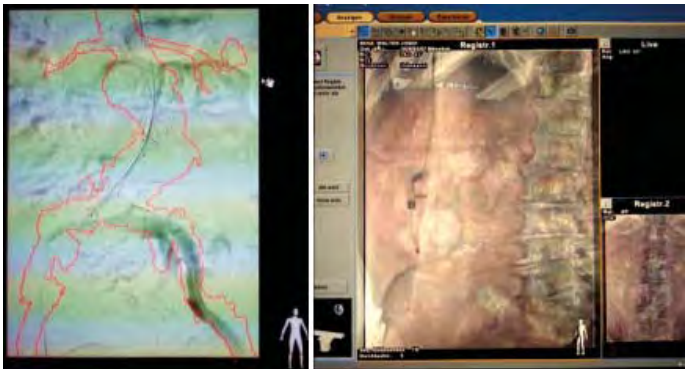
*L. Chaykovska, Z. Rancic, D. Mayer, M. Lachat*

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



## 2.1.4.4 Evaluation of automated image overlay system for EVAR

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

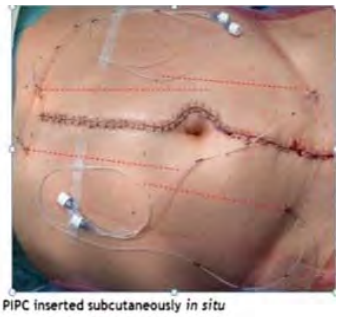


The digital subtraction technique has made the digital roadmap into an indispensable tool. The roadmap can be renewed every time the X-ray tube or the table needs to be readjusted for a better view using an X-Ray view of the bones.
The aim of this study was to evaluate the feasibility of image overlay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

## 2.1.4.5 Evaluation of different methods of local anesthesia for postoperative analgesia

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

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

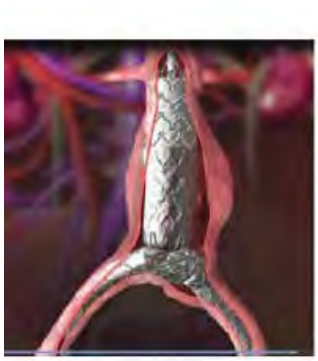


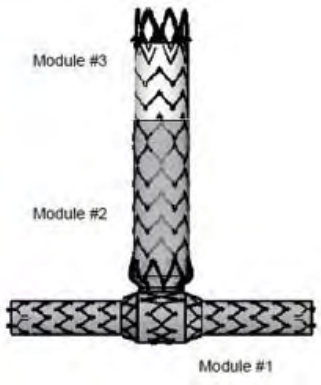
PIPC inserted subcutaneously *in situ*

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.

## 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.

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

*L. Chaykovska, Th. Pfammatter, M. Lachat*

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

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

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


**Collaborations:**

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

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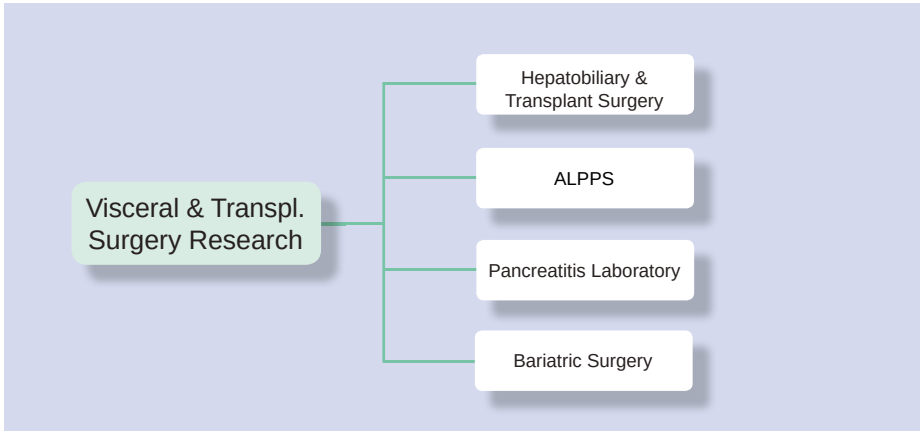
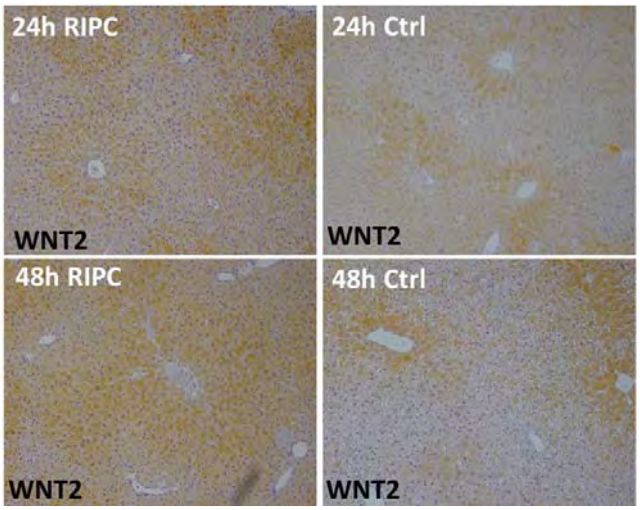


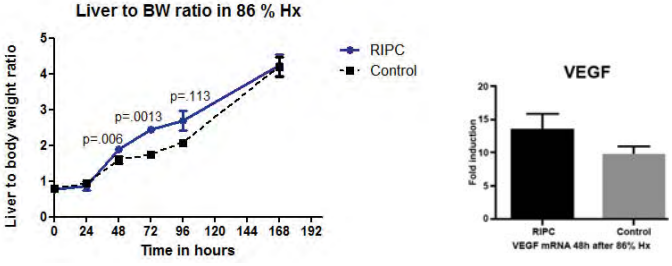

### 2.2.1 Hepatobiliary & Transplant Surgery

**Remote ischemic precoditioning for the improvement of regeneration after hepatectomy**

*P. Kambakamba, M. Linecker, P. Kron, R. Graf, B. Humar & P.-A. Clavien*

Remote ischemic preconditioning (RIPC) has systemic effects mediated through a platelet-serotonin-Vegf-Il10/Mmp8 axis. The systemic effect of RIPC showed also beneficial impact on liver regeneration via VEGFR2-ID1 mediated inductive angiogenesis in Liver sinusoidal cells (LSECS) through release of angiocrine factors Wnt2 and HGF.

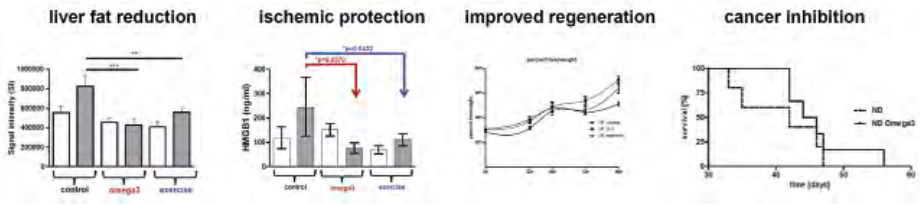


## Ω3-fatty acids and exercise inhibit hepatosteatosis, protect from ischemic injury, improve regeneration and hinder liver cancer

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

Surgical removal of liver tumors is associated with postoperative complications due to fatty liver, ischemic injury, inefficient regeneration, and a possible tumor occurrence. Ideal interventions to improve surgical outcomes would target all of these aspects. We show that Ω3-fatty acids and exercise can do all of the above, and hence may improve outcomes after complex liver surgery.

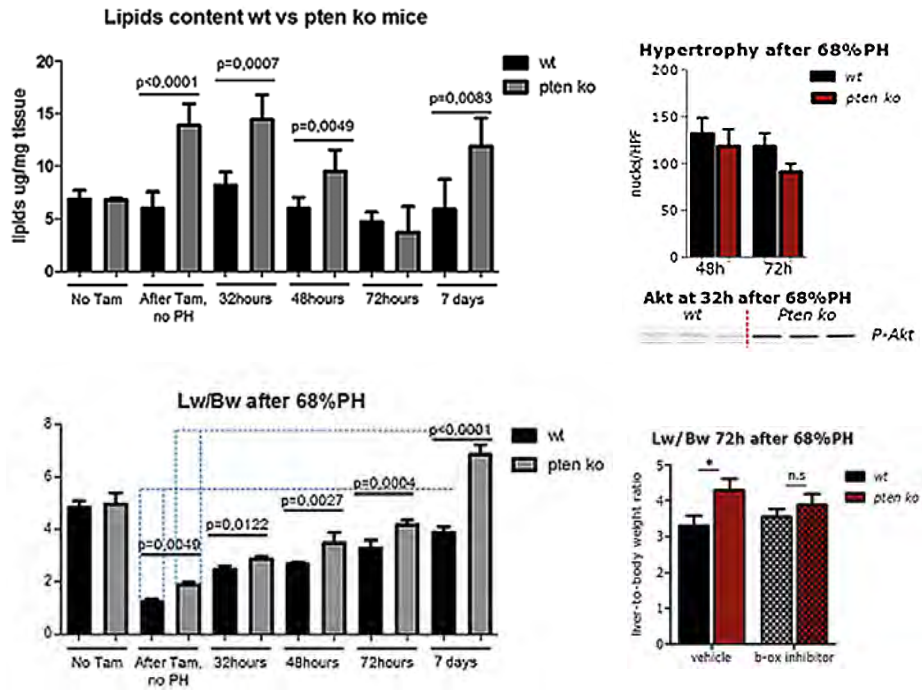



## Pten downregulation during liver regeneration for the promotion of energy metabolism and hepatocyte growth

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

Pten is a negative regulator of the growth-promoting PI3K-Akt-mTOR axis and is uncharacterized with regards to its role in liver regeneration. We use inducible, hepatocyte-specific Pten knockouts to study its function.

Our results suggest that Pten loss promotes liver regeneration through: (i) the release of inhibition of the hypertrophic Akt-mTORC pathway, (ii) the provision of energy via facilitated lipid metabolism, i.e. enhanced systemic turnover of TGs & cholesterol, as well as enhanced β-oxidation.

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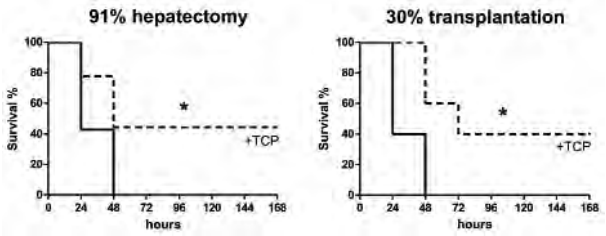
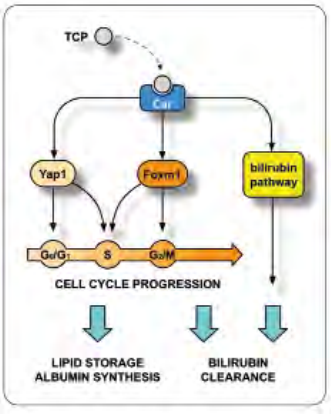
## Car-driven regeneration protects liver from failure following tissue loss

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




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

## CAR activation and its effect on colorectal liver metastasis

*P. Kressig, Ch. Tschuor, R. Graf, P. Borger, B. Humar & P.-A. Clavien*

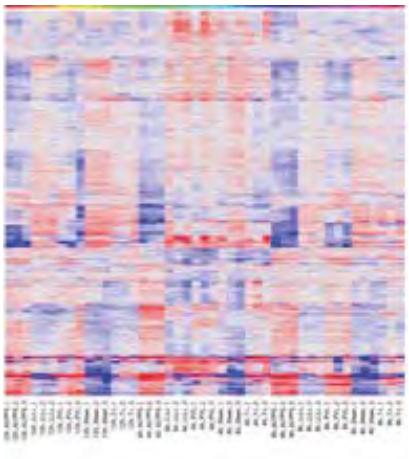

Through induction of liver growth by CAR activation we could rescue 40% of animals in two lethal models of the Small-for-Size Syndrome. Owing to the strong proliferative response mediated by CAR, other, potential applications of CAR activation are the induction of liver growth *ex situ* or the replacement of the first step of a 2-stage hepatectomy. Before implementation of such applications, we need to clarify the effects of CAR activation on preexisting or recurrent liver malignancy.

## Mechanisms underlying the accelerated liver regeneration induced by ALPPS surgery

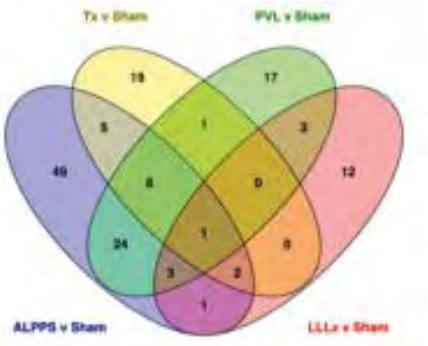
*M. Langiewicz, A. Schlegel, R. Graf, P. Borger, B. Humar & P.-A. Clavien*

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

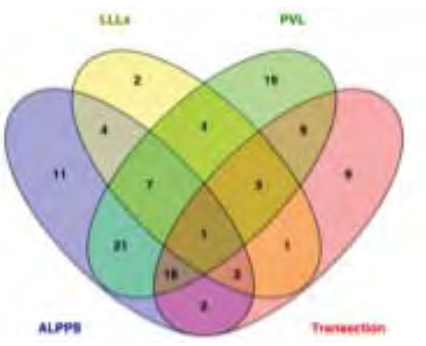
**ALPPS-specific transcriptome changes**



**ALPPS-unique genes**




**ALPPS-unique pathways**



## The interaction between serotonin, the nuclear receptors CAR and RXRα & their influence on liver regeneration

*M. Schneider, P. Borger, R. Graf, B. Humar & P.-A. Clavien*

Research in our lab has shown that peripheral serotonin as well as the nuclear receptor CAR are essential for normal liver regeneration. Interestingly, CAR activation with a specific agonist is without effect and fails to induce liver regeneration in TPH1 knockout mice lacking peripheral serotonin. We identified retinoid X receptor alpha as a potential link between serotonin and CAR effects on liver regeneration and are currently investigating pathways altered between mice lacking serotonin, CAR and RXRα via a transcriptomic approach to determine the interaction of these three molecules and their influence on proper liver regeneration. (Figure 1)

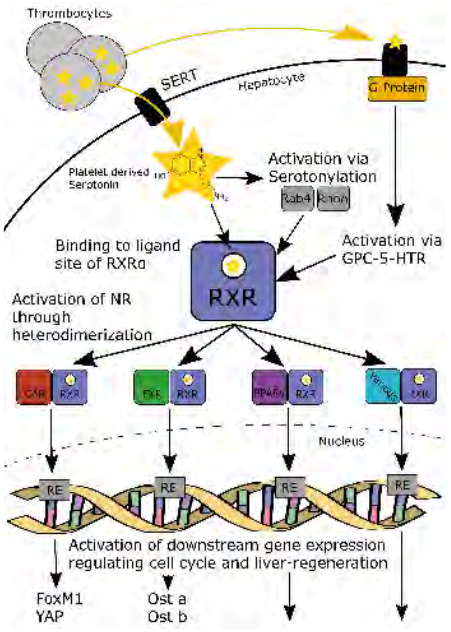



*Figure 1*

## The contribution of serotonin to the progression of nonalcoholic fatty liver disease to hepatocellular carcinoma

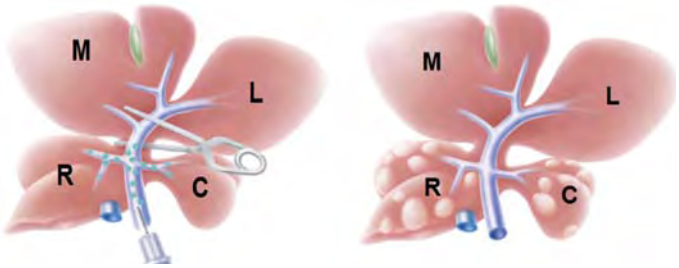
*N. Borgeaud, E. Kachaylo, J.-H. Jang, R. Graf, B. Humar & P.-A. Clavien*

Non-alcoholic liver disease (NAFLD) is strongly associated with obesity and the metabolic syndrome. Furthermore, it increases the risk of liver cancer. Serotonin is required for liver regeneration and might be a promoter of liver cancer. Nevertheless, it is also a mediator of different pathological conditions as it contributes to fibrosis and aggravates steatohepatitis. Fibrosis and steatohepatitis are both involved in tumorigenesis of hepatocellular carcinoma. Here we investigate the role of serotonin in the promotion of NAFLD and its further progression to steatohepatitis and then cancer.

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

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

Various animal models of liver tumors exist. Orthotopic systems based on grafting of cancer cells yield rapid tumor development and are well-suited for studying a tumor within its physiological (micro)environment. Syngeneic grafts additionally preserve the immunological competence of the host. Here, we describe selective portal injection as a versatile tool to generate orthotopic syngeneic models of liver tumors that share a short latency and a high penetrance, are reproducible, restricted to the liver, and provide unaffected control tissue. (Figure 2)



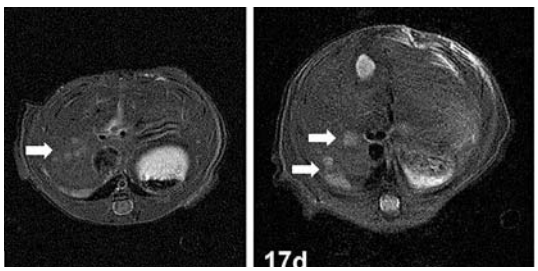



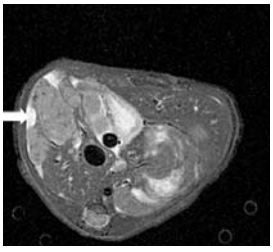

*Figure 2*

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

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

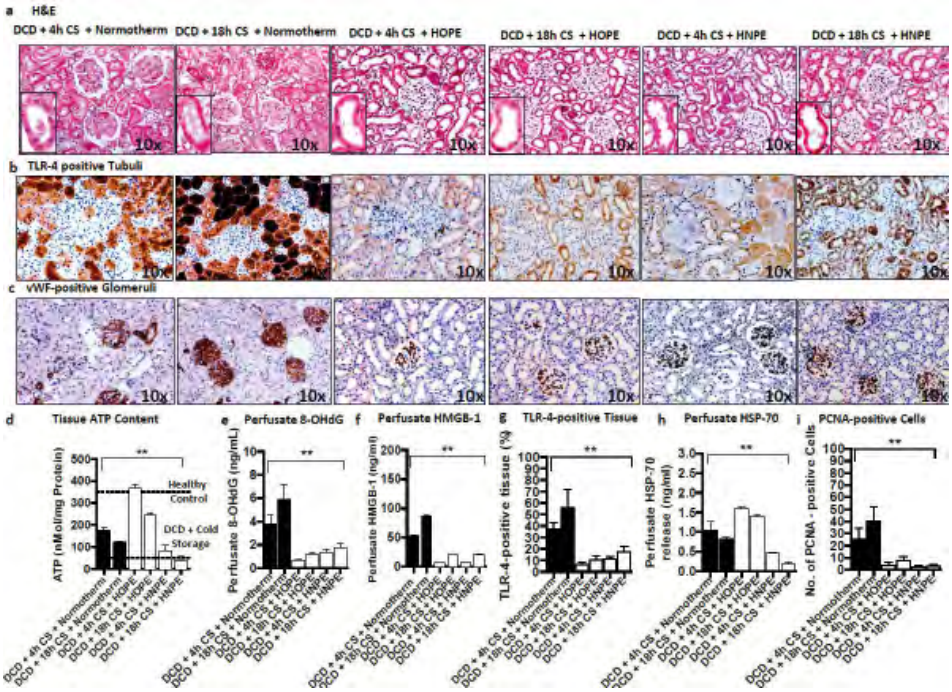
Hypoxia is a renown promoter of malignancy and is associated with many undesired effects such as endothelial dysfunction and the loss of chemotherapeutic efficacy.

Using the antihypoxic molecule ITPP, we could re-establish stable normoxia in experimental liver metastases, leading to a long-lasting inhibition of the hypoxic response, the normalization of vasculature, and a markedly improved efficacy of chemotherapy when compared to chemotherapy plus anti-angiogenic agents (Avastin) as assessed by survival. An according clinical trial has been initiated.



## Short, cool and well oxygenated – HOPE for kidney transplantation in a rodent model

*P. Kron, A. Schlegel, O. de Rougemont, C. E. Oberkofler, P.-A. Clavien, P. Dutkowski*



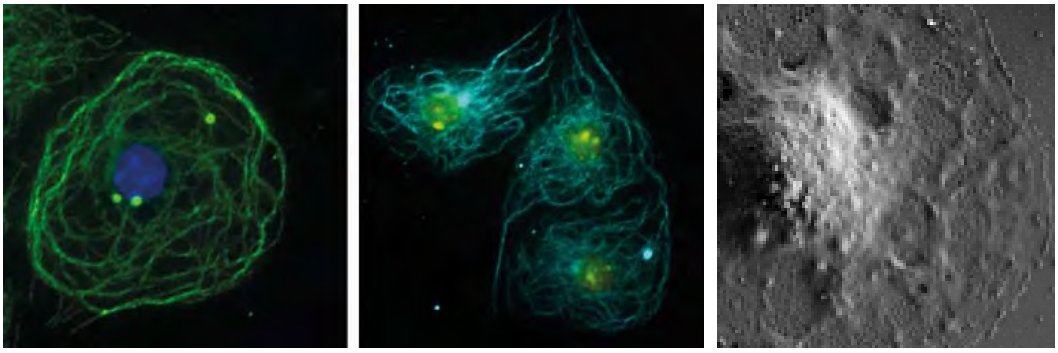

*Graft injury during 1h machine perfusion of cold stored DCD kidneys*

DCD organs, donation after cardiac death, suffer from a higher risk of dysfunction after implantation. In our experimental setting we showed dramatically better function of HOPE pretreated DCD grafts after transplantation, when compared to cold stored grafts in terms of nuclear injury, macrophage activation, endothelium activation, tubulus damage and graft function. A short period of warm oxygenated perfusion before implantation improved graft quality as compared to cold storage, but was significantly less effective in all endpoints compared to HOPE. The effect of HOPE was dependent on perfusate oxygenation in the cold. HOPE of DCD kidneys was superior to other clinically used preservation approaches, consistent to earlier results in livers. Based on this, we assume a strong and generalized effect on solid organ viability by HOPE before transplantation.

## Endothelial contribution to the tumor microenvironment of hepatocellular carcinoma

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

Liver endothelial cells have a key role in maintaining proper liver function. Whether and how these highly differentiated cells affect processes related to the transformation and malignant progression of hepatocytes is not known. Novel insight into endothelial-parenchymal interactions may therefore help to develop alternative cancer treatments.



**Collaborations / Sponsors:**

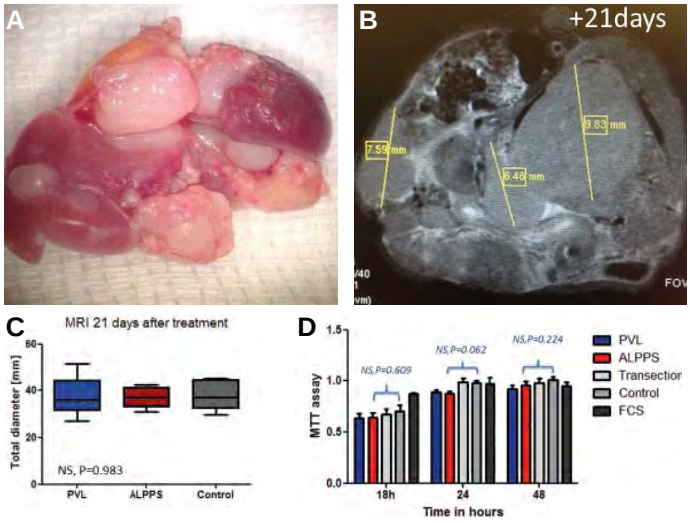
- Prof. Michelangelo Foti (University of Geneva)
- Prof. Jean-Francois Dufour (University of Bern)
- Prof. Gerald Schwank (ETH Zurich)
- Prof. Sabine Werner (ETH Zurich)
- Prof. Jean-Marie Lehn (University of Strasbourg)
- Various clinical collaborations

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

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

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

The aim of this project is to investigate in a mouse model whether ALPPS promotes tumor growth in mice. For this purpose we combine two well-established models in our department: liver colorectal tumor cell injection and ALPPS. Small animal MRI, survival experiments and *in vitro* cell proliferation did not show any proliferative effect of ALPPS on colorectal tumor growth.

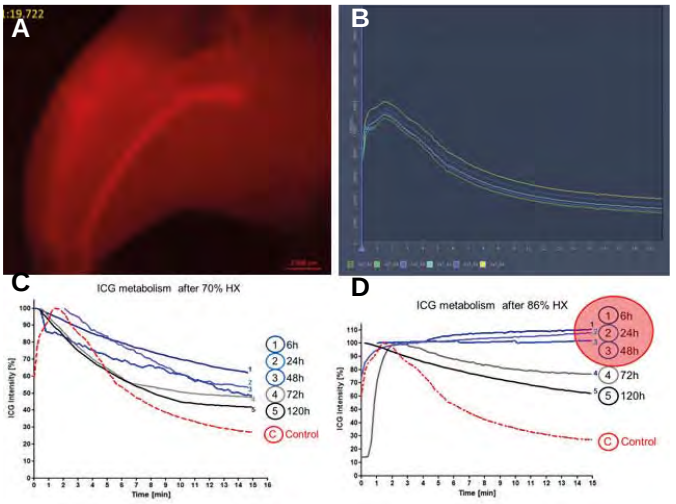



*A) Liver tumor load 21 days after cancer cell injection in the portal vein, B) T2 weighted small animal MRI in order to assess number of tumors and tumor volume in mice liver, C) Cumulative tumor diameter in different groups at day 21, D) MTT Assay of MC 38 cancer cells incubated with serum from mice undergoing ALPPS, PVL, transection only, or Sham surgery (Control), FCS: Fetal calf serum*

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

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

We aim at establishing a non-invasive, dynamic liver function test based on ICG clearance in mice in several models including normal liver, major hepatectomy, small-for-size liver, acute and chronic liver failure. Preliminary findings suggest an association between ICG metabolism and liver volume gain in both the 70% and 86% Hepatectomy.



