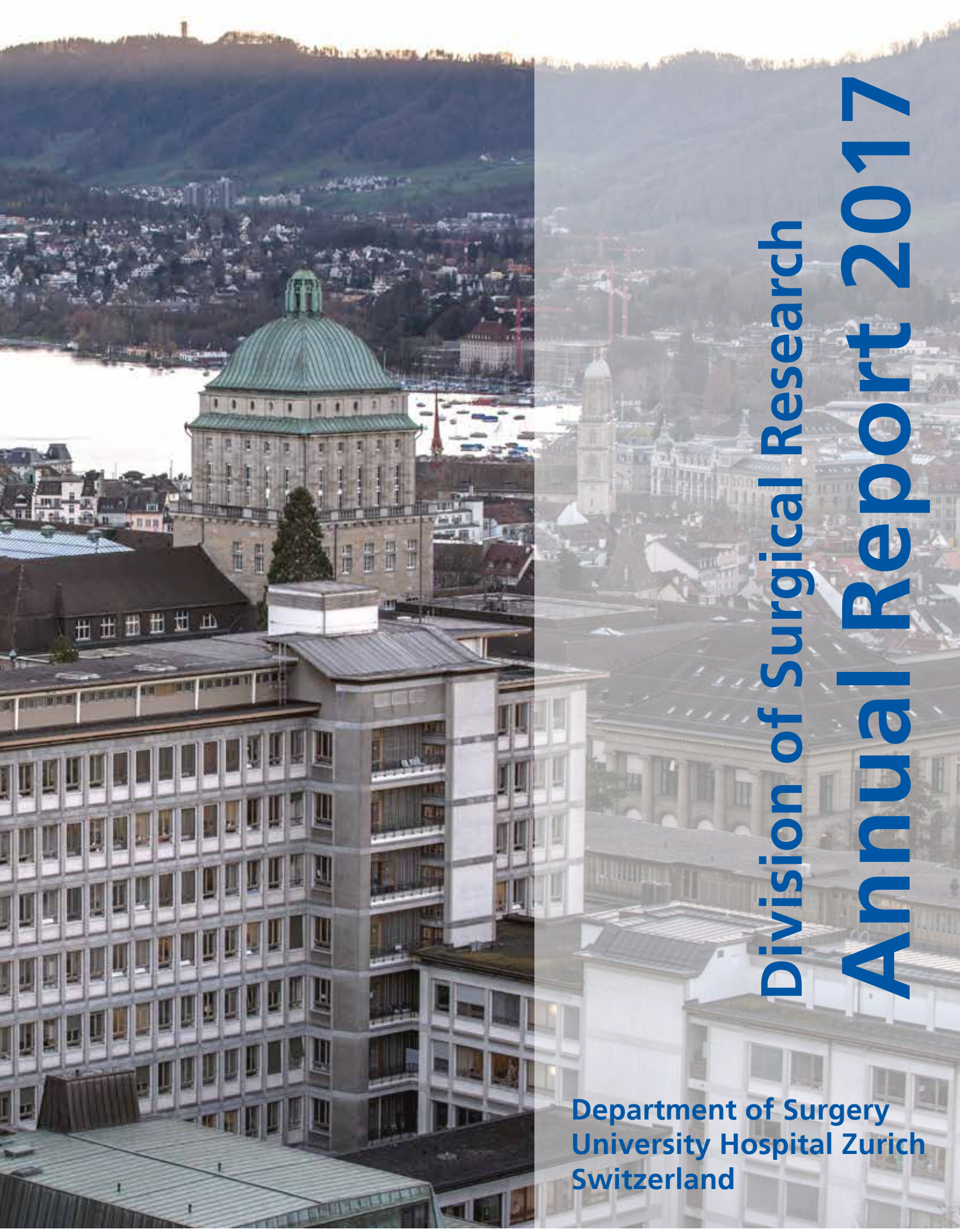

Annual Report 2017

Division of Surgical Research

Department of Surgery
University Hospital Zurich
Switzerland

University of Zurich[UZH]

UniversityHospital Zurich

Content

Preface

Dear Colleagues

The Division of Surgical Research had in 2017 again a very productive year. With more than 340 publications, some of them in prestigious Journals, we have straightened our role as a leading platform for basic, translational and clinical research in surgery. This success would not have been possible without the tremendous support of our central services: histology and immunohistochemistry labs, small and large animal labs and photography/graphics services. To mention are also the numerous interactions between the Labs of the Division of Surgical Research and other external scientific collaborators in Zurich and worldwide. Partners which