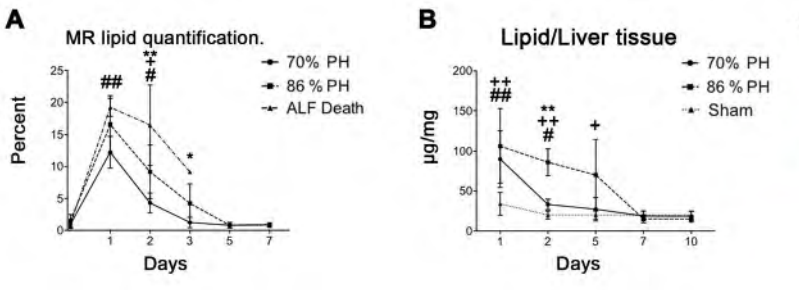

*A) Fluorescence camera showing ICG in inguinal vein, B) Calculated ICG decay curve over time, C) ICG metabolism over time after 70% hepatectomy, D) ICG metabolism over time after 86% hepatectomy.*

### MRI fat quantification in small-for-size syndrome after hepatectomy

Small for size syndrome (SFSS) describes an acute liver failure after extended hepatectomy. It is related to an impaired regeneration in the context of a too small liver remnant.

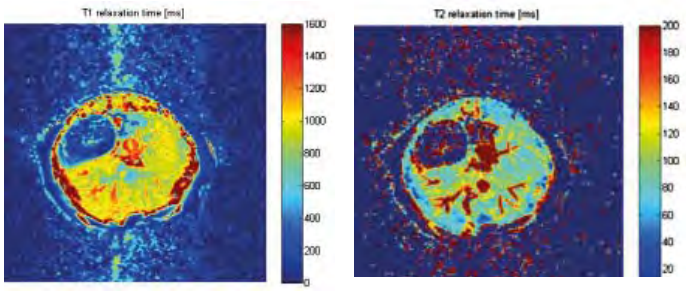
We aimed at exploring MRI as a non-invasive diagnostic tool for early detection of impending SFSS. Early diagnosis may enable any therapeutic intervention at an early stage and therefore improve outcomes.

Early lipid droplet accumulation has been found to distinguish SFSS and normal liver regeneration in rodents. Serial postoperative MRI sequences (in and opposed phase) after 70% and 86% hepatectomies were used to quantify liver lipid accumulation. MRI reliably detected lipid accumulation in SFSS and therefore might be used as a diagnostic tool. *(Figure see next page).*




*A) Liver lipid quantification assessed by MRI in regular regeneration (70%PH), SFSS (86%PH) and in mice dying from SFSS within the 7-day study period (Acute Liver Failure (ALF) death), B) Chemical liver lipid quantification, C) Red Oil O staining showing liver lipid accumulation 48h after 86% PH compared to 70% PH.*

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




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

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

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

**Collaborations/Sponsors:**

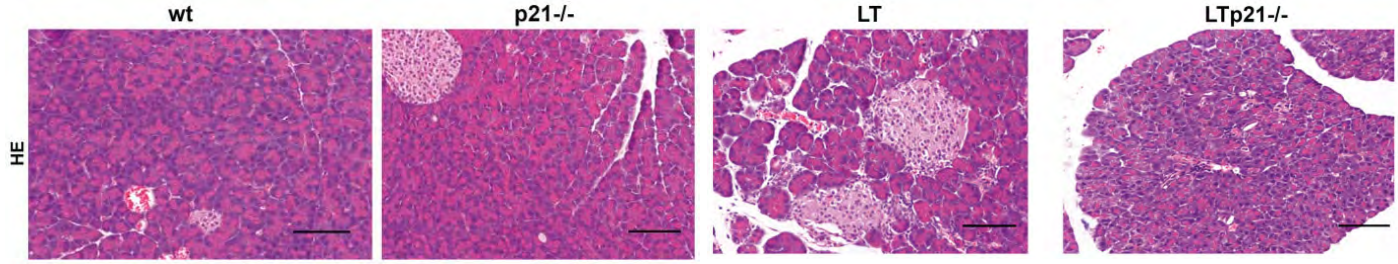
- PD Dr. Andreas Boss, Department of Radiology, University Hospital Zurich

## 2.2.3 Pancreatitis Research Laboratory

### Absence of p21 attenuates pancreatic inflammation but does not modulate the development of autoimmune pancreatitis

*G. M. Seleznik, T. Reding, L. Peter, A. Zabel, S. Sonda, M. Heikenwalder, R. Graf*

The goal of the project is to investigate how the absence of the cyclin dependent kinase (cdk) inhibitor p21, a critical regulator of inflammatory diseases influencing proliferation, activation and differentiation of inflammatory cells, affects the development of pancreatic inflammation and autoimmunity. Deficiency of p21 in a mouse model of pancreatitis (LT) prevented early pancreatic injury, as evidenced by normal pancreatic amylase levels, reduced inflammatory cell influx, decreased acinar cell proliferation and diminished inflammatory gene signature. Despite this initial attenuated inflammatory phenotype, autoimmunity was not influenced in LT;p21$^{-/-}$.



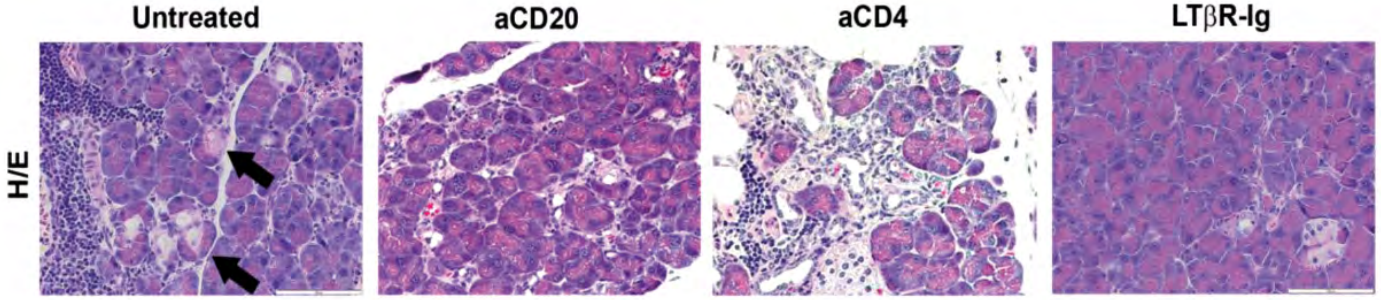

*Early pancreatic damage visualized on HE staining is more prominent in the LT (Tg(Ela1-Lta,b) group compared to LTp21$^{-/-}$ (Tg(Ela1-Lta,b); p21$^{-/-}$)*

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

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

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

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

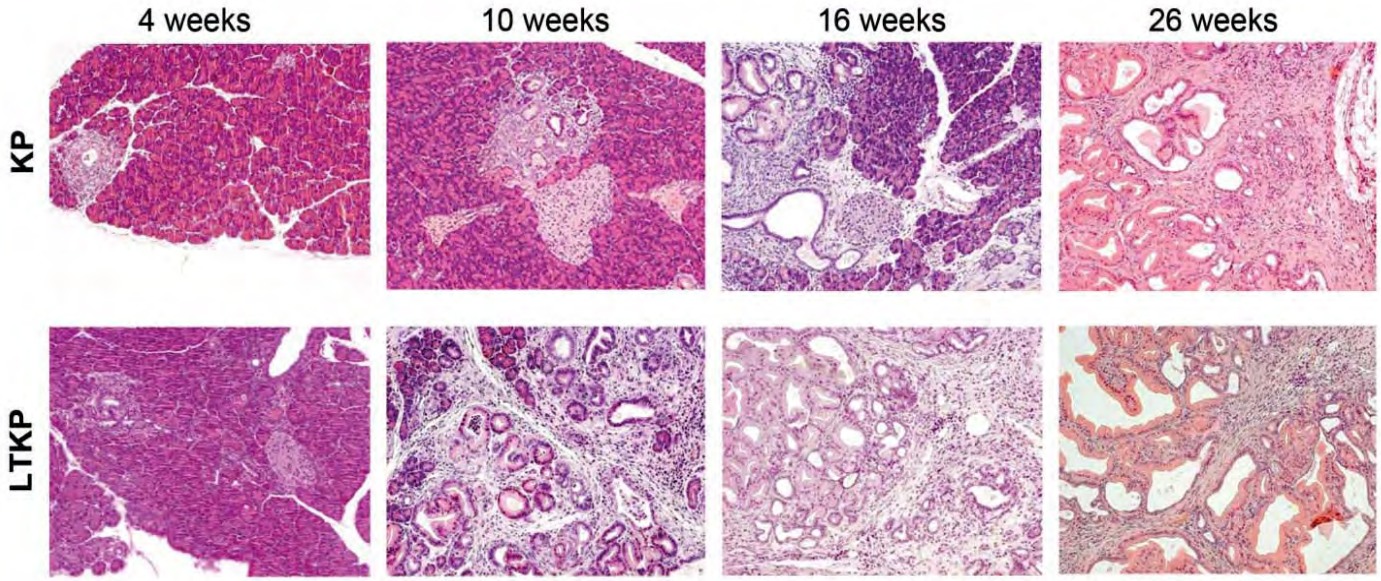



*Treatments applied in Tg(Ela1-Lta,b) mice.*

## Lymphotoxin accelerates pre-neoplastic conversion in pancreatic tumorigenesis by promoting acinar cell reprogramming

*G. Seleznik, T. Reding, S. Sonda, E. Diamantis, A. Perren, M. Heikenwälder, R. Graf*

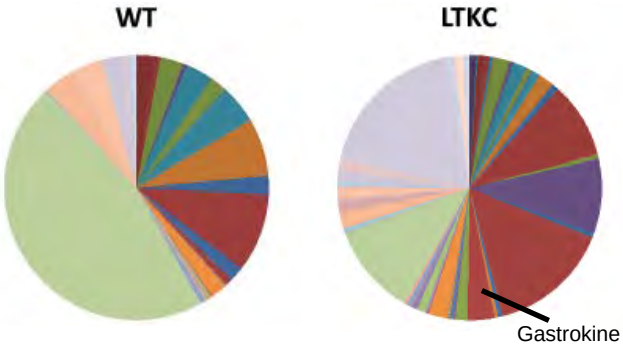
Pancreatic inflammation is a well-known risk factor for pancreatic ductal adenocarcinoma (PDAC) development in humans, but the underlining molecular mechanisms remain elusive. In a novel genetic mouse model (LTKP: *Tg*(Ela1-Lta,b); $p48^{+/Cre}$; $Kras^{+/G12D}$) our results indicate that Lymphotoxin expression accelerates the development of PDAC precursor formation by (1) inducing inflammatory environment and (2) trans-activating the EGFR.




*Lymphotoxin expression (LTKP) accelerates the development of premalignant PanIN lesions in mice harbouring Kras mutation (KP).*

## Gastrokine secreted into pancreatic juice as a novel potential biomarker for premalignant pancreatic lesions

*T. Reding, G. Seleznik, A. Zabel, C. Trachsel, N. Selevsek, J. Grossmann, R. Graf*



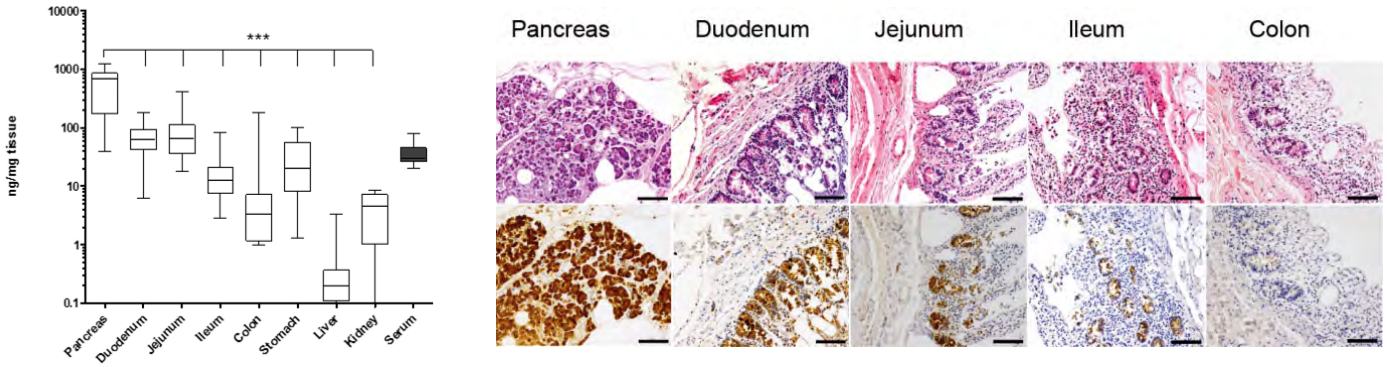

In a mouse model for pancreatic carcinogenesis, gastrokine (GKN) is highly up-regulated in premalignant PanIN lesions, but absent in malignant tumors. Since GKN is produced in acinar cells and it is likely to be secreted into the pancreatic juice, we collected mouse pancreatic juice and analyzed GKN-levels by a proteomic approach to establish a diagnostic tool. We found significant amounts of GKN in pancreatic juice of Kras (LTKC) mice with PanIN lesions but not in wild-type-mice (WT).

*Proteomic analysis of pancreatic juice from wilt-type (WT) and PanIN harboring mice (LTKC).*

## Quantification and localization of Pancreatic Stone Protein (PSP), a new marker of sepsis, in abdominal human organs

*T. Reding, C. Palmiere, L. Mancina, U. Süss, P. Fuchs, A. Zabel, R. Graf*

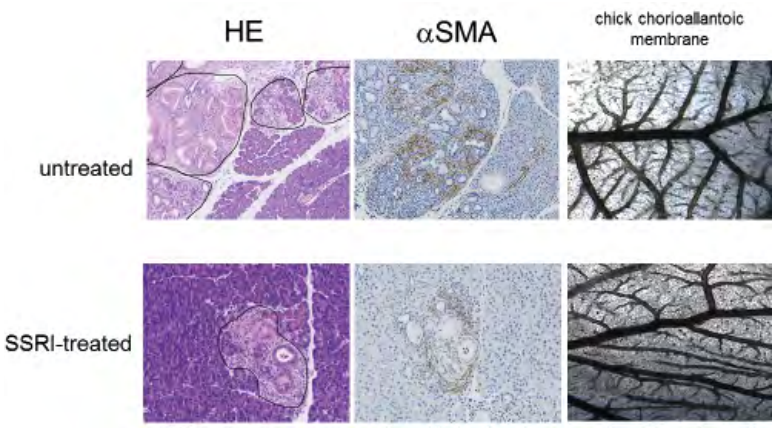
PSP is a marker of sepsis but its tissue-distribution has not been characterized yet. Quantification of PSP has been performed by ELISA in abdominal human organs and sera of 16 autopsies of septic patients and showed significantly higher amounts in the pancreas compared to all other organs. IHC staining in human sections showed that PSP is localized in the pancreatic acinar cells and primarily to the crypts of duodenum, jejunum and ileum but not colon.




*ELISA-based quantification (left panel) and IHC (right panel) of PSP in tissues of human septic patients*

## Serotonin-selective reuptake inhibitors (SSRI) as a novel approach to counteract pancreatic ductal adenocarcinoma progression

*E. Saponara, G. Seleznik, R. Buzzi, J. Buschmann, M. Visentin, R. Graf, S. Sonda*



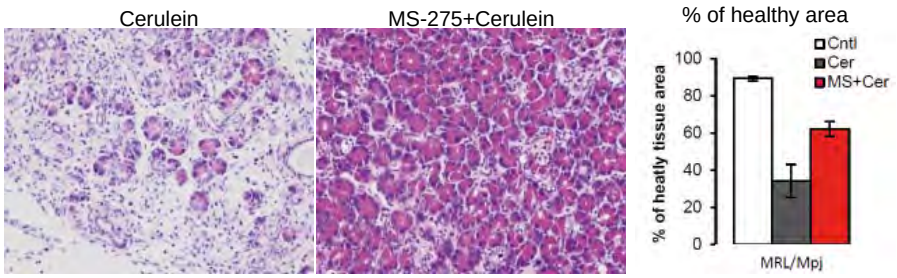

Pancreatic ductal adenocarcinoma (PDAC), one of the most recalcitrant amongst human malignancies, is sustained by significant stromal and immune reactions and supported by neo-angiogenesis. In the management of experimental PDAC, we discovered that FDA-approved serotonin-selective reuptake inhibitors (SSRIs) unexpectedly reduce both the progression of pre-malignant lesions and the establishment of tumor micro-environment. Therefore, SSRI, in combination with chemotherapy, may constitute a novel approach to counteract PDAC progression.

*SSRI-treatment reduces pre-malignant lesion formation, stromal reaction and vessels diameter*

## Ms275, a class I HDAC inhibitor, ameliorates the outcome of pancreatitis

*M. Bombardo Ayats, E. Saponara, E. Malagola, R. Graf and S. Sonda*

This study investigates whether the activity of histone deacetylases (HDACs) contributes to the development of pancreatitis and whether its inhibition could constitute a novel treatment for this severe disease. We found that class I HDACs are activated in the pancreas following induction of acute and chronic pancreatitis. *In vivo* treatment with MS-275, a selective class I HDAC inhibitor, reduced pancreatic inflammation, formation of acinar-to ductal metaplasia and development of fibrosis.

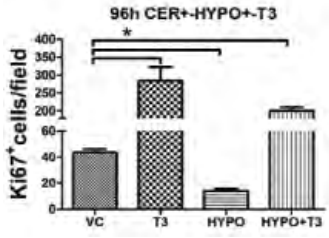


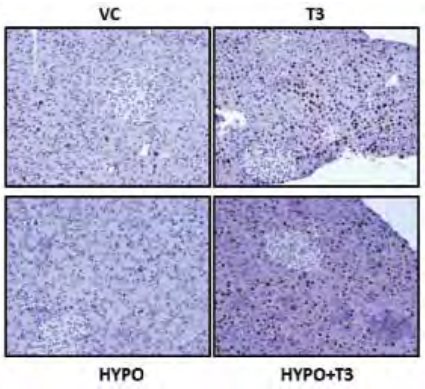

*Inhibition of class I HDAC with MS-275 reduces pancreatic damage following acute pancreatitis.*

## Thyroid hormone T3 is required for acinar cell proliferation following cerulein induced acute pancreatitis

*E. Malagola, M. Bombardo Ayats, E. Saponara, R. Graf and S. Sonda*

In the present study we asked whether acinar cell proliferation following acute pancreatitis is dependent on T3 action, which is considered the active form of thyroid hormones (TH). We observed that endogenous TH pathway is activated following acute pancreatitis and drives acinar cell proliferation. Moreover we found that T3 driven acinar cell proliferation is dependent on Akt and HDAC action. All together our data define an important role of TH in pancreas homeostasis and regeneration.



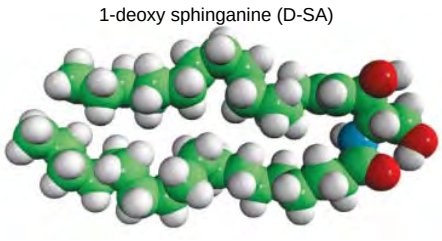



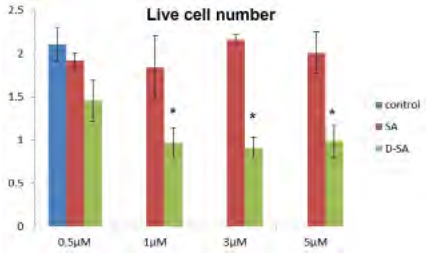

*Pharmacological hypothyroidism (HYPO) reduces acinar cell proliferation following cerulein treatment whereas T3 supplementation (HYPO+T3) rescues this phenotype without increasing damage or inflammation.*

## 1-Deoxy-sphingolipids, novel biomarkers of diabetes, are cytotoxic for exocrine pancreatic cells

*R. Chen, T. Hornemann, E. Saponara, R. Graf and S. Sonda*

Diabetes is frequently associated with exocrine dysfunctions and increased risk to develop pancreatitis. Diabetes is characterized by plasma elevation of 1-deoxy-sphingolipids, atypical sphingolipids that do not undergo the canonical degradation pathway and accumulate intracellularly. Here we show that 1-deoxy-sphingolipids directly damage acinar cells, suggesting a role for these lipids in the exocrine dysfunctions observed following diabetes.



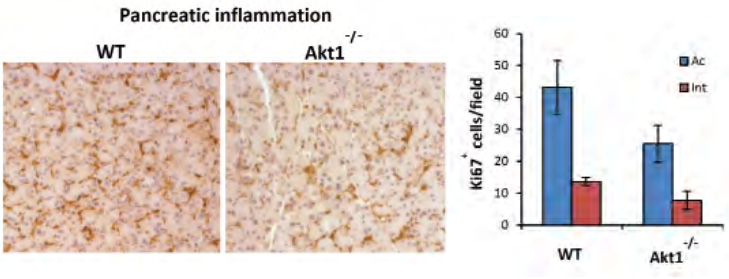




*Treatment with the 1-deoxy-sphingolipid 1-deoxysohinganine reduces the proliferation of acinar cells.*

## Akt1 regulates the development of inflammation and tissue regeneration during acute pancreatitis

*R. Chen, M. Dietrich, E. Malagola, E. Saponara, O. Tschopp, R. Graf and S. Sonda*

The serine/threonine kinase Akt/PKB, which plays a key role in the conserved phosphoinositide 3-kinase signaling pathway, exists in three isoforms (Akt1, Akt2, and Akt3) with non-redundant physiological functions. In this study we investigated whether Akt1 plays a critical role during the development of acute pancreatitis by using Akt1$^{-/-}$ mice. Akt1 signaling does not mediate the initial acinar cell damage observed at the onset of AP. We found that Akt1 signaling does not mediate the initial acinar cell damage but promotes both the inflammatory response and the regeneration of the pancreatic tissue. *(Figure see next page).*




*Lack of Akt1 reduces leukocyte infiltration and acinar cell proliferation following induction of pancreatitis.*

**Collaborations/Sponsors:**
- Prof. Dr. Mathias Heikenwälder, PhD, (TUM Munich)
- Prof. Dr. Adrian Hehl, MD, (University of Zurich)
- Prof. Dr. Achim Weber, MD, (University Hospital Zurich)
- Prof. Aurel Perren (Universität Bern)
- Prof. Arnold von Eckardstein (University Hospital Zurich)
- Prof. Thorsten Hornemann (University Hospital Zurich)

## 2.2.4 Bariatric Surgery

### The role of sphingolipids in the pathophysiology of obesity affecting the outcome after bariatric surgery

*M. Bueter, D. Raptis, T. Hornemann*

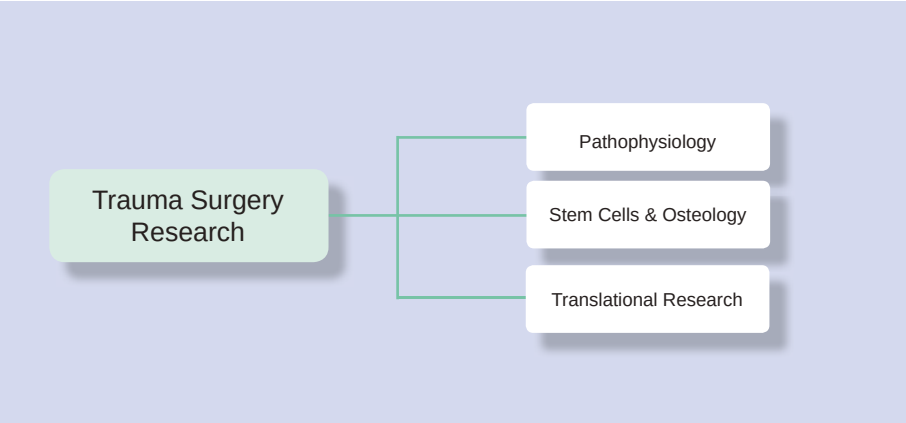
In a prospective pilot study at the Department of Surgery at the University Hospital Zurich (USZ) we compared sphingolipid (SL) levels in the plasma and metabolic outcome of obese subjects after Roux-en-Y Gastric Bypass (RYGB) and diet and lifestyle intervention. Anthropometric measurements (height, weight, Body Mass Index (BMI)) as well blood samples were collected before and 12 months after the intervention. It was found that patients in both groups were able to significantly reduce their BMI at 12 months after the intervention ($p<0.001$). However, the level of BMI reduction was less distinctive in the diet group. In the RYGB group, liver biopsies showed reduced steatosis and inflammation, reduced liver cell injury, improved fibrosis and significantly improved levels of the NAS Score. Interestingly, all findings were associated with significantly lower plasma levels of SL 12 months after RYGB surgery when compared to preoperative levels. In contrast, patients after diet and lifestyle treatment did neither show significantly reduced SL levels nor significant improvement of steatosis in their liver biopsies. Table 1 summarizes the results of our pilot study.

| **THERAPY** | **RYGB Surgery** | | | **Diet & Lifestyle** | | |
|---|---|---|---|---|---|---|
| **VARIABLE** | Baseline | 12 Mo FU | p-value | Baseline | 12 Mo FU | p-value |
| **Anthropometric data** | | | | | | |
| Body Mass Index (BMI) | 41.5 ± 0.9 | 29.4 ± 0.6 | **<0.001** | 36.8 ± 1.3 | 33.8 ± 1.3 | **<0.001** |
| **Sphingolipids** | | | | | | |
| C18-sphingosine | 87.8 ± 3.4 | 74.4 ± 2.8 | **<0.001** | 78.2 ± 3.1 | 75.9 ± 2.7 | 0.36 |
| C18-sphinganine | 3.62 ± 0.26 | 2.57 ± 0.16 | **<0.001** | 3.2 ± 0.2 | 2.8 ± 0.3 | 0.15 |
| 1-deoxy-sphingosine | 0.11 ± 0.01 | 0.08 ± 0.01 | **0.002** | 0.10 ± 0.01 | 0.09 ± 0.01 | 0.28 |
| 1-deoxy-sphinanine | 0.08 ± 0.01 | 0.05 ± 0.01 | **<0.001** | 0.06 ± 0.01 | 0.05 ± 0.01 | **0.02** |
| **Liver biopsy** | | | | | | |
| Steatosis grade | 1.4 ± 0.2 | 0.0 ± 0.0 | **<0.001** | 1.4 ± 0.3 | 1.1 ± 0.2 | 0.06 |
| Lobular inflammation | 1.1 ± 0.2 | 0.06 ± 0.1 | **<0.001** | 1.0 ± 0.2 | 0.7 ± 0.2 | 0.06 |
| Liver cell injury, Ballooning | 0.97 ± 0.13 | 0.17 ± 0.09 | **<0.001** | 1.0 ± 0.2 | 0.9 ±0.2 | 0.77 |
| Fibrosis stage | 1.00 ± 0.18 | 0.44 ± 0.17 | **0.013** | 0.68 ± 0.21 | 0.56 ± 0.23 | 0.50 |
| NAS score | 3.50 ± 0.39 | 0.23 ± 0.12 | **<0.001** | 3.77 ± 0.57 | 3.29 ± 0.55 | 0.10 |

*Table 1: Anthropometric data, biochemistry, sphingolipid levels, hepatic ultrasound and liver biopsies from patients at baseline and 12 months after RYGB surgery (n=14) or diet (n=12). Data are shown as mean ± SEM. Data were analyzed using a 2-tailed t-test. A p-value < 0.05 was considered statistically significant. Abbreviations: FU = Follow-Up; NAS score = Nonalcoholic fatty liver disease (NAFLD) Activity Score.*

**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

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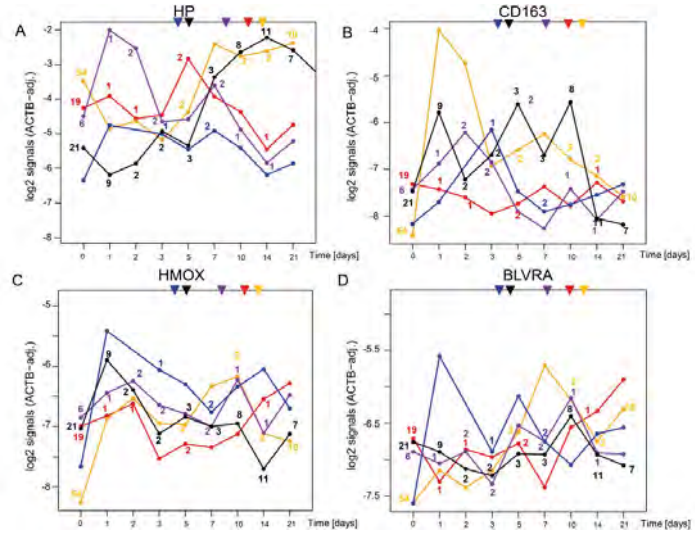
### 2.3.1 Pathophysiology

**Transcriptomic profiling in severely injured patients**

*D. Rittirsch, V. Schoenborn, S. Märsmann, E. Wanner, S. Günkel, K. Sprengel, P. Cinelli, G.A. Wanner*




*Temporal relationship of the expression of HP (A) CD163 (B), HMOX1 (C), and BLVRA (D) with the clinical course. The individual course of each patient with sepsis (n=5) of the discovery set (n=90 samples; 10 patients) are plotted as trajectories in different colors. The time points of diagnosis of sepsis are indicated by the arrows on the top of each figure. The amount of allogeneic blood transfusions (number of pRBCs) is indicated at specific time points for each patient*

Severe trauma triggers a systemic inflammatory response that contributes to secondary complications, such as nosocomial infections, sepsis or multi-organ failure. Our studies aim at the identification of mechanisms linked to complicated courses after severe trauma by a systems biology approach. We perform prospective studies by using RNA samples from circulating leukocytes from patients with multiple injuries and analyze the dynamic changes in gene expression over a period of 21 days. Transcriptome profiling is then combined with an extensive clinical data analysis in order to identify prognostic markers characteristic for systemic inflammation and sepsis. We found strongest changes between patients with either systemic inflammation or sepsis in gene expression of the heme degradation pathway. Analyses of the key components haptoglobin (HP), cluster of differentiation (CD) 163, heme oxygenase-1 (HMOX1), and biliverdin reductase A (BLVRA) showed robust changes following trauma. Upregulation of HP was associated with the severity of systemic inflammation and the development of sepsis. Patients who received allogeneic blood transfusions had a higher incidence of nosocomial infections and sepsis, and the amount of blood

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transfusion as source of free heme correlated with the expression pattern of HP. These findings indicate that the heme degradation pathway is associated with increased susceptibility to septic complications after trauma, which is indicated by HP expression in particular.

## 2.3.2 Stem Cells & Osteology

### Direct transplantation of native pericytes from adipose tissue for stimulating healing in critical size bone defects

*M. König, D. Canepa, E. Casanova Zimmermann, U. Graf, G. Wanner and P. Cinelli*

Fractures with a critical size bone defect (e.g., open fracture with segmental bone loss) are associated with high rates of delayed union and non-union. The prevention and treatment of these complications remain a serious issue in trauma and orthopaedic surgery. Autologous cancellous bone grafting is a well-established and widely used technique. However, it has drawbacks related to availability, increased morbidity and insufficient efficacy. Mesenchymal stromal cells can potentially be used to improve fracture healing. In particular, human fat tissue has been identified as a good source of multilineage adipose-derived stem cells, which can be differentiated into osteoblasts. The main issue is that mesenchymal stromal cells are a heterogeneous population of progenitors and lineage-committed cells with different potential to differentiate. In the present study, we aimed to test the possibility to enrich defined subpopulations of stem/progenitor cells for direct therapeutic application without requiring an *in vitro* expansion. We enriched a CD146+NG2+CD45– population of pericytes from freshly isolated stromal vascular fraction from mouse fat tissue and tested their osteogenic differentiation capacity *in vitro* and *in vivo* in a mouse model for critical size bone injury.

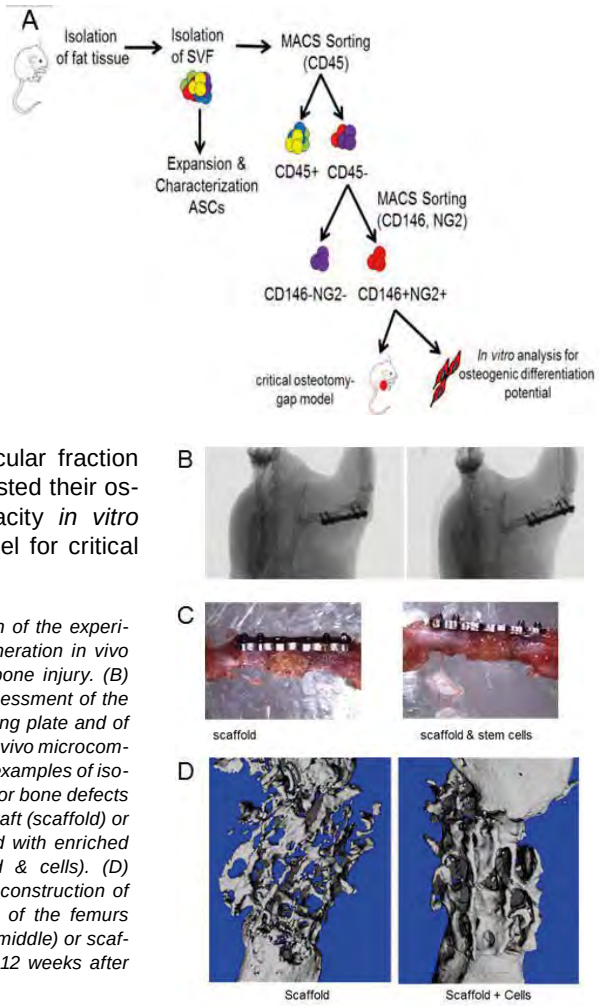


*Figure: (A) Schematic representation of the experiments performed. (B-D) Bone regeneration in vivo in a mouse model for critical size bone injury. (B) Representative examples for the assessment of the correct positioning of the micro-locking plate and of the scaffold 2 days after surgery by in vivo microcomputed tomography. (C) Macroscopic examples of isolated femurs 12 weeks after surgery for bone defects either filled with a cancellous bone graft (scaffold) or with a cancellous bone graft seeded with enriched CD146+NG2+CD45– cells (scaffold & cells). (D) Representative three dimensional reconstruction of microcomputed tomography images of the femurs with gap alone (left), scaffold alone (middle) or scaffold and CD146+NG2+CD45– cells 12 weeks after surgery (right).*

Our results confirm the ability of enriched CD146+NG2+CD45– cells to efficiently generate osteoblasts *in vitro*, to colonize cancellous bone scaffolds and to successfully contribute to regeneration of large bone defects *in vivo*. This study represents proof of principle for the direct use of enriched populations of cells with stem/progenitor identity for therapeutic applications.

## 2.3.3 Translational Research

**Balance of lactate and haptoglobin profiles is predictive for rhabdomyolysis and outcome in trauma patients**
*D. Rittirsch, V. Schoenborn, S. Märsmann, E. Wanner, S. Günkel, K. Sprengel, P. Cinelli, G. Wanner*

Rhabdomyolysis is a frequently observed syndrome in trauma patients caused by breakdown products of damaged muscle cells and contributes to organ failure and high mortality. It is diagnosed by creatine kinase (CK) levels and related components, such as myoglobin, are harmful to the organs if released into the bloodstream. Our results show that myoglobin predicts in over 90% of cases CK levels one day ahead, which in turn is dependent on lactate, its dehydrogenases and haptoglobin. If reciprocal lactate and haptoglobin levels and trajectories are associated to complicated outcome the decay and turnover in system biology models of dynamic show dependencies both on lactate and lactate dehydrogenase levels to haptoglobin. Sequential modelling therefore reveals that lactate deterministically predicts early myoglobin and CK levels and rhabdomyolysis in trauma. Our data suggest that stability analysis and unbalanced haptoglobin-lactate-dynamics can be useful for distinguishing prolonged and complicated outcome in trauma patients.

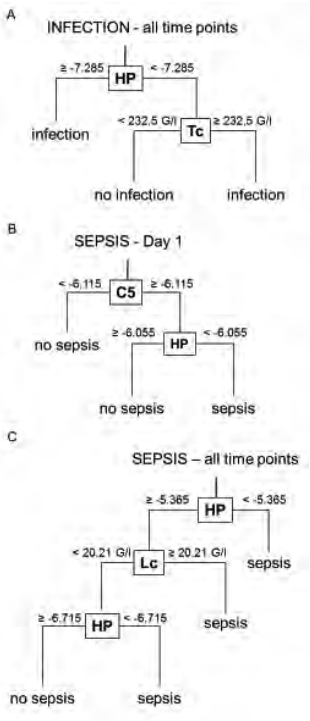


*Figure: Integrated use of clinical and transcriptomic markers assessed by decision tree cross-validation (10-fold cross-validation; decision trees/candidates were selected upon high specificity). a Decision tree for the incidence of nosocomial infections after trauma under consideration of all time points of the observation period (n = 413 samples). b Assessment of the risk for the development of sepsis during the further course using samples from day 1 after trauma (n = 77 samples). c Decision tree for sepsis under inclusion of all time points of the observation period (n = 502 samples). Threshold levels (ΔCt of gene expression or leukocyte/thrombocyte counts) for the decision of which path is taken are provided in the figures at the corresponding levels. C5 complement component C5, HP haptoglobin, Lc leukocytes, Tc thrombocytes.*

**Collaborations/Sponsors:**
- Clinical Trials Center, University Hospital Zurich
- Orthopedic Research Laboratory, Biomechanics, University Hospital Balgrist, Zurich
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## 2.4 Plastic, Hand & Reconstructive Surgery Research

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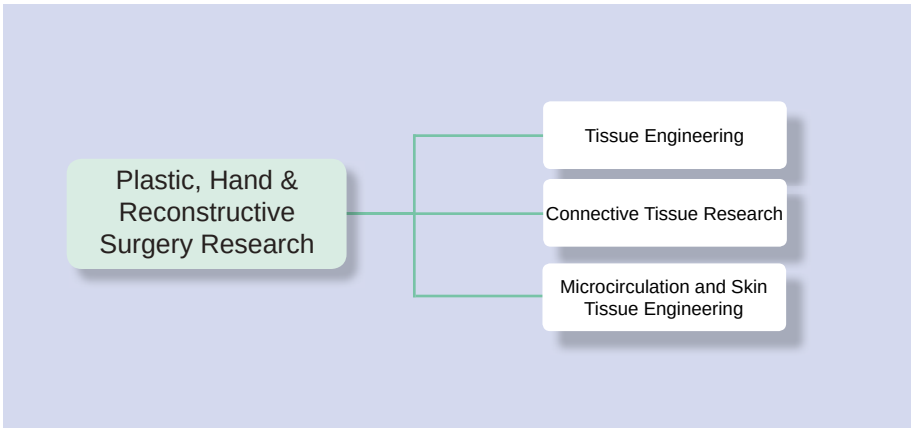



### 2.4.1 Tissue Engineering

**SPIO-enhanced MRI as a nondestructive *in vivo* method to assess vascularization of a 3D matricel collagen scaffold planted on the chorioallantoic membrane of the chick embryo *in ovo***

*C. F. Waschkies, F. Kivrak Pfiffner, M. Calcagni, P. Giovanoli, M. Rudin, J. Buschmann*

Perfusion capacities in biomaterials placed on the chick chorioallantoic membrane can be assessed by non-destructive *in vivo* magnetic resonance imaging (MRI) as has been recently reported (Kivrak Pfiffner, Waschkies et al. 2014). Changes in the longitudinal (T1) relaxation rates before and after injection of Gd-DOTA (Dotarem®, Guerbet S.A.) were measured. The local contrast agent concentration was dependent on perfusion, vascular permeability and extravascular compartment size. In this study intravascular super paramagnetic iron oxid (SPIO) particles of 30-40 nm (M) size (Viscover™, Miltenyi Biotec, Germany) were explored. Such particles stay in the vasculature to deliver a more direct measure of vascularization.

As a result, no signal change was observed within the egg yolk, consistent with the SPIO remaining in the vasculature. Consequently, T1 positive signal enhancement (reduction in T1) and T2 negative contrast (reduction in T2) were observed only in the vasculature and hence were restricted mainly to the surface of the CAM (**Figure 1**, arrowheads). Effect upon T2 was stronger than in T1. Interestingly, no change in contrast was observed inside the scaffold, which might relate to our observation that the slightly viscous contrast agent did not distribute easily but rather slowly within the finer segments of the vasculature. Consistent with this notion was the observation that T1 as well as T2 reduction was more prominently seen at 140 min than 8 min after i.v. injection of the SPIO.

**Coaxial electrospun Degrapol® meshes for sustained protein delivery**

*O. Evrova, M. Bamert, C. Scalera, M. Calcagni, P. Giovanoli, V Vogel, J. Buschmann*

In an attempt to improve tendon healing, a protein delivery device was developed. The DegraPol® tube was electrospun and set around a conventionally sutured tendon which did not show any adverse reaction. Electrospinning allows incorporation of proteins into the fibers via various techniques. One of these is to fabricate hollow fibers having the proteins in the core of the fibers. Therefore, coaxially electrospun DegraPol® meshes (**Figure 2**) were produced under different fabrication conditions.

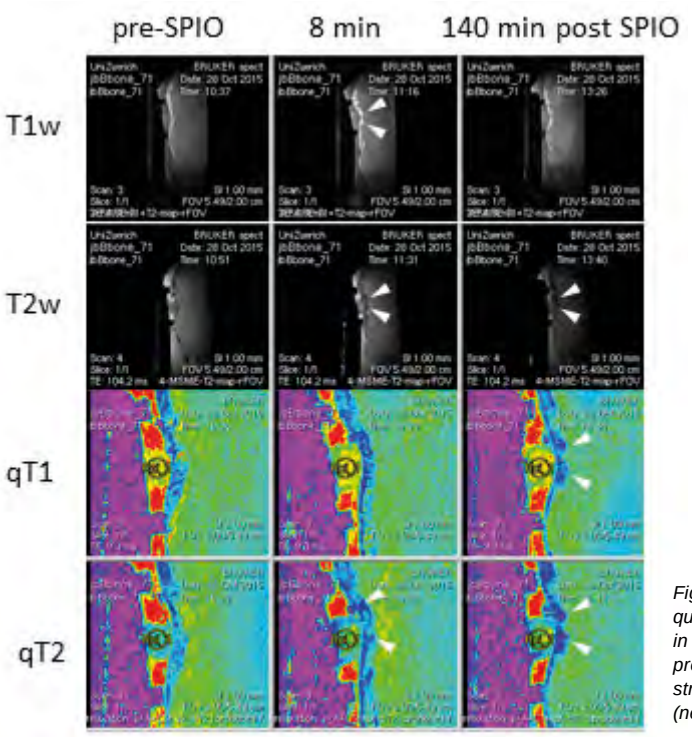



*Figure 1: In ovo T1- and T2-weighted MRI images and corresponding T1 and T2 quantitative maps acquired in a sagittal slice through the Matricel collagen scaffold in sample 2, shown zoomed into the plastic ring containing the scaffold. Left to right: pre, 8 min and 2h 20 min after i.v. injection of SPIOs. Arrowheads denote vessel structures on the CAM, which show contrast enhancement in T1 (positive) and T2 (negative) weighted images.*

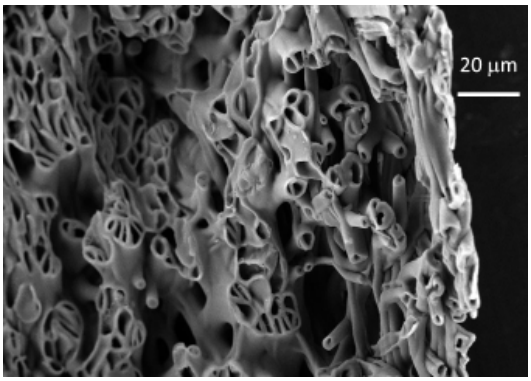



*Figure 2 Scanning electron microscopy image of a coaxially electrospun DegraPol® mesh. Note the empty core of the fibers. There, proteins can get incorporated allowing a sustained release and delivery to wound sites.*

## 2.4.2 Connective Tissue Research

*O. Evrova, C. Scalera, M. Calcagni, P. Giovanoli, V. Vogel, J. Buschmann*

### Emulsion electrospun meshes delivering PDGF-BB in a sustained controlled manner for tendon rupture repair: an *in vivo* rabbit achilles tendon model

Tendon rupture repairs suffer from fibrous healing where the scar tissue lacks the normal characteristics of healthy tendon tissue. The biomechanical properties of repaired tendons are therefore often of minor qualities, which may in the worst case lead to re-ruptures. Consequently, biological therapy in addition to conventional suturing is one option to improve tendon healing.

We developed an emulsion electrospun DegraPol® tube that is biocompatible, biodegradable and very elastic, enabling the surgeon an easy handling during implantation. This tube was loaded with PDGF-BB in order to promote tendon healing.

Biomechanical analysis three weeks post-operation revealed the beneficial effects of this growth factor: ultimate tensile load and ultimate tensile stress were significantly higher than for specimen without PDGF-BB.

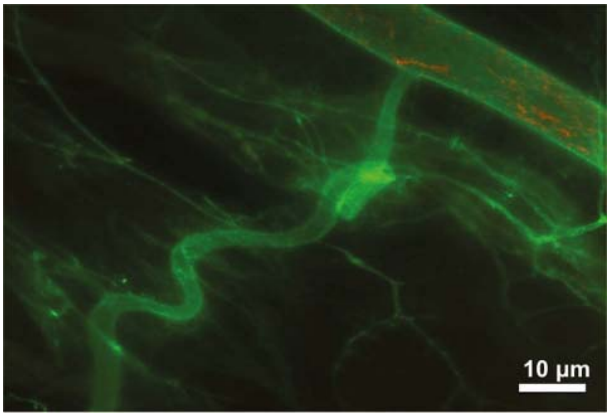
**Collaborations:**

- Prof. V. Vogel, ETH Zürich
- *ab medica*, Italy

## 2.4.3 Microcirculation and Skin Tissue Engineering

*N. Lindenblatt, N. Sanchez-Macedo, M. McLuckie, P. Giovanoli*

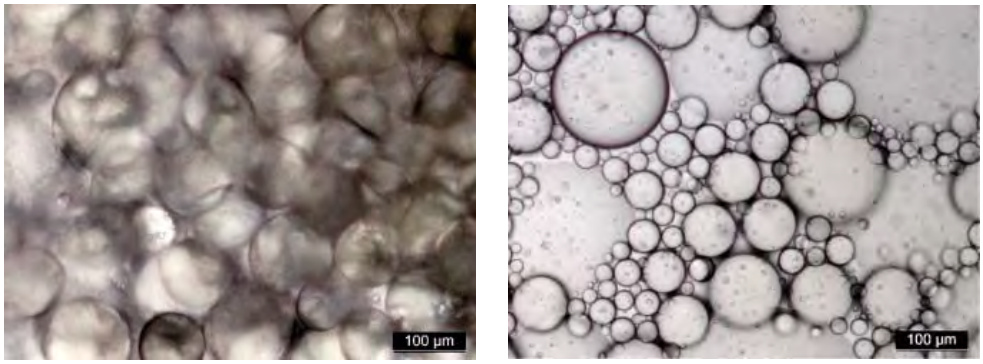
### New vascularization strategies for skin regeneration




A major challenge for both plastic surgeons and skin tissue engineers today is the limited survival of full thickness skin grafts (FTSGs) and full thickness skin substitutes (FTSSs). The grafts and substitutes often become necrotic as they undergo hypoxia due to failing to acquire a sufficient blood supply. To overcome this, we are taking a deeper look at active components of angiogenesis and tissue transplantation.

*Figure: LIVE/DEAD® assay of ex vivo tissue perfusion showing viable (green) vasculature, and nonliving components (red).*

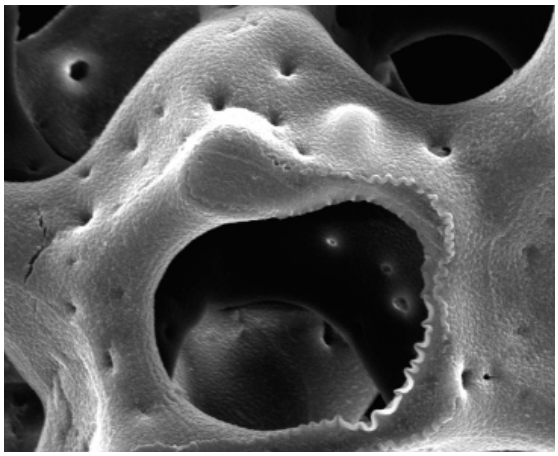
### Evaluation of scar reduction and the regenerative capacity of lipoaspirates, microfat, and *nanofat* in both clinical and research settings




Adipose tissue grafting has been used in clinical procedures for the past decade for aesthetic reconstructive purposes such as body contouring and soft tissue reconstruction. As of recently, nanofat has been utilized for scar and wrinkle reduction and therefore provides the potential to be used therapeutically in a number of regenerative applications.

*Figure: Microscopic comparison of lipoaspirates (left) and nanofat (right). Adipocytes and connective tissue are visible in lipoaspirates. Production of nanofat yields lipid droplets with no identifiable remaining cell bodies.*

### 3D porous polyurethane discs as a rapid vascularization strategy



It has been demonstrated that skin defects may benefit from a 3D structure, such as porous polyurethane (PU), by providing essential architecture to allow cells to quickly grow into.
With the addition of growth factors, the PU disc itself becomes even more attractive for cellular ingrowth as neovasculature is easily guided through the 150µm pores, therefore providing rapid access to oxygen and nutrients.

*Figure: SEM showing the interconnected polyurethane disc pores (150µm diameter), which provide a favorable environment for both cells and vasculature to grow into. Photo courtesy of Anel Oosthuysen in the South African team.*

## Structured bacterial cellulose for cell guidance in wound healing

Previously, structured surfaces have been shown to have an effect on cell guidance, migration, and even stem cell differentiation in *in vitro* studies. The use of surface-structured bacterial cellulose (BC) substrates as wound dressings or implants has displayed high durability and low inflammatory response in small animals, therefore demonstrating beneficial effects as a biomaterial.

Ongoing *in vivo* studies are aimed at defining the particular advantages that various shaped structures may have in translational medicine including reduction of tissue fibrosis and skin tissue regeneration.

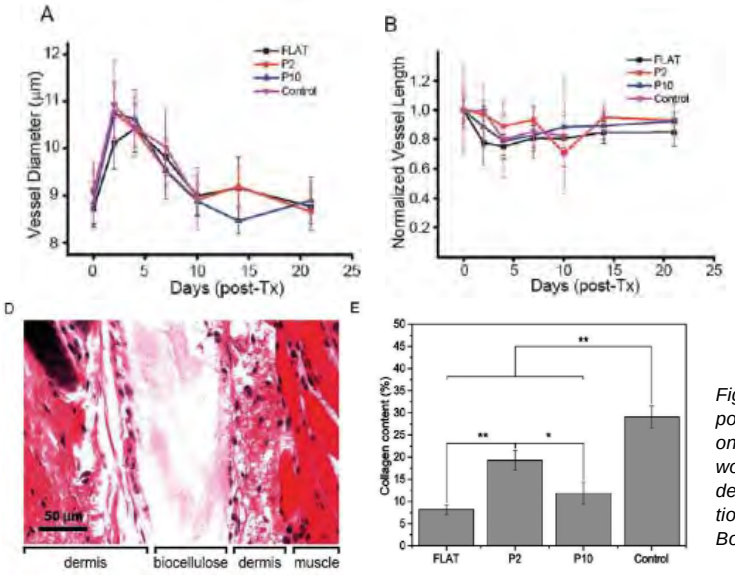



*Figure: Bacterial cellulose transplant in the dorsal skinfold chamber and dermal pocket (D) of mice to assess the effects of various sized structures and their effect on healing. Intravital microscopy (A, B) revealed a small angiogenic response to wound healing, followed by a characteristic inflammatory response (C). Collagen density (E) revealed that the P2 structures favorably influenced collagen production in comparison to unstructured (flat) or large structures (P10). (ASC Nano, Bottan, et al., 2014).*

## *In vivo* characterization of the integration and vascularization of a silk-derived urgical scaffold

I Acellular dermal matrices (ADMs) are frequently used in soft tissue replacement during breast reconstruction procedures, where they contribute to implant coverage and restoration of breast aesthetics. SERI® Surgical Scaffold is a synthetic, off-the-shelf, single use, silkderived fibroin multifilament scaffold that is frequently used in plastic and reconstructive surgery. Investigation of SERI® in *in vivo* studies showed that the scaffold itself attracts neovascular ingrowth and undergoes characteristic infiltration of inflammatory cells followed by successful wound closure.

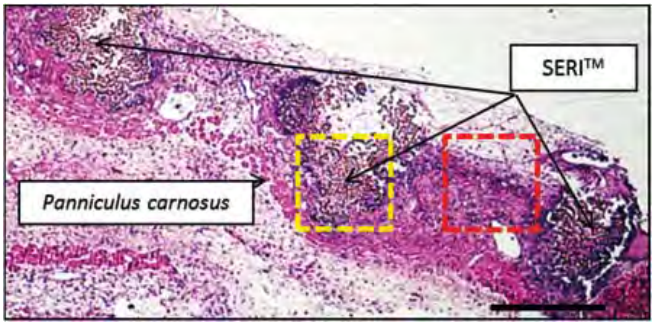



*Figure: H&E histology staining of cellular ingrowth and the integration of SERI® in the modified dorsal skinfold chamber with cellular ingrowth. (Kijanska et al. 2016)*

**Collaborations/Sponsors:**

- Dr. Aldo Ferrari, PhD, Dr. Simone Bottan, PhD. Laboratory of Thermodynamics in Emerging Technologies. ETH Zurich
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- Prof. Dr. Brigitte Vollmar, MD, Institute for Experimental Surgery, University of Rostock, Germany
- Prof. Dr. Martin Glocker, MD, Proteome Center, University of Rostock, Germany
- Prof. Dr. Michael D. Menger, MD, Institute for Clinical and Experimental Surgery, University of Saarland, Germany

# 2.5 Thoracic Surgery Research

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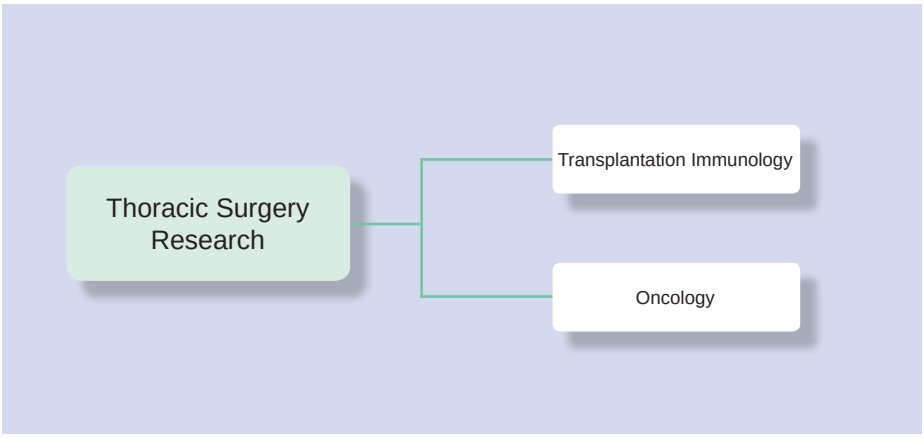
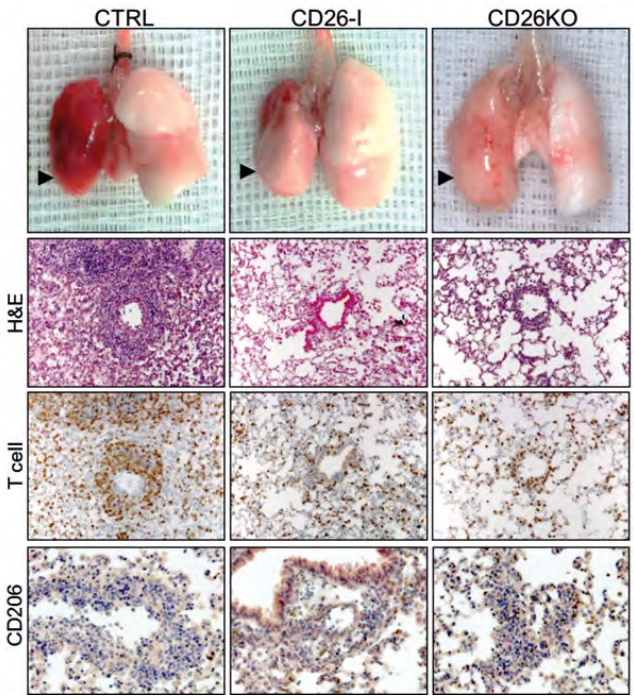



## 2.5.1 Transplantation Immunology

**CD26 co-stimulatory blockade improves lung allograft rejection and is associated with enhanced interleukin-10 expression**

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

The aim of the study is to target CD26 co-stimulatory activity for the attenuation of the allo-reactive Th-17 cell response during acute rejection after mouse lung transplantation. Lung transplantation between BALB/c (donor) and C57BL/6 (recipient) mice was performed including controls, CD26-inhibited (CD26-I, daily administration of Vildagliptin, 10 mg/kg sc.), and CD26 KO mice (CD26KO). Then, CD26-I treated and CD-26KO mice showed significantly preserved macroscopic and histological characteristics ($p<0.01$), a higher PaO2/FiO2 ratio ($p\leq0.05$), less IL-17+ cells, more levels of IL-10, less infiltrating CD3+-T cells ($p<0.01$), but more CD206+ alternately activated M2 macrophages ($p<0.01$), compared to control. We concluded that CD26 co-stimulatory blockade promotes lung allograft acceptance via reduced T cell infiltration, less expression of IL-17 and increased expression of IL-10, likely to be derived from alternatively activated macrophages.




*Legend: the control group (CTRL) shows robust acute rejection of allograft (arrow) in macroscopic appearance, stronger cell infiltrations in peribronchial areas in H&E staining, and more CD3+ T cells and less CD206+ M2 macrophages in immunohistochemistry, compared to CD26/DPPIV-inhibited mice (CD26-I) and CD26 knock-out mice (CD26KO).*

## Inhibition of tumor growth by CD26/DPP4 inhibitor

*J.-H. Jang, F. Janker, Y. Yamada, W. Weder, W. Jungraithmayr*

The transmembrane molecule CD26/DPP4 has been associated with various malignancies including breast cancer, lymphoma, and colorectal cancer. Recently, we found an anti-tumor effect by treatment with the CD26/DPP4 inhibitor Vildagliptin in colorectal cancer lung metastasis models in mice.

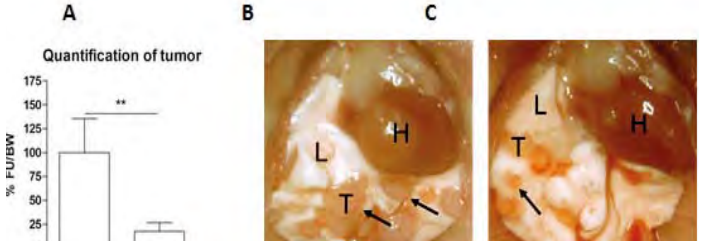



*Fig: Quantification of mouse colorectal cancer cell line (MC38) growth three weeks after injecting into the vena cava, detected by GFP-labeling. Vildagliptin was given in drinking water (50mg/kg day). Vildagliptin reduced significantly the metastatic tumor growth (A). Representative images show a reduced tumor growth by Vildagliptin (C) compared to control (B). FU: fluorescent unit; BW: body weight; H: heart; L: lung; T: tumor.*

The formation of metastasis and growth of metastases were significantly inhibited by Vildagliptin treatment through modulating both the epithelial-mesenchymal transition (EMT) pathway and autophagy mechanism which resulted in increased apoptotic death.

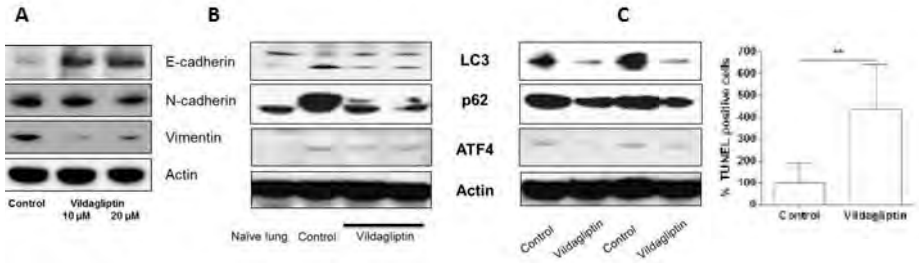



*Fig.: Anti-tumor effect of CD26/DPP4 inhibitor, Vildagliptin, in colorectal cancer lung metastasis model in mouse. EMT markers were significantly modulated by Vildagliptin in vitro (A). Imbalance between autophagy and apoptosis by Vildagliptin treatment in tumor in vivo. The autophagy markers LC3, p62, and ATF4 were significantly decreased in the tumors of lungs and subcutaneous tumors also (B). Apoptotic cell death (TUNEL) was induced by Vildagliptin treatment in tumor (C).*

In our ongoing research, we found that the treatment with the CD26/DPP4 inhibitor treatment had also an effect on primary lung cancer growth through means of enhanced macrophages but also by recruiting and activating NK cells into the tumor. Here, tumors decreased in size *in vivo* in both models, in lung tumors as well as in subcutaneously injected tumors.

Based on these data, we can conclude that the inhibition of CD26/DPP4 effectively reduces tumor in mouse models of secondary and primary lung tumors.

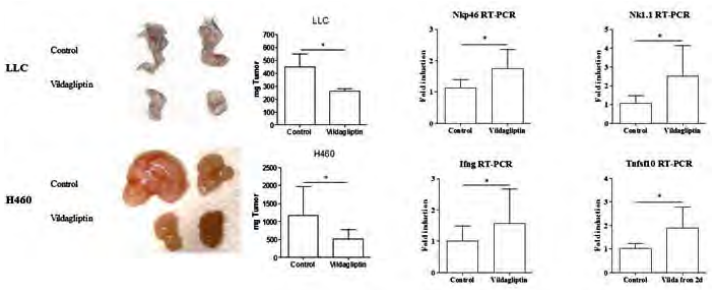



*Figure 3: Anti-tumor effect of Vildagliptin in various tumor models. Vildagliptin reduced tumor size in the subcutaneous cell line injection model (A). A human lung cancer cell line (H460) was injected onto nude mice. NK cell markers (Nkp46, Nk1.1) and cytokines produced by NK cells (IFN-g, TNF-s10) were analyzed by RT-PCR in the tumor developed by subcutaneous LLC injection (B). Vildagliptin treatment increased the tumor NK cell population.*

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Agata Okonska, PhD Student

Kathrin Oehl, PhD Student

Jelena Kresoja, PhD Student

Dr. Tugba Cosgun, Research Associate

Florian Janker, Doctoral Student

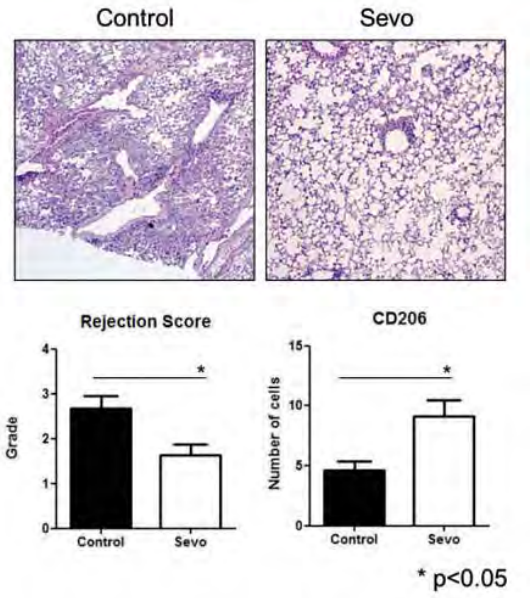
Gabriela Ziltener, Lab Technician

Priska Leisibach Doctoral Student

## The impact of preconditioning by Sevoflurane in experimental mouse lung transplantation

*Y. Yamada, I. Laube, J.-H. Jang, J. Bonvini, I. Inci, B. Beck Schimmer, W. Weder, W. Jungraithmayr*

The aim of this study is to evaluate if preconditioning by sevoflurane could potentially protect from primary graft dysfunction (PGD) or acute rejection (AR) after lung transplantation (Tx). We performed mouse lung transplantations in various combinations 18 hours after preconditioning of donor by Sevoflurane for 2 hours. Allogeneic grafts with Sevoflurane preconditioning showed attenuation of acute rejection pathology on day 3, with upregulation of anti-inflammatory macrophage (M2), and syngeneic grafts with the treatment also yielded higher levels of TNF-α and IL-6 and lower level of IL-10, compared to the non-treated control. We concluded that sevoflurane preconditioning showed protective effects on lung transplants in PGD and AR.

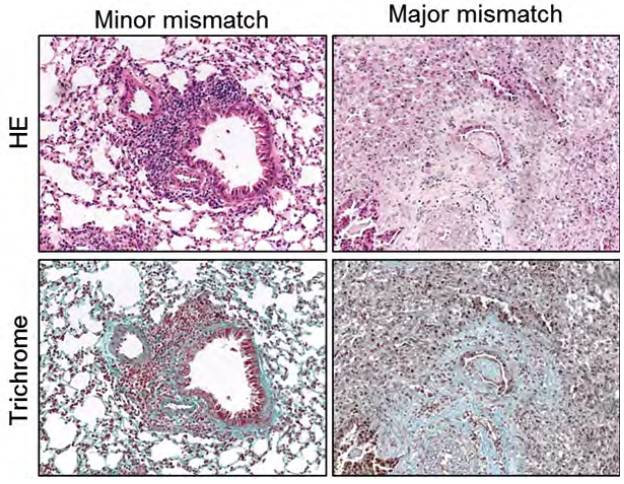



*Hematoxylin and eosin histology of lung allografts harvested on day 3 presented more lymphocytic infiltration on the control group compared to the sevoflurane preconditioned group (Sevo), and the acute rejection score in Sevo was significantly lower (p<0.05). In immunohistochemistry, Sevo presented significantly more CD206+ anti-inflammatory alternative activated macrophages (p<0.05).*

## Experimental chronic lung allograft rejection – which mouse model is reliable?

*Y. Yamada, J.-H. Jang, D. Kenkel, J.-H. Jang, C. Opelz, I. Inci, A. Boss, W. Weder, W. Jungraithmayr*

The aim of this study was to investigate an appropriate experimental protocol for chronic rejection after mouse lung transplantation. We performed single mouse lung transplantation in various protocols. Chronic rejection lesions were most prominently induced in the MHC major mismatch combination with suboptimal dose of immunosuppressant on the 8th week, compared to the minor mismatch combination. We concluded that this protocol is the most reliable CR model.




*Allografts of the MHC major mismatch combination yielded more eminent pathological findings of chronic rejection compared to the minor mismatch combination, such as peribronchial fibrotic change and intra luminal fibrotic polyposis.*

**Collaborations:**

- Institut klinische Biochemie der Universität Antwerpen, Belgien
- Diagnostische Radiologie des USZ Zürich, CH
- Eidgenössische Technische Hochschule (ETH) Zürich, CH
- Klinik für Pneumologie, Universität Leuven, Belgien
- Institute of Physiology, Perelman University Pennsylvania, Philadelphia, USA
- Institut für Molekularbiologie, Universitätsspital Zürich, Universität Zürich, CH
- Klinik für Immunologie, Universitätsspital Zürich, CH
- Centre Hospitalier, Department of Thoracic Surgery, Strasbourg, France (Gilbert Massard)

## *Ex vivo* administration of trimetazidine improves post-transplant lung function in a pig model

*T. Cosgun, I. Iskender, Y. Yamada, S. Arni, M. Lipiski, K. van Tilburg, W. Weder, I. Inci*

*Ex vivo* lung perfusion (EVLP) is an establish method to reassess marginal donor lungs. It is also a platform to deliver therapeutics outside the body. Previously we have shown the beneficial effects of trimetazidine (TMZ) on ischemia reperfusion injury in a rat model. This study evaluated the effect of *ex vivo* delivered TMZ in a pig lung transplant model.

Pig lungs were retrieved and stored 24h at 4°C followed by 4h of EVLP according to the Toronto protocol on randomly allocated two groups (n=5,each): control (CON) and treatment (TMZ). TMZ (5mg/kg) was added in the prime solution prior to EVLP. Left lungs were then transplanted and recipients were observed for 4h. Lung function and mechanics were recorded hourly throughout reperfusion. At the end of 4h of reperfusion, the right pulmonary artery was occluded for 5 minutes to assess isolated allograft function. Bronchoalveolar lavage (BAL) and tissue samples were harvested for biochemical assessments.

TMZ group showed a significantly better oxygenation throughout the 4-h reperfusion period (p=0.04) and after isolation of the allograft (p=0.04). During EVLP, TMZ group showed a trend toward higher oxygenation (p=0.06). Dynamic compliance and pulmonary vascular resistance were comparable between the two groups during EVLP. Tissue thiobarbituric acid level, myeloperoxidase activity and total protein concentration in BAL were significantly lower in the TMZ group at the end of EVLP. Detailed EVLP and transplantation findings are shown in Table 1.

*Ex vivo* administration of TMZ improved pulmonary gas exchange after reperfusion. Protective effect of TMZ was attributed to inhibition of lipid peroxidation and neutrophil infiltration during EVLP. Further studies are warranted to elucidate mechanisms of the beneficial effect of TMZ in this setting.

| | CON Group (5) | TMZ Group (5) | p-value |
|---|---|---|---|
| **Donor parameters** | | | |
| Weight (kg) | 31.4±2.6 | 30.8±1.3 | 0.6 |
| Baseline PaO2 (kPa) | 64.7±27.7 | 66.3±6.6 | 0.4 |
| | | | |
| **Recipient parameters** | | | |
| PaO2* (kPa) | 34.7±24 | 72.5±4.5 | 0.04 |
| TBARS (nmol/mg) | 0.5±0.2 | 0.5±0.2 | 0.9 |
| MPO (mU/mg) | 0.3±0.1 | 0.2±0.2 | 0.3 |
| BAL protein assay (µg/ml) | 4030±2498 | 2075±977 | 0.2 |
| ATP level (µmol/ml) | 0.4±0.2 | 0.6±0.1 | 0.3 |

*Table 1: EVLP: Ex Vivo Lung Perfusion, TBARS: Thiobarbituric Acid Reactive Substances, MPO: Myeloperoxidase activity, BAL: Broncho alveolar lavage, *: 5 minutes after occlusion of the right pulmonary artery, kPa: kilo Pascal. All values presented as mean±SD*

## Cytokine filtration modulates pulmonary metabolism and edema formation during *ex vivo* lung perfusion

*I. Iskender, T. Cosgun, S. Arni, M. Trinkwitz, S. Fehlings, N. Cesarovic, T. Frauenfelder, W. Weder, I. Inci*

*Ex vivo* lung perfusion (EVLP) improved the algorithm in donor lung management. Cytokine accumulation has been shown in both the clinical and experimental EVLP settings, which may be harmful for pneumocytes especially during extended EVLP. Our objective was to test the safety and efficacy of continuous cytokine filtration during prolonged EVLP in a pig model.

Donor lungs were retrieved from randomly allocated female pigs and stored for 24h at 4°C. EVLP was performed during 12h according to the Toronto protocol. In the treatment group, the perfusate was continuously filtered with an absorbent device (CytoSorb®) via a venovenous shunt after the reservoir, whereas we did not implement the additional filter in the control group (n=5/each) (Figure 1).

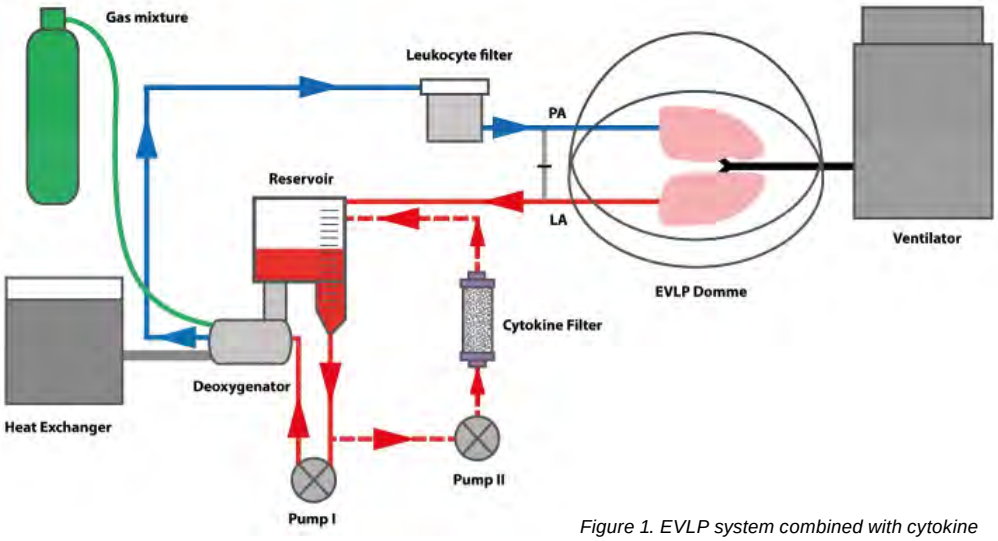



*Figure 1. EVLP system combined with cytokine*

EVLP physiology, perfusate gases and biochemistry were monitored hourly, along with lung X-ray studies at the end of perfusion. Perfusate samples were analyzed with a multiplexed cytokine assay at 1h, 3h, 6h, and 12h time points. Cytokine filtration significantly improved dynamic compliance during the 12h perfusion period (Fig 2A). In the filter group, we characterized a decrease in both glucose consumption (Fig 2B) and lactate production, along with reduced amount of hydrogen, potassium, and calcium-ions. Lung X-rays taken at the end of perfusion showed increased consolidation in the control group (Fig 2C). Interleukin (IL)-1α, IL-1β, IL-6, IL-8 (Fig 2D, shown as example), IL-10, IL-12, IL-18, and TNF-α levels were significantly reduced in the filter group.

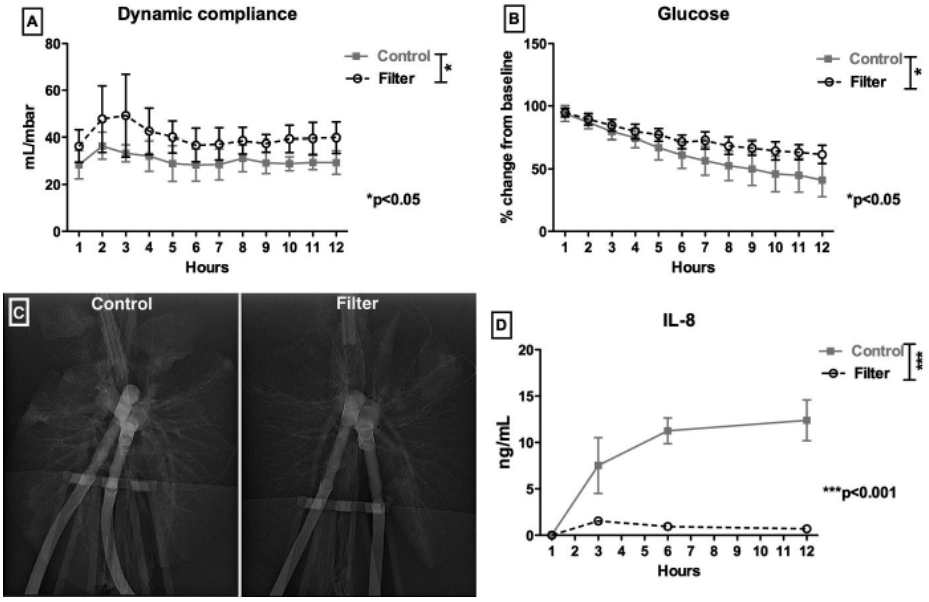



*Figure 2: Results*

Continuous perfusate filtration through sorbent beads is effective and safe during prolonged EVLP. Cytokine removal decreased the development of pulmonary edema and suppressed anaerobic glycolysis in this setting. Further studies are needed to test the beneficial effect of cytokine filtration on post-transplant lung function.

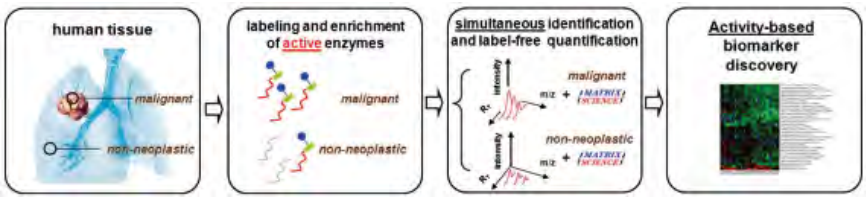
**Collaborations:**
- Dr. Shampa Chatterjee, Associate Professor, Institute for Environmental Medicine University of Pennsylvania
- Gilles Willemin, Mouse Metabolic Evaluation Facility (MEF), Center for Integrative Genomics, University of Lausanne
- Dr. Serena Di Palma, Functional Genomics Center Zurich, ETH Zurich/University of Zurich
- Dr. Keke Yu, Department of Pathology, Shanghai Chest Hospital, Shanghai, China

## 2.5.2 Oncology

### 2.5.2.1 Lung cancer

**Activity-based proteomics: biomarker identification in human lung adenocarcinoma**
*S. Arni, S. Hillinger*

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



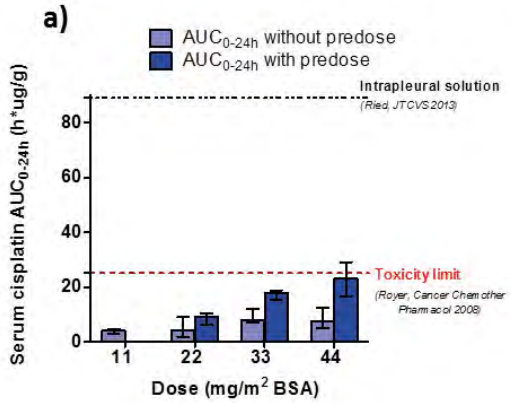

*Principle of the lung adenocarcinoma activity based biomarker discovery platform previously developed in our lab.*

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

## 2.5.2.2 Malignant pleural mesothelioma

**Localized intracavitary therapy for MPM – from bench to bedside:**
Phase I dose-escalation monocentric open trial for the evaluation of the safety of ***In***tracavitary cisplatin-***F***ibrin ***L***ocalized ***C***hemotherapy after pleurectomy/decortication or extrapleural pneumonectomy for the treatment of patients with malignant pleural ***Meso***thelioma (***INFLuenCe – Meso I***)

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




b)

**Chest wall concentrations of cisplatin at 90 min after treatment started**

| Cisplatin dose (mg/m²BSA) | Patients (n) | Tissue 90min µg/g (median and interval) | |
|---|---|---|---|
| 11 | 3 | 26.6 | (16.9 - 100.1) |
| 22 | 3 | 46.3 | (21.7 - 85.9) |
| 33 | 3 | 48.8 | (15.5 - 60.8) |
| 44 | 2* | 72.2 | (12.0 - 133.3) |

** Measurement failure of one patient sample*

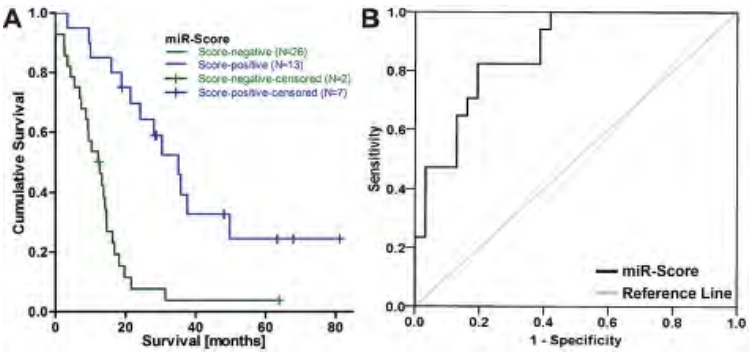
Safety and tolerability of intracavitary chemotherapy with cisplatin-fibrin were assessed in a Phase I-dose-escalation trial that enrolled 12 mesothelioma patients. Four dose levels of Cisplatin (11, 22, 33 and 44 mg/m² BSA; (n=3 per group) mixed with fibrin gel was sprayed to the chest wall and the surface of the lungs after macroscopic complete resection of tumors.
We demonstrated that the administration of intracavitary cisplatin-fibrin as high as 44mg/m² BSA is safe. We detected no dose limiting toxicity. The median serum cisplatin $AUC_{0-24}$ of all dosages are still below the suggested renal toxicity risk level, 25 h*µg/g (figure 1a), while local tissue cisplatin concentration was high above cytotoxic limit (figure 1b).

We are currently conducting a Phase II trial for the confirmation of safety and tolerability of this treatment approach (Phase II Monocentric Open Trial for the Evaluation of the Safety of Intracavitary Cisplatin-Fibrin Localized Chemotherapy after Pleurectomy/Decortication or Extrapleural Pneumonectomy for the Treatment of Patients with Malignant Pleural **Meso**thelioma (**INFLuenCe – Meso II**). In this trial, additional 20 patients will be enrolled.

Until end of 2015, 2 patients were treated.

**MicroRNAs as prognostic and predictive tumour markers assisting the selection of patients with malignant pleural mesothelioma for multimodality treatment**

*M. Kirschner, M. Meerang, M. Friess, B. Vrugt, P. Wild, N. van Zandwijk, G. Reid, W. Weder, I. Opitz*




In this project, we are investigating the prognostic value of microRNAs, i.e. the six microRNA signature miR-Score, which has been shown to be associated with survival outcomes with high prognostic accuracy (Kirschner et al, Mol Oncol 2015). In addition, associations between microRNA expression and response to standard chemotherapy regimens are also being investigated.

*(A) Kaplan-Meier analysis after stratification by miR-Score (HR for score-negative patients = 4.12, P=0.00009). (B) ROC curve analysis of the miR-Score resulted in an AUC of 0.867 (95% CI:0.76-0.96).*
*Figure adapted from Kirschner et al, Mol Oncol 2015*

## Prognostic and predictive biomarkers for malignant pleural mesothelioma

*M. Meerang, K. Bérard, M. Friess, B.K.Y. Bitanihirwe, A. Soltermann, B. Vrugt, E. Felley-Bosco, R. Bueno, W. Richards, B. Seifert, R. Stahel, W. Weder, I. Opitz*

Malignant Pleural Mesothelioma (MPM) is an aggressive and heterogeneous tumor, thus biomarkers predicting outcomes and treatment effectiveness are needed. We employed tissue microarrays as a tool to investigate prognostic significance of proteins and pathways known to be frequently altered in MPM.

In the recent study, we found that the expression of two proteins frequently altered in MPM, Merlin and Survivin, was associated with survival outcomes (figure). These results were confirmed using 2 independent cohorts of MPM patients.

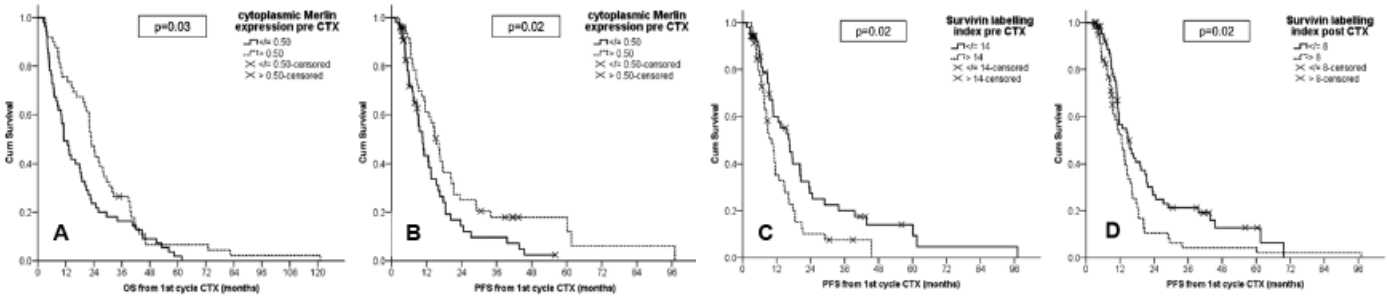
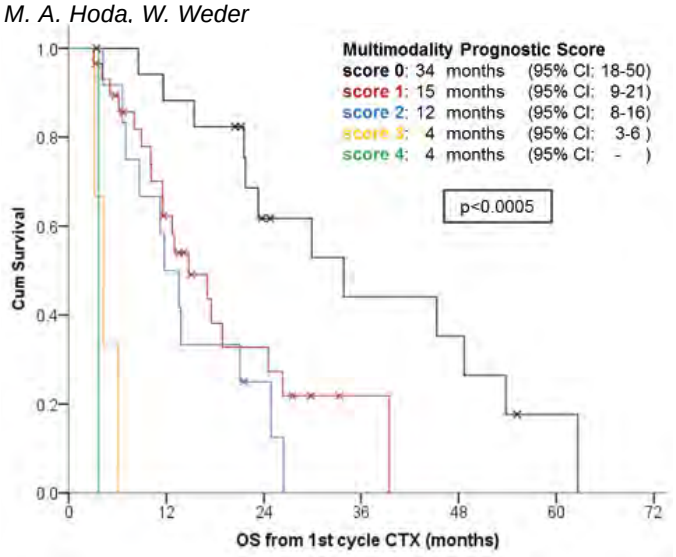



*Figure. Low Merlin expression and high Survivin labeling index is associated with poor outcomes of MPM. Kaplan-Meier survival curves according to dichotomized expression of cytoplasmic Merlin in pre-CTX samples (A: OS, B: PFS) and Survivin labeling indices in pre- and post-CTX tissues (C: pre-CTX, D: post-CTX). CI, confidence interval; CTX, chemotherapy; OS, overall survival; PFS, progression free survival*

*(A) median OS (months) (95% CI) low (n=55): 11 (8-14) vs high (n=49): 23 (20-26)*
*(B) median PFS (months) (95% CI) low (n=55): 11 (8-13) vs high (n=49): 15 (12-18)*
*(C) median PFS (months) (95% CI) low (n=52): 17 (12-21) vs high (n=46): 10 (8-13)*
*(D) median PFS (months) (95% CI) low (n=67): 15 (10-19) vs high (n=61): 13 (10-15)*

## A new prognostic score supporting treatment allocation for multimodality therapy for malignant pleural mesothelioma - an update

*I. Opitz, M. Friess, S. Hillinger, I. Inci, D. Schneiter, R. Stahel, T. Frauenfelder, D.L. Nguyen-Kim, B. Seifert, W. Klepetko, M. A. Hoda. W. Weder*




A prognostic score was defined considering tumor volume, histology, CRP and response to chemotherapy and identified patient groups not benefitting from multimodality treatment in a cohort of patients receiving cisplatin-based induction chemotherapy followed by extrapleural pneumonectomy (EPP) at the University Hospital Zurich.

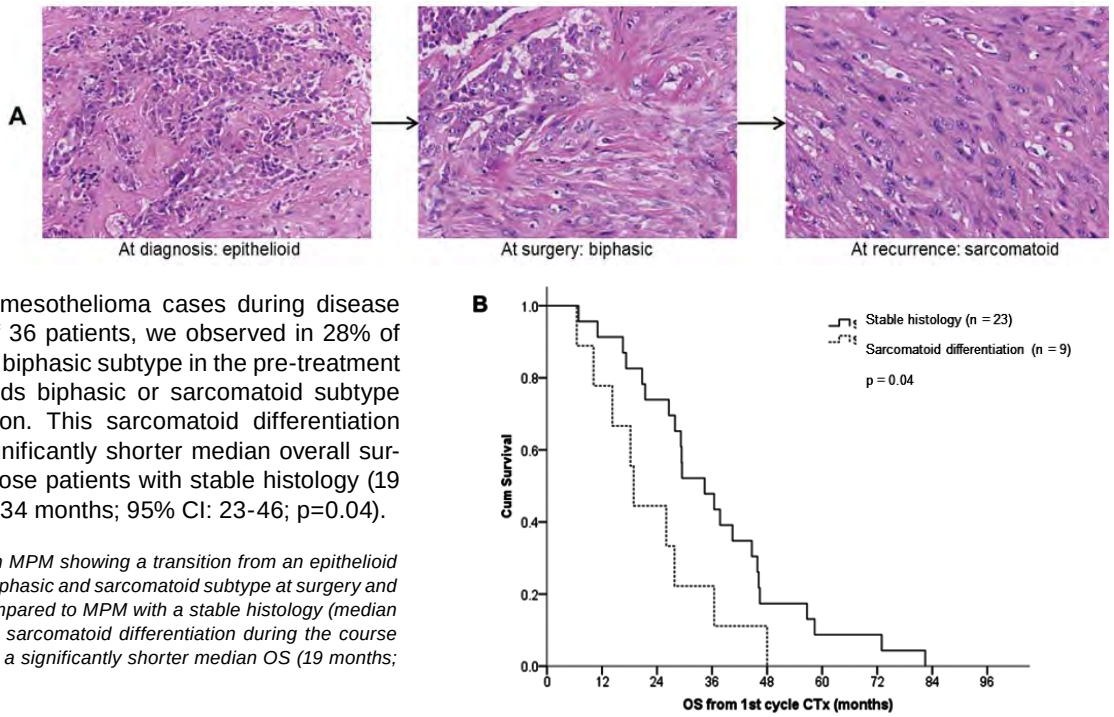
The MMPS was tested in 63 patients undergoing induction chemotherapy followed by EPP between 1999 and 2015. Patients with score 0 survived significantly longer than patients with score 3 or higher (Figure).

*Figure. Kaplan-Meier curve of overall survival (OS) in months of patients undergoing induction chemotherapy followed by EPP with the different MMPS (including 4 variables: volumetry pre CTX > 500ml, CRP pre CTX > 30mg/l, non-epithelioid histology in pre CTX biopsy, PD according to modified RECIST criteria).*

## Sarcomatoid differentiation during progression of malignant pleural mesothelioma

*B. Vrugt, E. Felley-Bosco, S. Simmler, M. Friess, M. Meerang, M. Kirschner, A. Soltermann, H. Moch, R. Stahel, W. Weder, I.Opitz*

Malignant pleural mesothelioma presents in the three histological subtypes epithelioid, biphasic and sacromatoid, of which epithelioid is the most common and the subtype associated with the best prognosis. Investigating histopathological characteristics of mesothelioma cases during disease progression in a series of 36 patients, we observed in 28% of patients with epithelioid or biphasic subtype in the pre-treatment biopsy, a transition towards biphasic or sarcomatoid subtype during disease progression. This sarcomatoid differentiation was associated with a significantly shorter median overall survival (OS) compared to those patients with stable histology (19 months; 95% CI: 17-21 vs 34 months; 95% CI: 23-46; p=0.04).




*(A) Sarcomatoid differentiation in MPM showing a transition from an epithelioid subtype at diagnosis towards a biphasic and sarcomatoid subtype at surgery and recurrence, respectively. (B) Compared to MPM with a stable histology (median OS 34 months; 95% CI: 23-46), sarcomatoid differentiation during the course of the disease is associated with a significantly shorter median OS (19 months; 95% CI: 17-21).*

## Investigation of genetic alterations underlying chemotherapy resistance and novel drug targets for malignant pleural mesothelioma by next generation sequencing

*K. Oehl, B. Vrugt, Q. Zhong, U. Wagner, A. Christiansen, M. Rechsteiner, M. Meerang, M. Kirschner, M. Friess, W. Weder, I. Opitz, P. Wild*

We employ next generation sequencing to investigate the fundamental mechanisms of malignant pleural mesothelioma (MPM) development and treatment resistance and to find predictive biomarkers and new drug targets.

The objectives of this study are (i) to investigate the intra-tumor heterogeneity and to track the clonal origin and treatment resistant clones at different time points during treatment; ii) to identify genetic alterations that are associated with the response to chemotherapy and (iii) to systematically investigate MPM samples using the Oncomine Focus Assay that enables simultaneous detection of thousands of variants across 52 genes targetable by available oncology drugs.

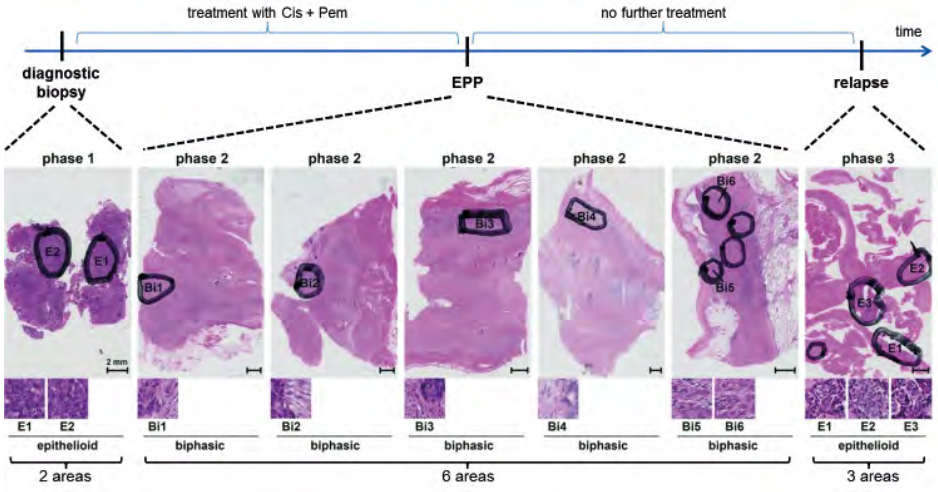
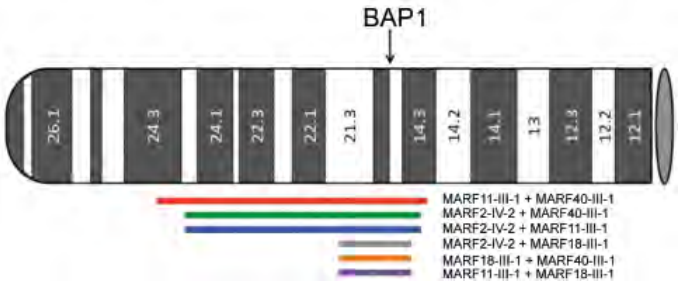



*Figure. Example of an MPM patient, with the initial diagnosis of an epithelioid MPM, undergoing multimodal treatment with cisplatin/pemetrexed induction chemotherapy followed by surgery. MPM tissue samples were taken at the initial treatment-naïve biopsy (referred to as phase 1), at extrapleural pneumonectomy after combined induction chemotherapy (phase 2) and at relapse (phase 3). DNA was isolated from punches taken from two areas in phase 1, six areas in phase 2 and three areas in phase 3, followed by ultra-deep amplicon resequencing. Subsequently, based on a systematic literature review, a custom-designed MPM-specific sequencing panel was established, targeting the coding sequence of the 30 most frequently mutated genes in MPM.*

## Genetic and genealogic studies evaluating the Swiss origin of a specific BAP1 cancer syndrome

*I. Opitz, O. Lauk, M. Kirschner, M. Friess, W. Weder, G. Gaudino, H. Yang, M. Carbone*

The presence of germline mutations in the gene encoding the BRCA1-associated protein (BAP1) has been identified as common heritable factor predisposing to a number of cancers, including malignant pleural mesothelioma (MPM). Genetic and genealogic studies of one specific BAP1 mutation found in four US-families, have recently suggested the origin of this mutation to be in Switzerland. In this project we are further screening possible descendants of the supposed founder family in order to formally confirm the origin of the rare BAP1 germline mutation in Switzerland.




*Idiogram showing Identity By Descent (IBD) shared haplotypes of the DNA regions surrounding BAP1 in the germline DNA of the 4 patients studied in the US. Figure from Carbone et al, PLoS Genetics 2015*

## Exploring novel treatment for malignant pleural mesothelioma: Effects of hedgehog antagonist in an orthotopic malignant pleural mesothelioma rat model

*M. Meerang, K. Bérard, E. Felley-Bosco, O. Lauk, B. Vrugt, A. Boss, D. Kenkel, A. Broggini-Tenzer, R. Stahel, S. Arni, W. Weder, I. Opitz*

An autocrine driven upregulation of the Hedgehog (Hh) signaling pathway has been described in malignant pleural mesothelioma (MPM) tumors. However, our investigation revealed that the Hh pathway is activated in both tumor and stroma of MPM tumor specimens and an orthotopic immunocompetent rat MPM model (Figure; Meerang et. al, Mol Cancer Ther 2016).
The rat MPM model receiving daily treatment with a Hh antagonist, vismodegib, showed a significant reduction of tumor volume, and tumor growth delay.
We detected reduced levels of Hh target genes namely Glioma associated oncogene 1 (GLI1) and Hedgehog Interacting Protein (HHIP) only in stromal part of vismodegib treated tumors.
Our study provides a novel data regarding paracrine Hh activation in MPM and emphasized the role of Hh signaling as a treatment target for MPM.

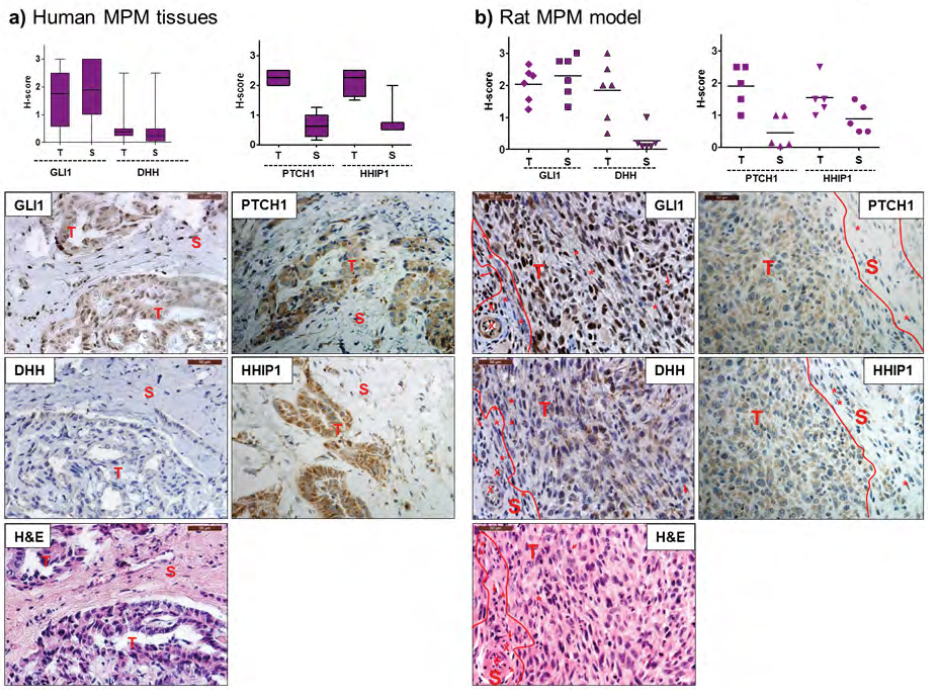



*Figure. Analysis of Hh pathway activation in human MPM specimens and rat MPM model in tumor and stromal fractions.*
*a) Immunohistochemical detection of GLI1, DHH, PTCH1 and HHIP in tumor (T) and stroma (S) and box plot of semi-quantitative expression levels (H-score) of GLI1 and DHH in146 MPM specimens, and PTCH1 and HHIP in 8 MPM specimens (lines indicate medians).*
*b) Histology of rat MPM model revealed cellular areas of closely packed spindled tumor cells (T) with relatively large, irregular nuclei, adjacent to stroma (S) containing fibroblasts (organized small spindle cells, *), blood vessels (X) and inflammatory cells (small round cells with dense blue chromatin; arrow). Of note is the presence of some fibroblasts and inflammatory cells also in the tumor area. Scatter plot shows semi-quantitative expression levels of GLI1, DHH, PTCH1 and HHIP (H-score) of 6 tumors (lines indicate medians).*

**Collaborations:**

- Prof. Dr. R. Stahel, PD Dr. E. Felley-Bosco, Labor für Molekulare Onkologie, UniversitätsSpital Zürich
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- Prof. Dr. H. Moch, PD Dr. A. Soltermann, Dr. B. Vrugt, Institut für klinische Pathologie, UniversitätsSpital Zürich
- Prof. Dr. M. de Perrot, Dr. G. Allo, Dr. M. Tsao, Division of Thoracic Surgery, Toronto General Hospital and Princess Margaret Hospital, University of Toronto, Toronto, Canada
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- Prof. Dr. M. Pruschy, Dr. A. Broggini-Tenzer, Institut für molekulare Radiologie, UniversitätsSpital Zürich
- PD Dr. A. Boss, Institut für Diagnostische und Interventionelle Radiologie, UniversitätsSpital Zürich
- Prof. Dr. M. Carbone, Prof. Dr. H. Yang, Prof. Dr. G. Gaudino, University of Hawai'i, Cancer Center, Honolulu
- Prof. Dr. G Reid, Prof. Dr. N. van Zandwijk, Asbestos Diseases Research Institute, Sydney, Australia

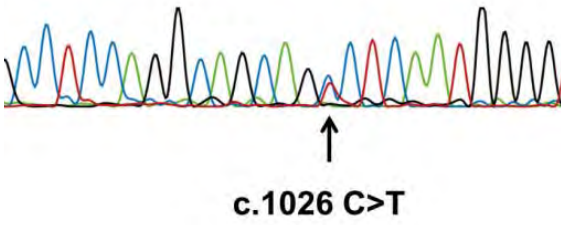
## Prevalence of BRCA-1 associated protein 1 germline mutation in sporadic malignant pleural mesothelioma cases

*A. Rusch, G. Ziltener, K. Nackaerts, W. Weder, R. A. Stahel, E. Felley-Bosco*

A large proportion of mesothelioma tumor specimens have a mutation in the BRCA1-associated protein 1 (BAP1) gene and germline BAP1 mutations predispose to malignant pleural mesothelioma (MPM). Our aim was to investigate germline BAP1 mutations in sporadic MPM patients.

One out of 78 patients showed a germline synonymous mutation in exon 11. In all other patients wild-type sequence without any single-nucleotide polymorphisms was detected.

Taking into account previous similar screenings, the prevalence of germline BAP1 mutations in sporadic MPM patients can be estimated around 1-2%, suggesting a minor role of germline BAP1 mutation in the pathogenesis of sporadic MPM.




## Preclinical malignant pleural mesothelioma models to accelerate clinical research on targeted therapies

*N. Echeverry, G. Ziltener, D. Barbone, W. Weder , R. A. Stahel, C. Broaddus, E. Felley-Bosco*

Given the limited effect of chemotherapy in malignant pleural mesothelioma (MPM), a big effort is being made to find new treatment options. The PI3K/mTOR pathway was reported to be upregulated in MPM. We tested the cell growth inhibition properties of two dual PI3K/mTOR inhibitors NVP-BEZ235 and GDC-0980 on 19 MPM cell lines. We could identify resistant and sensitive lines; however there was no correlation to the down-regulation of PI3K/mTOR activity markers. As a result of mTOR inhibition both drugs efficiently induced long-term autophagy but not cell death.

Autophagy blockade by chloroquine in combination with the dual PI3K/mTOR inhibitors significantly induced caspase-independent cell death involving RIP1 in the sensitive cell line SPC212. Cell death in the resistant cell line Mero-82 was less pronounced and it was not induced via RIP1 dependent mechanism, suggesting the involvement of RIP1 downstream effectors. Based on these results, we identify autophagy as one of the main mechanisms of cell death resistance against dual PI3K/mTOR inhibitors in MPM. As PI3K/mTOR inhibitors are under investigation in clinical trials, these results may help interpreting their outcome, and suggest ways for intervention *(Figure next page).*

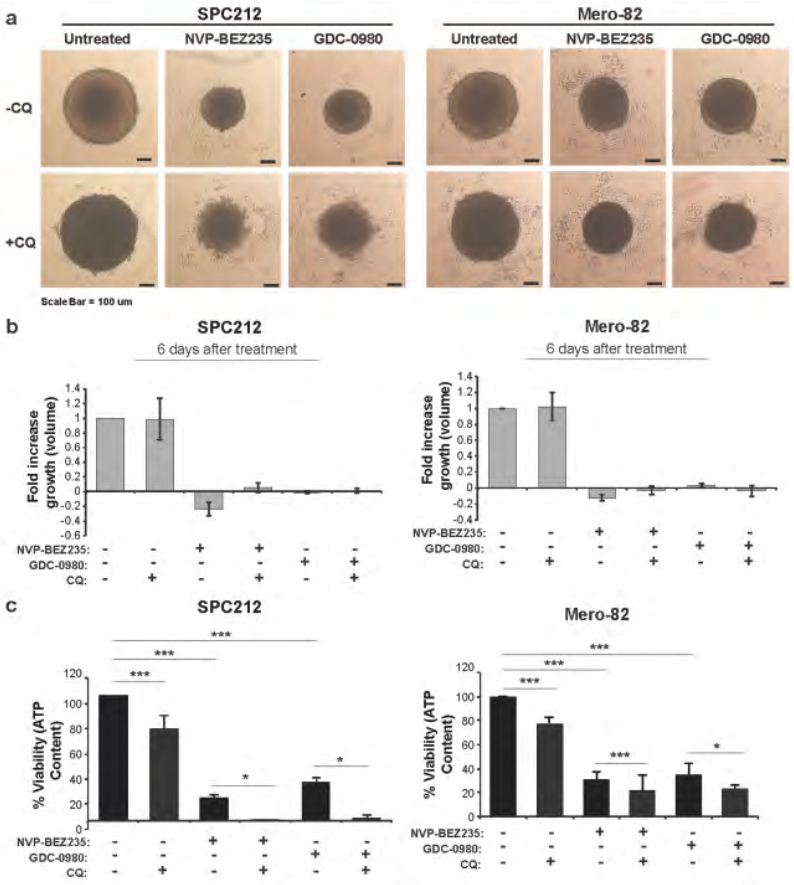
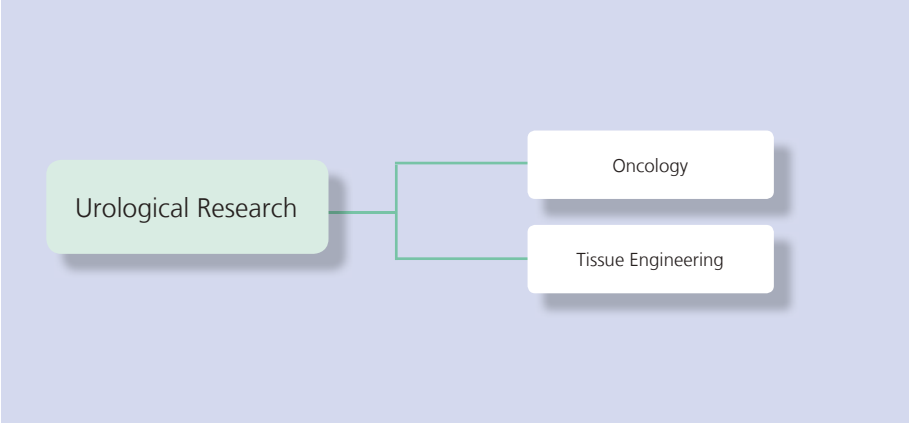



*Figure. Inhibition of autophagy with chloroquine combined with inhibition of PI3K/mTOR signaling induces spheroid cell death.*
*(a) Representative light micrographs of SPC212 and Mero-82 spheroids treated as indicated with 1 μM NVP-BEZ235, 1 μM GDC-0980 and 20 μM CQ for 6 days.*
*(b) Fold increase volume (growth) of spheroids shown in (a).*
*(c) Viability is presented as percentage of ATP content SPC212 and Mero-82 spheroids treated as described in (a).*
*Data are presented as means +/- SD from ≥3 independent experiments. Significance was determined by Anova test (***p<0.005, **p<0.01 and *p<0.05; n.s.: not significant).*

**Collaborations:**

- Dr. Alessandra Curioni, Prof. Rolf Stahel, Clinic of Oncology, Zurich University Hospital
- Dr. Bart Vrugt, Institute for Surgical Pathology, Zurich University Hospital
- Dr. Hubert Rehrauer, Functional Genomic Center, University of Zurich
- Prof. Lorenza Penengo, IMCR, University of Zurich
- Prof. Beat Schwaller, Department of Medicine, University of Fribourg
- Prof. Marc de Perrot, Dr. Licun Wu, Division of Thoracic Surgery, Toronto General Hospital
- Prof. Egbert Smit, NKI, Amsterdam
- Dr. Victor Van Beusechem, Department of Medical Oncology VUmc, Amsterdam

## 2.6 Urological Research




PD Dr. med. Maurizio Provenzano, PhD

Prof. Dr. med. Tullio Sulser, Director

PD Dr. med. Daniel Eberli, PhD

Damina Balmer, Scientific Coordination

### 2.6.1 Oncology

**Antibody response to BK polyomavirus as a prognostic biomarker and potential therapeutic target in prostate cancer**

*E.X. Keller, M. Provenzano*

The oncogenic potential of BKPyV is mainly due to the activity of its regulatory protein LTag. In PCa patients with evidence of disease recurrence and BKPyV positive tumors, the LTag induces a tolerogenic immune response able to sustain the malignancy and favor a bad prognosis. Therefore, exploiting the immunogenic activity of LTag in PCa patients with BKPyV-driven tolerogenic signature is of utmost importance. We are currently working on the generation of immunogenic tools able to counteract the BKPyV-regulatory activity in the prostate. We recently found that the preoperative BKPyV LTag serostatus of PCa patients undergoing surgery at first diagnosis might act as an independent predictor of biochemical recurrence and serve as a promising novel therapeutic approach targeting LTag.

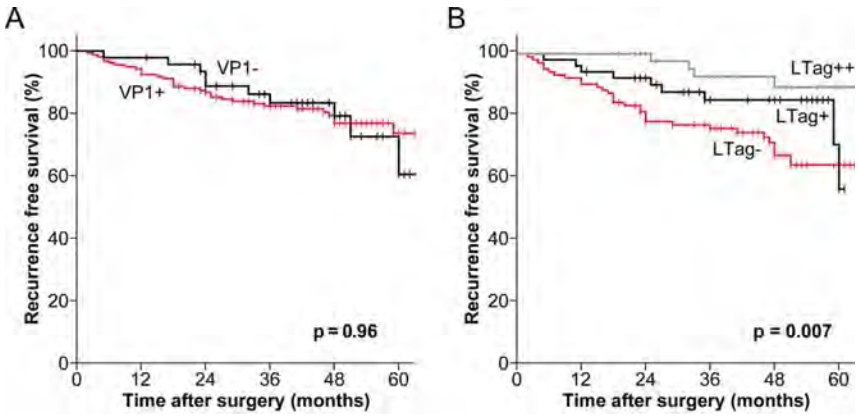



*Figure 1: Kaplan-Meier estimates of recurrence free survival (RFS) by BK polyomavirus (BKPyV) serostatus in patients who underwent radical prostatectomy for primary prostate cancer (PCa). (A) Estimates of RFS stratified by the established cutoff for viral capsid protein 1 (VP1) seropositivity (OD492 = 0.11) (black line = VP1- and red line = VP1+). (B) Estimates of RFS stratified by the 50th and the 75th percentile large T antigen (LTag) IgG OD492 ratio (1.0226 and 1.1478, respectively) (grey line = LTag++, black line = LTag+ and red line = LTag-). All p values were two-sided log-rank tests. (Oncotarget 2015, (6)8; 6459-6469)*

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Dr. med. Thomas Hermanns

Souzan Salemi, PhD

Sarah Nötzli, M.Sc.

Dr. med. Karim Saba

Dr. med. Christian Fankhauser

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Deana Haralampieva, PhD

Mykhailo Razumenko, PhD

Jakub Smolar, PhD Student

Daniel Keller, Master Student

Dr. med. Etienne Xavier Keller

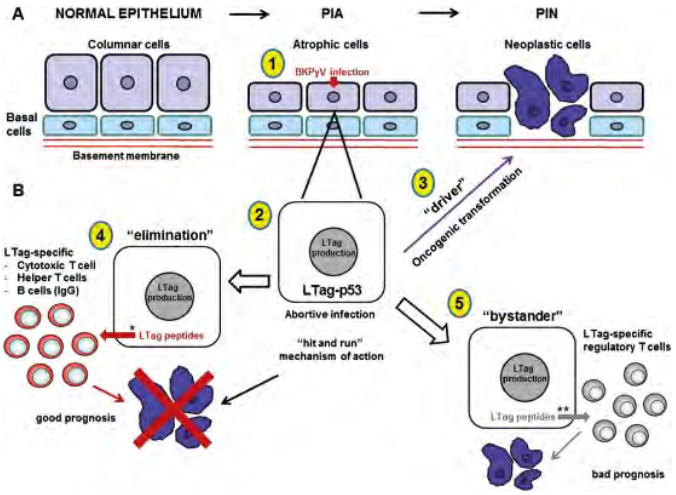
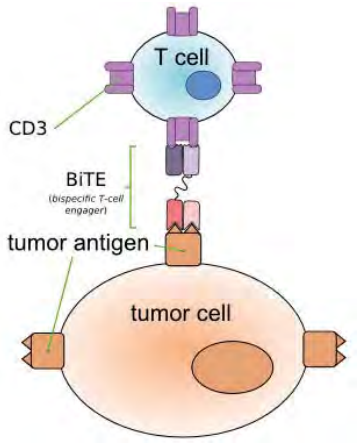



*Figure 2: Polyomavirus BK and prostate cancer: a complex interaction of potential clinical relevance. (A) Two steps leading to the development of PCa: from normal epithelium to early stage proliferative inflammatory atrophy (PIA) and finally to prostatic intraepithelial neoplasia (PIN). (B) BKPyV infection, transformation, and interaction with the immune system. (1) PIA represents a risk lesion for PCa, in which BKPyV infection may occur. (2) Upon viral entry, the absence of viral replication due to lack of specific host factors (abortive infection) allows only the expression of LTag in the nucleus of infected cells (uncoupling of early gene expression from late gene expression). LTag binds p53 in its wild-type form and exerts sequestration in the cytoplasm of infected cells (main hallmark for BKPyV implication in PCa development). (3) The sequestration of p53 might lead to oncogenic transformation of the infected cells (BKPyVas a "driver," purple arrow) because of the accumulation of mutations (purple cells). The destiny of the virus depends on the combination of events for which specific immune responses elicited by portion of LTag might be relevant (white arrows). (4) The LTag peptide processing may generate immunogenic portions (LTag peptides in red), which are able to recall both memory T and B cells (bold red arrow), favoring a good prognosis (light red arrow). *The potential effector immune response of LTag-specific memory T cells is due to their recall through the recognition of cognate immunogenic peptides expressed in the context of specific HLA restrictions on the surface of professional APC recruited in the tumor microenvironment. (5) Conversely, the production of tolerogenic peptides (LTag peptides in gray) leads to the maintenance of a regulatory microenvironment by engaging LTag-specific regulatory T cells (bold gray arrow) with suppressive properties, thus favoring a bad prognosis (light gray arrow). As such, the bystander presence of the virus at late stages (PIN or overt PCa), although sporadic, might inform about previous viral activity in the prostate. **The potential regulatory functions of LTag-specific regulatory T cells is due to their recall through the recognition of cognate tolerogenic peptides expressed in the context of specific HLA restrictions on the surface of tolerogenic APC generated within the tumor microenvironment (Rev Med Virol 2015, 25(6); 366-378)*

**Collaborations:**
- Prof. Hans H. Hirsch, Transplantation and Clinical Virology, Department of Biomedicine, University of Basel
- Prof. Pasquale Ferrante and Dr. Serena Delbue, Department of Biomedical Surgery and Dental Sciences, University of Milan, Italy
- Prof. Mauro Tognon, Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Italy

## Prostate cancer-specific bispecific antibodies (biAbs) to prevent and treat prostate cancer

*M. Razumenko, M. Provenzano*




*BiTE (bispecific T-cell engager) a type of bispecific antibody. In essence, BiTEs are comprised of two single-chain variable fragments (scFvs) of which one binds to the T cell antigen CD3 and the other to a cell surface tumor-associated antigen (TAA).*

Current standard-of-care therapeutic options for prostate cancer (PCa) may prolong overall survival and improve quality of life but they are not curative. Incurability is partially explained by different sensitivities to therapies. We intend to improve immunology-based therapies for PCa introducing bi-specific antibodies (biAbs) that specifically crosslink cytotoxic T-cells and prostatic tumor cells.

## Investigations on prognostic markers and changes in methylation patterns in superficial bladder cancer

*T. Hermanns, C. Poyet*

In this prospective study we investigate new prognostic markers and the methylation patterns in tissues, urine, and serum of patients suffering from superficial bladder cancer. These markers or hypomethylation processes might allow detection of a recurrent bladder cancer in urine or serum in a non-invasive manner.

**Collaborations:**
- PD Dr. med. S. Santourlidis, Heinrich-Heine University, Düsseldorf (Germany)
- Prof. Dr. Peter Wild, Institute of Surgical Pathology, University Hospital Zurich

### Evaluation of angio- and lymphangiogenesis in invasive bladder cancer

*C. Poyet, T. Hermanns*

In this prospective cohort study we investigate the behavior of invasive bladder cancer with a special focus on angio/lmyphangiogensis. Applying a series of different detection methods we investigate upregulated genes specifically affecting angio- and/or lymphangiogensesis and thereby increasing the metastatic potential of the tumor.

**Collaborations:**

- Prof. Dr. Peter Wild, Institute of Surgical Pathology, University Hospital Zurich
- Prof. Dr. Michael Detmar, Institute of Pharmaceutical Sciences, ETHZ

### Markers of progression in tissue of muscle invasive and non-muscle invasive bladder cancer

*C. Poyet, T. Hermanns, K. Saba*

The aim of this study is the evaluation of biomarkers as candidates for bladder cancer prognosis. Our approach includes a Tissue Micro Arrays as well as a whole exome DNA sequencing to detect point mutations, gene fusions or chromosomal amplifications. The detected alterations will then be evaluated for their prognostic significance.

**Collaborations:**

- Prof. Dr. Peter Wild, Institute of Surgical Pathology, University Hospital Zurich

### proCOC (Prostate cancer outcome study)

*C. Poyet, Ch. Fankhauser, T. Hermanns*

proCOC is an observational study of patients with localized prostate cancer who underwent surgery. Serum as well as the prostate tissue of these patients are collected and stored in a biobank.

**Collaborations:**

- Prof. Dr. Peter Wild, Institute of Surgical Pathology, University Hospital Zurich
- Proteomedix AG, Zürich
- ETH Zürich
- University of Applied Science North Western Switzerland (FHNW)

### Heterophilic antibodies and their effect in prostate cancer diagnosis

*C. Poyet*

Heterophilic antibodies might interfere with a diagnostic PSA testing and thereby falsify the resulting PSA value. In a prospective study and in collaboration with the Institute of Clinical Chemistry we investigate the frequency and the extent to which PSA-testing is altered by heterophilic antibodies.

**Collaborations:**

- Prof. Dr. Arnold von Eckardstein, Institute of Clinical Chemistry, University Hospital Zurich

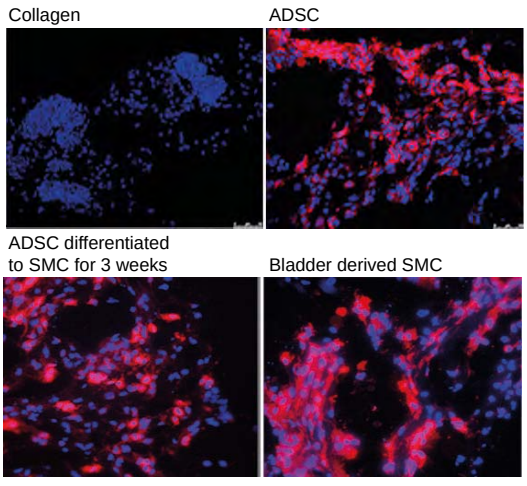
## 2.6.2 Tissue Engineering for Urologic Tissue

### Differentiated adipose aerived stem cells for functional smooth muscle bioengineering

*S. Salemi, D. Keller, D. Eberli*

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

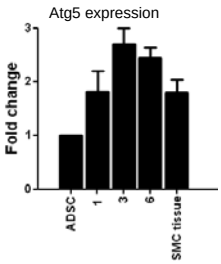
Survival of PKH labelled cells in nude mice after 1 month




*The cells were pre- labelled with PKH-26 (red) and were injected with collagen subcutaneously to back of the nude mice. The intact nuclei and red cytoplasm indicate the presence and survival of engineered cells in vivo.*

## The role of autophagy during the differentiation of adipose derived stem cells to smooth muscle

*S. Salemi, D. Eberli*

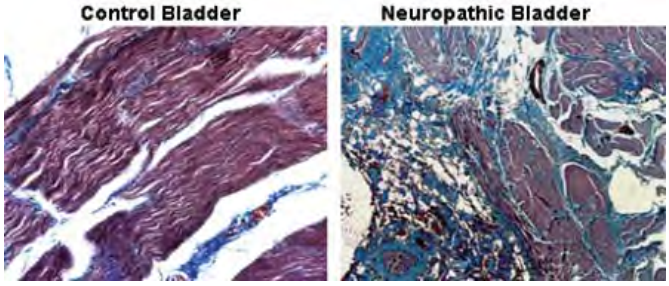



As autologous smooth muscle cells (SMC) cannot be harvested from organs with end-stage disease and tissue regeneration requires large amount of functional SMC, there is urgent need for other cell sources. Adipose derived stem cells (ADSC) are suitable cell source for SM tissue engineering. We investigated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

*Gene expression analysis of ADSC, ADSC differentiated for 1, 3 and 6 weeks and normal bladder bladder derived SMC for Atg5 determined by quantitative RT-PCR.*

## Autophagy is required for functionality of smooth muscle cells in neuropathic bladder

*S. Salemi, M. Horst, D. Eberli*




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

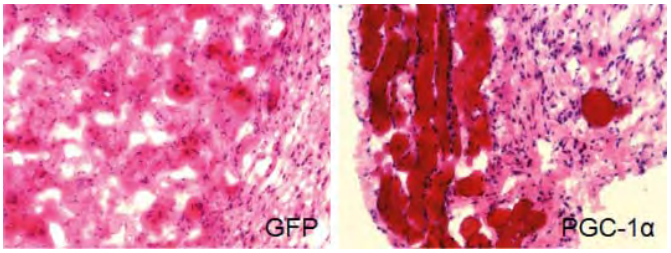
Neurogenic bladder dysfunction is the result of disease or injury to the neural pathways and commonly occurs in patients with meningomyelocele or after spinal cord injury. We hypothesis autophagy may play an important role in remodeling of bladder smooth muscle cells in children with neuropathic bladder.

**Collaborations:**

- Prof. Rita Gobet and Dr. Maya Horst, Division of Pediatric Urology, University Children's Hospital Zurich
- Prof. Hans Uwe Simon, Pharmacology Institute, Bern

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

*D.Haralampieva, S.Salemi, D.Eberli*




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

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

**Collaborations:**

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

## The effect of PGC-1α on skeletal muscle regeneration after trauma

*D.Haralampieva, S.Salemi, D.Eberli*

In this project we are analyzing the impact of PGC-1α-genetically modified human muscle precursor cells on *in situ* muscle tissue regeneration in a *Tibialis anterior* crush injury mouse model.

**Collaborations:**

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

## Non-invasive tracking of hMPCs using PET imaging

*D. Haralampieva, D. Eberli, S. M. Ametamey*

In this project we studied the possibility of tracking genetically modified hMPCs (overexpressing the human Dopamine receptor) using highly-specific PET-radioligands for optimization of the cell therapy and further application in a clinical setting.

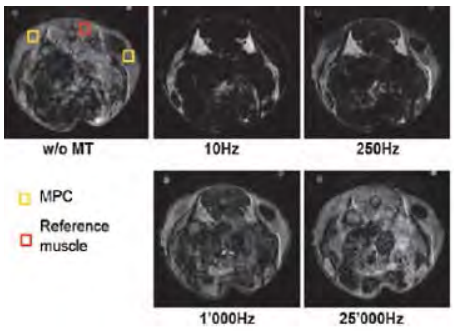
**Collaborations:**

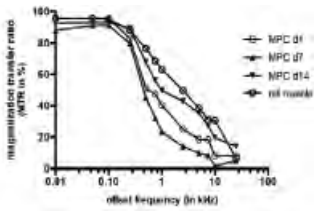
- Prof. Dr. Simon M. Ametamey, Dpt. Pharmaceutical Sciences, ETH Zurich, Switzerland
- Prof. Dr. Christoph Handschin, Biozentrum Basel, Switzerland

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

*D. Keller, C. Eberhardt, M. Rottmar, M. Wurnig, A. Boss, D. Eberli*

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




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

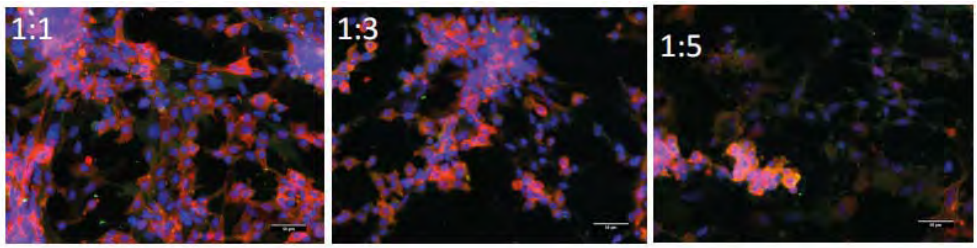
**Collaborations:**

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

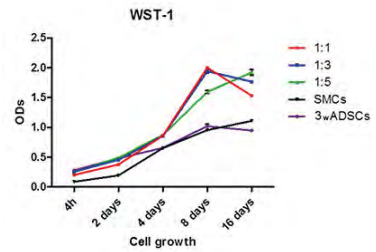
## *Co-culture of bladder-derived smooth muscle cells with smooth muscle-like adipose-derived stem cells leads to smooth muscle microtissue formation in 2D and 3D systems*

*J. Smolar, D. Eberli*

We aim at developing a substitute for the improvement of bladder wall function for patients suffering from end-stage bladder disease. We are currently investigating the effect of bladder-derived smooth muscle cells (SMCs) on the survival, proliferation and phenotype stability of pre-differentiated adipose-derived stem cells (pADSCs) in 2D and 3D systems using synthetic and natural hydrogel scaffolds.




*Microtissues show different size, morphology and expression of specific SMC-markers, depending on the SMC:pADSC ratio after 2 weeks of co-culture.*




*Cells show significantly increased viability when co-cultured compared to single-cell cultures. Measured by WST-1 assay.*

**Collaborations:**

- Dr. sc. nat. Martin Ehrbar, Division of Obstetrics, University Hospital Zurich
- Prof. Rita Gobet, Division of Pediatric Urology, University Children's Hospital Zurich
- Dr. Maya Horst, Division of Pediatric Urology, University Children's Hospital Zurich

# 2.7 Cranio-Maxillofacial Surgery Research

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PhD

Prof.
Dr. med. dent.
Martin Rücker

Marius Bredell

Chafik Ghayor,
PhD

PD
Dr. med. dent.
Harald Essig

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Paul Schumann

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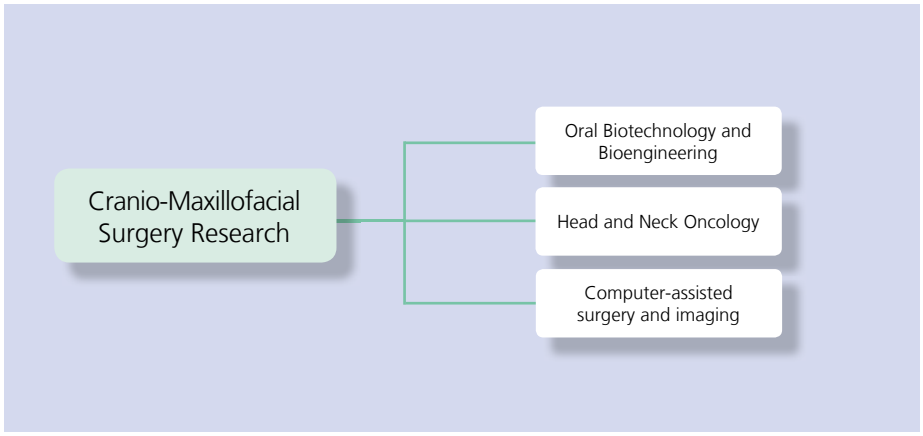


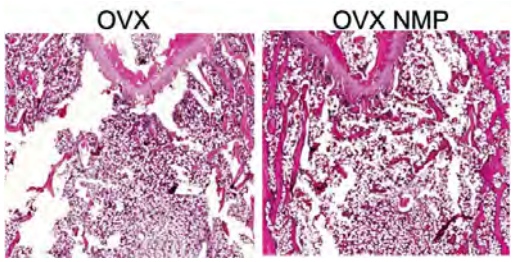

## 2.7.1 Oral Biotechnology and Bioengineering

### Bone, cartilage and tooth regeneration

*F. Weber, Ch. Ghayor, N. Roungsawasdi, B. Gjoksi, B. Siegenthaler, O. Schätti, A. Tchouboukov, Y. Bloemhard, A. Perez, T.-H. Chen*

### Epigenetically active small chemicals in bone regeneration and osteoporosis treatment

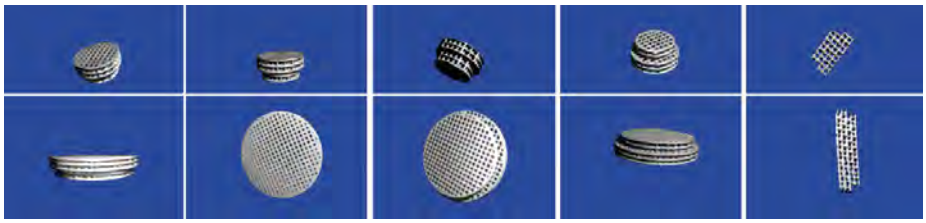
Heritable changes in gene expression or cellular phenotype not linked to changes in the underlying DNA sequence are studied in epigenetics. Acetylations are one form of heritable changes and recognized by bromodomains. The small chemical N-methyl pyrrolidone (NMP) is a low affinity Bromodomain inhibitor and proved useful in osteoporosis treatment, especially when bone regeneration has to be preserved.




*Estrogen deficiency induced osteoporosis leads to bone loss, that can be recovered by NMP (red: bone)*

### Osteoconductive bone substitute materials

In a SNF funded project our group together with Prof. M. de Wild (Fachhochschule Nordwestschweiz) and Prof. H. Man and Prof. M. Savalani (Hong Kong Polytechnic University, Kowloon) we characterize and develop novel osteoconductive bone substitute materials including titanium, magnesium and calcium phosphate based 3D scaffolds.



*MicroCT from calcium phosphate based degradable scaffolds produced by additive manufacturing.*

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

The main objective of this EU-project is to develop a biomimetic substitute for the nucleus pulposus for immediate and short term treatment. The synthetic scaffold will be integrated with a bioactive-nano-polymer highly potent in supporting Nucleus Pulposus cells (EPCs) for long-term cure. In addition growth factors will be integrated into the material in a way so that their release suits the needs of this avascular site (Figure 1).

### 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 (Figure 2).

### Pulp regeneration

Among the regenerative dental procedures, revascularization of a necrotic pulp space appears to be the treatment option that holds the most promise for the immediate future. The goal of this project is to establish a new soft tissue in the pulp space that is capable of continuing hard tissue formation. This project is based on our vast experience in hydrogels and growth factor delivery and on a close collaboration to clinical partners at the ZZM *(Prof. Matthias Zehnder and Prof. Thomas Attin)* (Figure 3).

Figures:

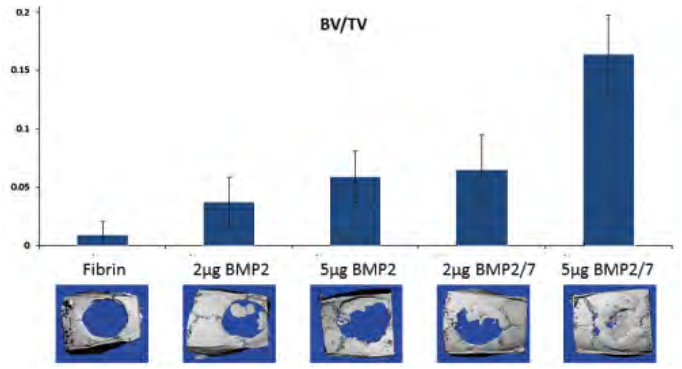



*Figure 1: The engineered growth factor BMP2/7 is more potent than BMP2 in the healing of a critical size defect in the calvarium of a rat.*

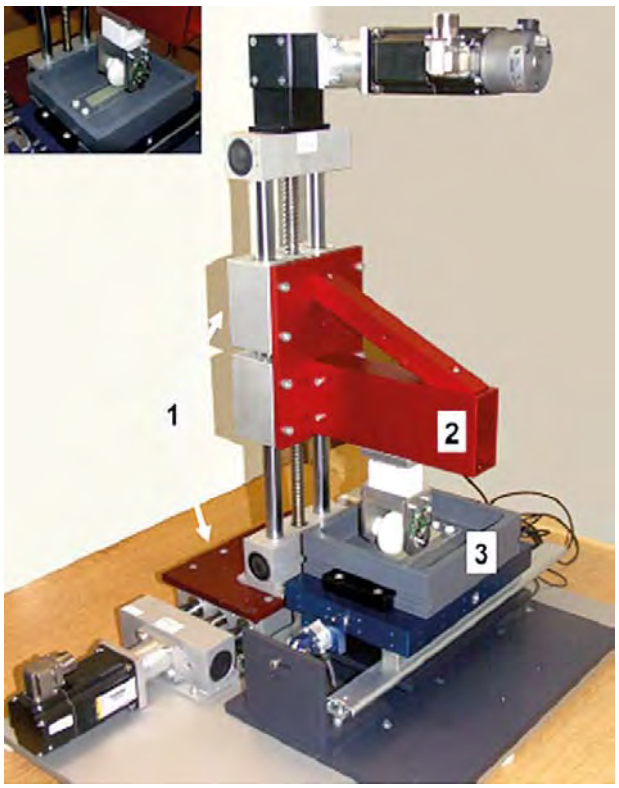



*Figure 2: Rolling, plowing cartilage test system*

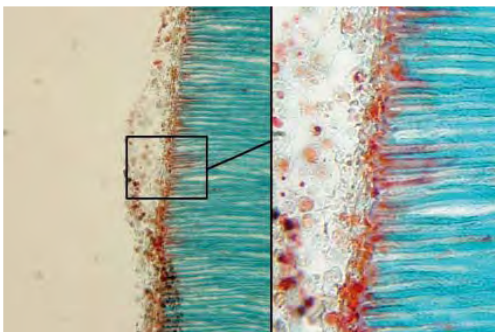
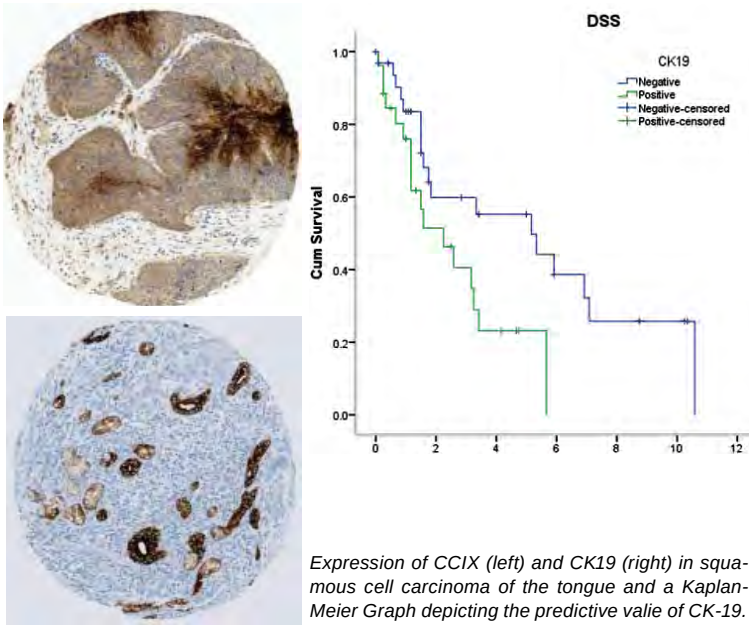


*Figure 3: Pulp space treated with EDTA allowed cell homing and induced the extension of odontoblast like cells into dentin.*

## 2.7.2 Head and Neck Oncology

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

Patients with hypoxic tumors have a poorer prognosis. Knowledge of the tumors hypoxia status will assist in optimal treatment of Head and Neck Cancer.
A large clinical database and tissue micro array (TMA) for tongue cancer patients has been developed to validate an array of biomarkers. CK19 was established as the most predictive marker for overall and disease specific survival. In a unique prospective clinical study, various MRI sequences and PET-CT are being correlated with tissue microdialysis, tissue histology and a panel of innovative biomarkers as well as saliva and serum factors in the quest to establish non-invasive methods to determine tumor hypoxia.




*Expression of CCIX (left) and CK19 (right) in squamous cell carcinoma of the tongue and a Kaplan-Meier Graph depicting the predictive valie of CK-19.*

## 2.7.3 Computer Assisted Surgery (CAS)

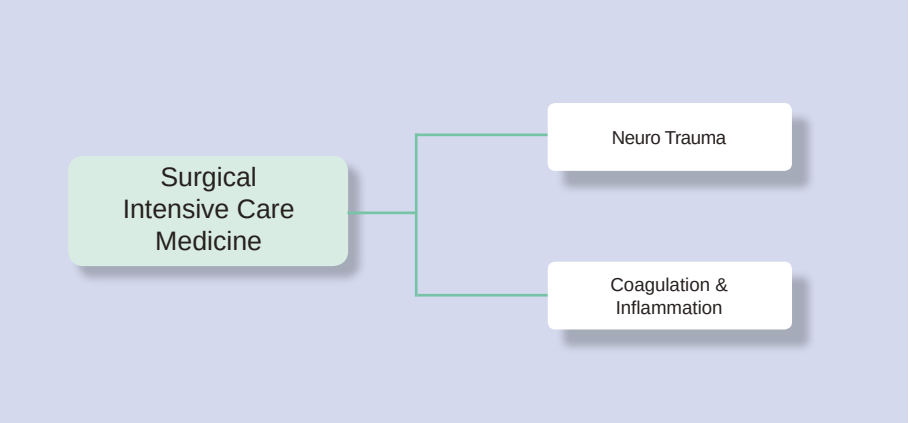
*M. Rücker, H. Essig, P. Schumann, T. Gander*

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

**Collaborations:**

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

## 2.8 Surgical Intensive Care Medicine





Dr. med.
Peter Steiger


PD Dr. med.
Reto Schüpbach,
M.Sc.


PD Dr. med.
Markus Béchir

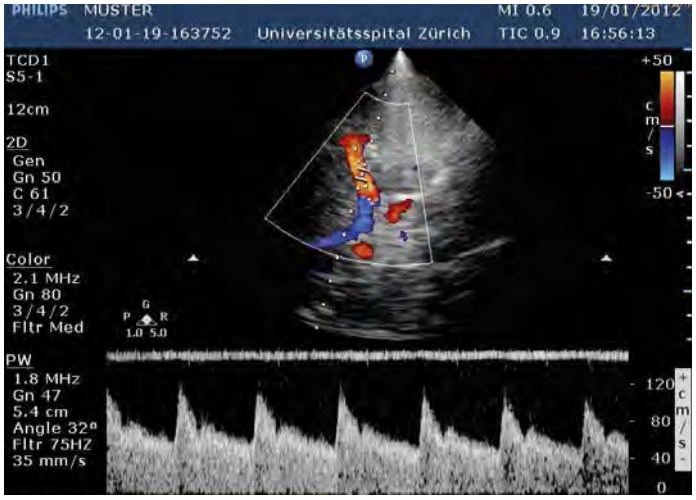
### 2.8.1 Neuro Trauma

*P. Steiger, M. Béchir, G. Brandi, S. Klinzing, F. Stretti*

The main focus of the neuro research group is to optimize bed side monitoring of cerebral blood flow in patients with severe acute traumatic brain injury (TBI). Maintaining an optimal cerebral perfusion is the primary goal in these patients to minimize ischemia induced injury.

**Transcranial color-coded duplex sonography to investigate $CO^2$ reactivity in patients with severe traumatic brain injury**

$CO^2$ reactivity is often impaired in patients with severe traumatic brain injury associated with unfavorable changes in cerebral perfusion and impaired outcome. The aim of this project is to determine whether impairment in $CO^2$ reactivity is related to the location of injury and the timely course after injury. $CO^2$ reactivity of the arteria cerebri media is determined by transcranial color-coded duplex sonography in patients with severe TBI affecting different vasculary territories and at defined time after injury. $CO^2$ reactivity of TBI patients is compared to healthy volunteers and mechanically ventilated patients without intracerebral pathology.




*TCCD provides rapid, noninvasive, real-time measures of cerebrovascular function by serial measurements of flow velocity in the basal arteries of the brain .*


Dr. med.
Stephanie
Klinzing


Dr. med.
Giovanna
Brandi


Dr.
Jerzy Madon,
Research
Associate

**Postdoctoral Fellows and Students**


Alessandro
Franchini,
PhD


Dorothea
Heuberger,
PhD Student

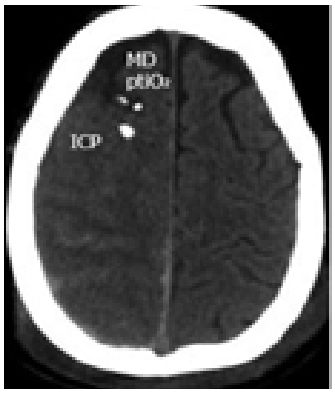

Laura
Vazquez Rojo,
MS Student


Dr. med.
Federica Stretti

### Prolonged moderate hyperventilation in management of patients with severe traumatic brain injury

*P. Steiger, M. Béchir, G. Brandi, S. Klinzing, F. Stretti*

Hyperventilation for management of elevated intracranial pressure in TBI patients is one of the most controversially discussed topics among clinicians and neuroscientists due to the potential risk of reducing the cerebral blood flow to an ischemic threshold. The aim of this project is to examine the impact of maintained moderate hyperventilation on cerebral hemodynamics, investigated by transcranial color-coded duplex sonography, and on cerebral oxygenation and metabolism as a marker to detect potential early sign of ischemia.




*Intracranial pressure (ICP) and brain tissue partial pressure of oxygen (ptiO2) are monitored continuously in the frontal matter by means of an intraparenchymal ICP transducer and the Licox sensor system. The cerebral microdialysis (MD) probe permits to obtain cerebral concentrations of glucose, lactate and pyruvate. Microdialysate samples are taken in 60-min intervals.*

### Baseline characteristics, management and outcome of traumatic brain injury patients admitted to the intensive care unit: the experience of the University Hospital of Zurich

*G. Brandi, R. Ehrlebach , St. Klinzing, F. Stretti, P. Steiger*

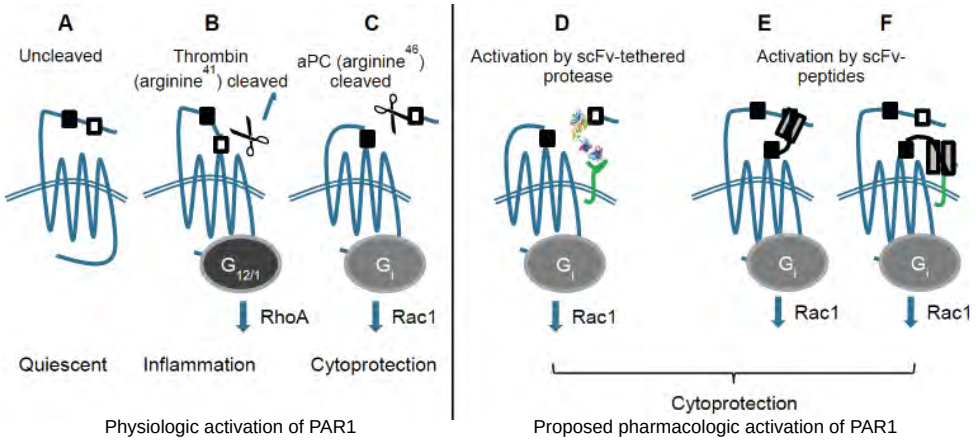
The aim of this epidemiological study is a profound description of population characteristics of patients with moderate to severe traumatic brain injury admitted to the intensive care unit of our trauma center and analysis of different prognostic factors on short and six-month outcome.

## 2.8.2 Coagulation and Inflammation

*A. Franchini, J. Madon, F. Ugolini, D. Heuberger, R. Schüpbach*

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 anti-inflammatory pathways and opens up therapeutic options on how PAR1 could be pharmacologically used in inflammatory driven diseases such as sepsis.

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. As novel approach we are currently investigating scFv tethered peptides potentially opening up novel strategies in pharmacologically activating protease activated receptors.




*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-F) Proposed mechanisms for pharmacological activation of PAR1. (D) Activation by scFv tethered aPC. High (μM)concentrations of soluble peptides homologous to the physiological tethered PAR1 ligands have been shown to induce signaling (not shown) We propose to tether ligand peptides to scFv (single chain antibodies) targeting (E) either PAR1 itself or (F) a cell surface protein colocalized to PAR1 (endothelial protein C receptor; EPCR; green).*

**Collaborations:**

- Prof. Dr. A. Zinkernagel, Klinik für Infektionskrankheiten und Spitalhygiene, UniversitätsSpital Zurich, Switzerland

## 2.9 Animal Welfare in Biomedical Research

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

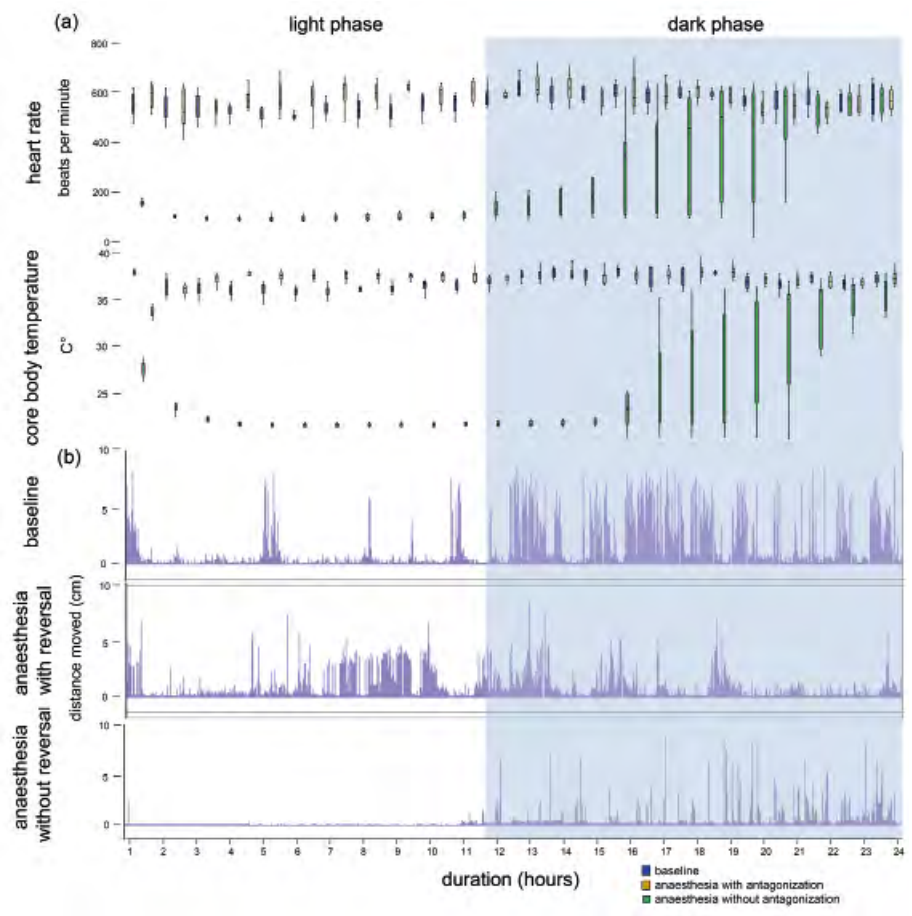



*Figure 1: Injection anaesthesia with fentanyl-midazolam-medetomidine in adult female mice. Post-anaesthetic period (24 h). (A) Telemetric recordings of HR and core BT for 24 h during baseline and after anaesthesia with and without reversal are presented as box-plots for each hour. (B) Activity shown as distance moved during 24h. A single representative data-set of locomotor activity levels (represented as distance of animals' centre point moved in cm) during baseline as well as after anaesthesia with or without reversal as analyzed by Ethovision® software is presented.*
*Reference: Fleischmann et al. 2016, Injection anaesthesia with fentanyl-midazolam-medetomidine in adult female mice: importance of antagonisation and peri-operative care, Laboratory Animals.*

**Collaborations:**

- Alain Rudiger, Department of Anesthesiology, UniversityHospital Zurich
- Annemarie Lang, Clinic for Rheumatology and Clinical Immunology, Charité Berlin, Germany
- Michael Guarnieri, Johns Hopkins University, Baltimore, USA
- Knut Husmann, Orthopädische Universitätsklinik Balgrist und Schweizerisches Paraplegikerzentrum Nottwil, University of Zurich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Nikola Cesarovic, DVM, PhD


Flora Nicholls, Dipl. biol.


Miriam Lipiski, DVM


Paulin Jirkof, PhD


Thea Fleischmann, DVM


Mareike Sauer, mag. med. vet.

# 3. Core Services



Prof.
Margarete Arras,
DVM

Nikola Cesarovic,
DVM, PhD

Nico Wick,
Photographer

Lea Schütz,
Photographer

Carol De Simio,
Scientific
Illustrator

Stefan Schwyter,
Scientific
Illustrator

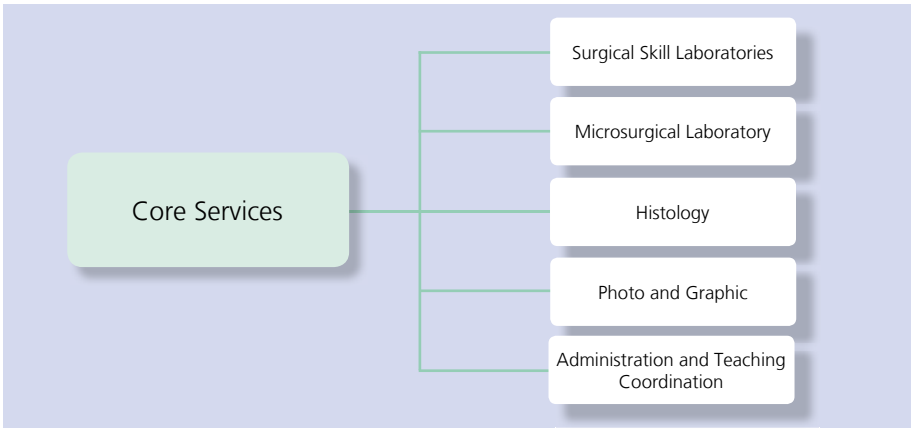
Pia Fuchs,
Lab. Technician

Ursula Süss,
PhD

Donata Gröflin,
Teaching
Coordination
Division of
Surgical
Research

Corinne Renold,
Teaching
Coordination
Division of
Surgical
Research

Susanne
Frehner,
Administration
Division of
Surgical
Research




## 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

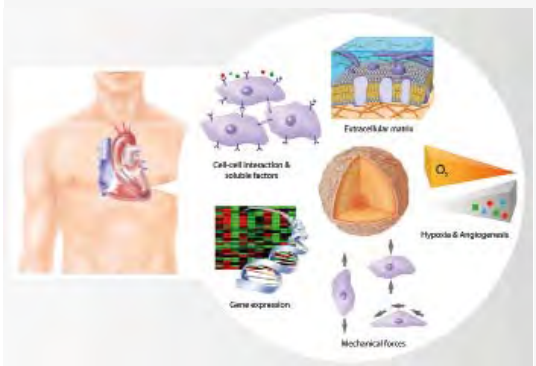
- Coordination and organization of the learning and teaching units in the Department of Surgery from 1st to 6th years of study including lectures and clinical courses in the compulsory part of the curriculum as well as in the electives.
- Coordination, organization of the clinical rotations during the 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.

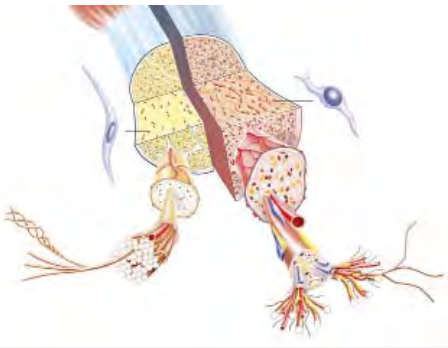
## 3.6 Photo and Graphic Services

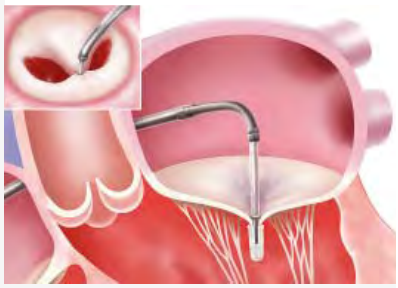
**A quick, flexible, versatile and professional service.**

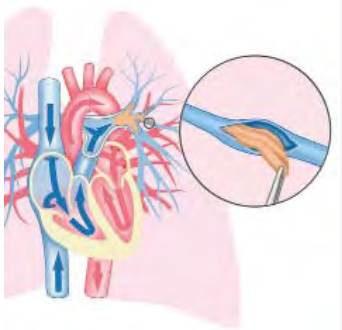
We offer

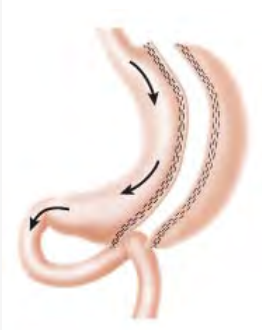
- photographic documentation of patients and events
- technical photography, on location or in our studio
- photography, graphic and design of illustrations for papers and books
- reproduction and digitalization of any original
- layout of printing matters
- preparation of files for external printing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

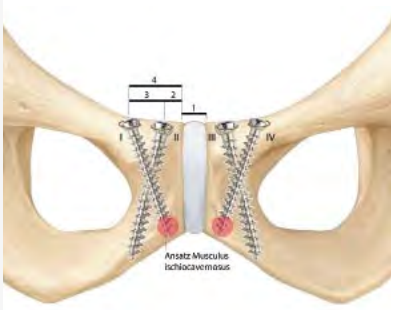






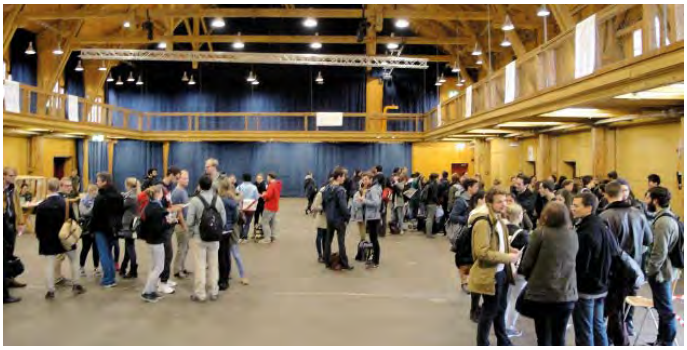




# 4. Events and Workshops at the Division of Surgical Research 2015




*14th Day of Clinical Research, April 9*



*Surgical Suture Skills Course, Winterthur, May 20*


*CTC Symposium, September 15*


*Lab Retreat, Vulpera, January 9 - 11*

*Christmas Party, December 8*

# 5. Publications 2015



### Cardiovascular Surgery

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## Urology

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### Intensive Care Unit


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### Veterinary Services


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# 6. Grants 2015

**Cardiovascular Surgery**

| Source | Title of Project | Project Leader |
|---|---|---|
| Research Grant from the University of Zurich | Improved cardiac allograft preservation with sub-normothermic machine perfusion | M. Wilhelm |
| CABMM Start-up Grant | Establishment of the differential proteomic and biofunctional analysis of the secretome of human mesenchymal stem cell sources | B. Weber |
| Forschungskredit der Universität Zürich | *In vitro* engineering of a human cell-based three dimensional dynamic model of artherosclerosis | M. Generali |
| ETH Foundation Grant | Endothelialization of a hyperelastomeric membrane for biomimetic blood propulsion | S. Hoerstrup |
| SwissTransMed<br>Source: Staatssekretariat für Bildung Forschung und Innovation SBFI (Eidgenössisches Departement für Wirtschaft, Bildung und Forschung WBFM) | LifeMatrix: Engineered, dynamically evolving living tissues for repairing the child's heart | S. Hoerstrup |
| Wyss Translational Center Zurich | Zurich LifeMatrix (Engineered, dynamically evolving living tissues for repairing the child's heart | K. Schlinkmann |
| CVON | 1-Valve (one valve for life), | S. Hoerstrup |
| CVON | i-Valve (Intelligent Valve) | S. Hoerstrup, P. Dijkman |
| | | |
| Commission of the European Communities EU-FP7 | Living autologous heart valves for minimally invasive implantable procedures - LifeValve | S. Hoerstrup |
| Commission of the European Communities EU-FP7 | Intelligent materials for *in-situ* heart Valve tissue engineering - ImaValve | S. Hoerstrup |
| EU intra-European Fellowships | Improvement of the clinical applicability of tissue-engineered vascular grafts as new regenerative therapy for children with congenital cardiovascular malformations - LivaGraft | S. Hoerstrup |
| Swiss National Science Foundation | Prenatal minimally invasive implantation of fetal cell-based autologous living heart valves - a novel approach using naive and amniotic fluid-derived induced pluripotent stem cells | B. Weber |
| Schweizerische Herzstiftung, Bern | Living Heart Valves for the few | S. Hoerstrup |
| Schweizerische Herzstiftung, Bern | Imaging based *in vivo* evaluation of human mesemchymal stem cell-based three dimensional microtissues in a unique immunotolerant fetal sheep myocardial infarction model | S. Hoerstrup |
| Kommission für Technologie und Innovation<br>KTI , Bern | Early detection of microscopic epithelial tumors: *In-vivo* Proof-of-Concept | S. Hoerstrup |
| Kommission für Technologie und Innovation<br>KTI, Bern | Proof of concept: Human FAP-targeting Antibodies as Infarction Prevention Medications | 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 |
| Mäxistiftung und Baugartenstiftung | Tissue engineered hybrid heart valves and interfaces | S. Hoerstrup |
| Fonds für Medizinische Forschung | Nogo-A is a negative regulator of CNS angiogenesis – molecular mechanisms and applications in brain tumors. | T. Wälchli |
| OPO-Stiftung | Nogo-A is a negative regulator of CNS angiogenesis – molecular mechanisms and applications in brain tumors | T. Wälchli |

**Cardiovascular Surgery**

| | | |
|---|---|---|
| Baasch-Medicus-Stiftung | Nogo-A is a negative regulator of CNS angiogenesis – molecular mechanisms and applications in brain tumors | T. Wälchli |
| Forschungskredit 2014 (Stiftung für Forschung an der Medizinischen Fakultät) | Improved long-term *in vivo* functionality of stented tissue engineered heart valves | P. Dijkman |
| Forschungskredit 2014 | Development of a murine model for the *in vivo* assessment of orthotopically integrated human bioartificial decellularized heart valves in heterotopically transplanted fully loaded heart grafts | B. Weber |
| Fonds für Medizinische Forschung | Fabrication and functional performance of human living autologous tissue engineered heart valves based on amniotic fluid cell-derived induced pluripotent stem cells. | B. Weber |
| Stiftung Forschung 3R | *in vitro* engineering of a dynamic threedimensional atherosclerotic lesion disease model | S. Hoerstrup |
| Commission of the European Communities | European Clinical Study for Application of Regenerative Heart Valves | M. Hübler |
| St Jude Medical Coordination Center BVBA, Zaventem Belgium | Trifecta Durability Study. Studie zur Langlebigkeit von Trifecta | F. Maisano |
| Edwards Lifesciences / USA | Carpentier-Edwards / Perimount Magna / Mitral Periocardial Bioprostheses | D. Reser |
| 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 | F. Maisano |
| BerlinHeart GmbH, Germany | Early Product Surveillance (EPS) of EXCOR® blood pumps with bileaflet valves | M. Wilhelm |
| Direct Flow Medical lnc, USA | A Registry to Evaluate the Direct Flow Medical® Transcatheter Aortic Valve System for the Treatment of Patients with Severe Aortic Stenosis | F. Maisano |
| lnterValve lnc., USA | Impact of Postdilatation with the lnterValve V8 Aortic Valvuloplasty Balloon following Medtronic CoreValve or other self-expanding TAVI procedure | F. Maisano |
| Medtronic Bakken Research Center B.V., The Netherlands | Medtronic PERIcardial SurGical AOrtic Valve Replacement Pivotal Trial (PERIGON) | T. Holubec |
| Medtronic Bakken Research Center B.V., The Netherlands | Surgical Replacement and Transcatheter Aortic Valve Implantation | F. Maisano |
| Valtech Cardio Ltd., Israel | Cardioband Adjustable Annuloplasty System For Transcatheter Repair of Mitral Valve Regurgitation | O. Gämperli |

**Visceral & Transplant Surgery**

| **Source** | **Title of Project** | **Project Leader** |
|---|---|---|
| **Hepatobiliary Laboratory** | | |
| SNF Sinergia Grant | Metabolic control of hepatocyte proliferation in regeneration and cancer | Bostjan Humar, Pierre-Alain Clavien |
| SNF Bonus of Excellence | Serotonin and regeneration in the normal, old and diseased liver | P.-A. Clavien, R. Graf, Bostjan Humar |
| Swiss National Science Foundation | Combining portal vein ligation with liver parenchyma transection to accelerate liver regeneration in liver surgery | M. Lesurtel |
| Swiss National Science Foundation | Reversible portal vein embolization for safer liver surgery and transplantation | M. Lesurtel |
| Swiss National Science Foundation | Uzbekistan International Cooperation: Transition to Modern Hepato-Pancreato-Biliary Surgery | M. Lesurtel |
| Swiss National Science Foundation | Establishment of a Morbidity Index to Assess Surgery | K. Slankamenac |

**Visceral & Transplant Surgery**

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|---|---|---|
| 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 | Machine liver perfusion for protection from biliary injury | P. Dutkowski |
| National Institutes of Health (R01DK 092608-01A1) | Intestinal satiation in Roux-en-Y gastric bypass rats: brain mechanisms and sex differences | M. Bueter (Co-Principal Investigator) |
| ZIHP - Zurich Center for Integrative Human Physiology | Immediate improvement of lipid metabolism, liver and endothelial function after Roux-en-Y gastric bypass (RYGB) surgery in obese humans and rodents | M. Bueter (Co-Applicant) |
| ETH Zürich as the Swiss Leading House for the SSSTC | Sino-Swiss Science and Technology Cooperation | P.-A. Clavien |
| Krebsliga Schweiz | Inositol tris-pyrophosphate (ITPP) – treating cancer by increasing oxygen supply | Pierre-Alain Clavien, Bostjan Humar, Perparim Limani |
| University of Zurich (Klinische Forschungsschwerpunkte) | Non-resectable liver tumors: from palliation to cure | P.-A. Clavien |
| University of Zurich (Klinische Forschungsschwerpunkte) | Molecular Imaging Network, Zürich | M. Lesurtel / A. Boss |
| Sassella-Stiftung | Adjuvant gemcitabitabine versus neoadjuvant gemcitabine / oxaliplatin and adjuvant chemotherapy with gemcitabine in patients with resectable pancreatic cancer | P.-A. Clavien |
| Sassella Stiftung | ALPPS versus Two- Stage Hepatectomy in colorectal liver metastases (monitoring and translational research) | Michael Linecker |
| Sassella Stiftung | Myo-inositol trispyrophosphate (ITPP) and its anti-hypoxic potential in colorectal metastases of the liver | Perparim Limani, Bostjan Humar |
| Wyss Translational Center Zurich | Liver4Life | PA Clavien (USZ)<br>Ph. Rudolf von Rohr (ETH) |

**Pancreatitis Laboratory**

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|---|---|---|
| Swiss National Science Foundation | Serotonin regulates secretion and regeneration of pancreatic acinar cells | R. Graf & S. Sonda |
| Gebert Rüf Stiftung, Basel | PSP and Sepsis | R. Graf & S. Sonda |
| Waring Foundation | Novel insights into the etiology of pancreatic cancer | R. Graf & S. Sonda |
| Waring Foundation | Role of deoxy-sphingolipids in acinar cell pathobiology following diabetes mellitus | R. Graf & S. Sonda |
| Baugarten Stiftung | Mechanisms of Disease: chronic inflammation and cancer in the pancreas – a potential role for Lymphotoxin signalling | R. Graf & G. Seleznik |
| Novartis Foundation | Serotonin regulates cytoskeletal remodeling driving the formation of pancreatic acinar-to-ductal-metaplasia | S. Sonda & E. Saponara |
| Sassella Foundation | Serotonin regulates cytoskeletal remodeling driving the formation of pancreatic acinar-to-ductal-metaplasia | S. Sonda & E. Saponara |

**Trauma Surgery**

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

**Plastic, Hand and Reconstructive Surgery**

| Source | Title of Project | Project Leader |
|---|---|---|
| Allergan Inc., Irvine, CA, USA) , SNSF through NCCR Kidney.CH | *In vivo* characterization of the integration and vascularization of a silk-derived Surgical Scaffold | N. Lindenblatt |
| Swiss National Science Foundation | Cellular and molecular mechanisms of vascular maturation for therapeutic angiogenesis | A. Banfi, Basel; N. Lindenblatt (Co-Applicant) |
| Swiss National Science Foundation | New vascularization strategies for skin tissue engineering | N. Lindenblatt |
| Research Grant Olga Mayenfisch Stiftung, Zürich, Schweiz | Effect of fat and adipose-derived stem cells (ADSCs) on vascularisation and nerve regeneration in a new *in vivo* mouse model | N. Lindenblatt |
| Research Grant Allergan, Irvine, USA | Evaluation of the vascularisation and inflammatory reaction of the silk-based synthethic surgical scaffold SERI *in vivo* | N. Lindenblatt |
| Hartmann-Müller Stiftung, Zürich, Schweiz | Guided wound healing in full and split thickness wounds‘ | N. Lindenblatt |
| Hartmann Müller-Stiftung für Med. Forschung | Fat grafting nerve | N. Lindenblatt |
| Forschung und Nachwuchsförderung der Universität Zürich | Hauttransplantate | N. Lindenblatt |

**Plastic, Hand and Reconstructive Surgery**

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|---|---|---|
| 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 |
| Hartmann-Müller Stiftung für Med. Forschung | Knochenersatzkonstrukte | J. Buschmann |
| 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 |
| Hartmann-Müller Stiftung | Sehnenreparatur unter Zuhilfenahme eines mit PDGF-BB bestückten Degrapol-Rohrs | J. Buschmann |
| Kurt und Senta Hermann Stiftung | Fabrikation eines Polymer-Trägers: Bioaktivität und Release-Kinetik des Wachstumsfaktors Platelet-Derived Growth Factor-BB (PDG-BB) vom elektrogesponnenen Träger DegraPol® | J. Buschmann |

**Thoracic Surgery**

| **Source** | **Title of Project** | **Project Leader** |
|---|---|---|
| Swiss National Science Foundation | From asbestos-exposure to cancer: a systemic approach to detect loss of homeostatic control in the mesothelial environment | E. Felley-Bosco |
| Baugarten Stiftung | Preclinical Malignant Pleural Mesothelioma models to accelerate clinical research on targeted therapy | E. Felley-Bosco |
| Walter Bruckerhoff Stiftung | Targeting epigenetic deregulation | E. Felley-Bosco |
| Polianthes Foundation | Overcoming development of resistance and progression to mesenchymal phenotype in mesothelioma | E. Felley-Bosco |
| Polianthes Foundation | Comprehensive investigation of predictive biomarkers for chemotherapy response and novel drug targets in patients with MPM by next generation sequencing | I. Schmitt-Opitz |
| Krebsforschung Schweiz | Mesoscape 001-pS6: Construction of a multi-institutional European tissue bank | I. Schmitt-Opitz |
| Swiss National Science Foundation | Magnetic resonance imaging for the detection of chronic lung allograft rejection in mouse lung transplantation | W. Jungraithmayr (Co-Applicant)<br>Applicant: PD Dr. A. Boss |
| Swiss National Science Foundation, Förderungsprofessuren | Malignant Pleural Mesothelioma - an integral approach for better outcome | I. Schmitt-Opitz |
| Forschungskredit der Universität Zürich | Attenuation of acute lung allograft rejection by CD26 inhibition – a preclinical model | W. Jungraithmayr |
| Stiftung für wissenschaftliche Forschung, Zürich | Lung tumor growth reduction by CD26 inhibition | W. Jungraithmayr |
| Assistenz-Professur an der UZH | Lungentransplantation | W. Jungraithmayr |
| Förderungsprogramm “Filling the Gap”, FTG-1617-02 | Attenuation of acute lung allograft rejection by CD26 inhibition – a preclinical model | W. Jungraithmayr |
| Hermann Klaus-Stiftung | Primary lung tumor growth inhibition by CD26 | W. Jungraithmayr |
| Innovationspool | Assessment and reconditioning of donor lungs with *ex vivo* lung perfusion system | I. Inci |
| Lungenliga Zürich | *Ex vivo* reconditioning of donor lungs with inhaled N-Acetyl cysteine after prolonged cold ischemia | I. Inci |
| Hermann-Klaus Stiftung | *Ex vivo* reconditioning of donor lungs with Trimetazidine after prolonged cold ischemia | I. Inci |

**Thoracic Surgery**

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|---|---|---|
| Hartmann-Müller Stiftung | *Ex vivo* reconditioning of donor lungs with inhaled N-Acetyl cysteine after prolonged cold ischemia | I. Inci |
| Hartmann-Müller Stiftung | The role of cytokine filtration during *ex vivo* lung perfusion | I. Inci |
| Lunge Zürich | MicroRNAs as prognostic and predictive tumor markers assisting the selection of patients with Malignant Pleural Mesothelioma for multimodality treatment | I. Schmitt-Opitz, M. Kirschner |
| 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 |
| Krebsliga Zürich | Prognostic Marker for Malignant Pleural Mesothelioma | I. Schmitt-Opitz |
| BECON AG Foundation | Prognostische Marker für das Maligne Pleuramesotheliom | I. Schmitt-Opitz |
| Vontobel Stiftung | MikroRNAs als prognostische und prädikative Tumormarker für die multimodale Behandlung des malignen Pleuramesothelioms | I. Schmitt-Opitz, M. Kirschner |
| Stiftung für angewandte Krebsforschung | 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 |
| EMDO-Stiftung, Zurich, Switzerland | Impact of sevoflurane anesthesia on primary graft dysfunction after experimental mouse lung transplantation | W. Jungraithmayr |
| Universität Zürich, Projektförderung (Abt. I-III) | Suppression of lung tumor growth by CD26/DPP4-inhibition | W. Jungraithmayr |
| Kurt und Senta Herrmann-Stiftung, Liechtenstein, VADUZ | Blockade of CD26/DPP4-costimulation to improve lung transplant survival | W. Jungraithmayr |
| Helene Bieber-Fonds | The CD26-costimlatory pathway is critical for Th17-mediated lung transplant improvement | W. Jungraithmayr |

**Urology**

| **Source** | **Title of Project** | **Project Leader** |
|---|---|---|
| Swiss National Science Foundation | Non-invasive monitoring of muscle precursor cell differentiation *in vivo* by magnetic resonance imaging | D. Eberli, Co-Applicant |
| Helmut Horten Stiftung | Cell-enriched hydrogel biomaterial with optimized release of NGF and VEGF for the improvement of innervation and functionality of bioengineered bladder tissue | D. Eberli |
| Janssen Pharamaceutica NV | Antitumor effect of androgen synthesis inhibitors and autophagy inhibition in prostate cancer cells | 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 |
| 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 | Cell-enriched hydrogel biomaterial with optimized release of NGF and VEGF for the improvement of innervation and functionality of bioengineered bladder tissue | D. Eberli |

### Urology

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|---|---|---|
| Helmut Horten Stiftung | The role of autophagy in the differentiation of adipose derived stem cells for functional smooth muscle tissue bioengineering | S. Salemi |
| Research Grant Innovations-Fond University Zürich for the clinical research project | Focal Therapy for Prostate Cancer | D. Eberli |
| Stiftung für Urologische Forschung | Prostate cancer-specific bispecific antibodies to prevent and treat metastatic castrate-resistant prostate cancer (mCRPC) | M. Provenzano |
| Commission for technology and Innovation (CTI) | Banking of human antibody repertoires for therapeutic use | M. Provenzano |

### Cranio Maxillofacial Surgery

| Source | Title of Project | Project Leader |
|---|---|---|
| Swiss National Science Foundation | The potential of N-methylpyrrolidone to prevent osteoporosis and to enhance bone regeneration | F. Weber |
| Swiss National Science Foundation | Osteoconductive and osteoinductive customized implants for large mandibular defects | F. Weber |
| EU-FP7 | Biomimetic nano-fiber-based nucleus pulposus regeneration for the treatment of degenerative disc disease | F. Weber |
| Swiss dental society, SSO | Cell homing during pulp regeneration in human teeth implanted in rodents | F. Weber |

### 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 |
| Vontobel-Stiftung | Biased PAR-2 Signaling by Thrombomodulin Bound Thrombin | R. Schüpbach |

### Veterinary Services

| Source | Title of Project | Project Leader |
|---|---|---|
| GV Solas Research Funding | Pain management in laboratory mice | P. Jirkof, |
| Swiss Federal Food Safety and Veterinary Office (FSVO) | Etablierung von effizienten Schmerzbehandlungsmethoden für die Labormaus | P. Jirkof,<br>M. Arras |

# 7. Awards 2015



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

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

- Magda Langiewicz
  **Young Investigator Award – Oetliker Prize**
  Swiss Physiological Society, Basel, Sept.2015

- Magda Langiewicz
  **ZIHP Symposium Best Poster Award**
  Zurich Center for Integrative Human Physiology (ZIHP), Zurich, August 2015

- Magda Langiewicz
  **Best Poster Award**
  14th Day of Clinical Research, Zurich, 9 April 2015

- Enrica Saponara
  **Best Basic Research Award**
  Department of Visceral and Transplantation Surgery, December 2015.

- Sabrina Sonda
  **Poster Prize**
  14th Day of Clinical Research, Zurich, 9 April 2015.

- Wolfgang Jungraithmayr
  **Experimentell-wissenschaftlicher Preis 2015**
  "CD26 Co-stimulatory blockade improves lung allograft rejection and is associated with enhanced IL-10 expression"
  UniversitätsSpital Zürich, Transplantationszentrum, Zürich, 20.11.2015.

- Wolfgang Jungraithmayr
  **Beste experimentelle freie Mitteilung**
  "Lung allograft acceptance by CD26 co-stimulatory blockade is due to a balanced expression of IL17 and IL10"
  Schweizerische Gesellschaft für Thoraxchirurgie, Bern, 25.11.2015.

- Etienne Xavier Keller
  **Jahrespreis 2015** for the Dissertation:
  "Antibody response to BK polyomavirus as a prognostic biomarker and potential therapeutic target in prostate cancer" (Oncotarget 2015, (6)8; 6459-6469)
  Faculty of Medicine, UZH 2015

- Ashkan Mortezavi
  **Poster Prize**
  "Inhibition of autophagy significantly increases the antitumor effect of Abiraterone in LnCap prostate cancer cells"
  Schweizerische Gesellschaft für Urologie (SGU), St. Gallen 2015

- Souzan Salemi
  **Poster Prize Stem Cell Research**
  "Synergistic effects of combining undifferentiated adult stem cells and differentiated cells for the engineering of functional bladder smooth muscle tissue"
  Annual Meeting of the European Association of Urology (EAU), Madrid 2015

- Christian Fankhauser
  **Forschungsförderungsprojekt (FFP)**
  Preis der medAlumni Zürich, 2015

- Dr. Paulin Jirkof
  **IQ Consortium and AALAC International Global 3Rs Award, 2015**
  Phoenix, Arizona, USA, November 2015

**Editorial**
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Prof. Dr. Rolf Graf, PhD

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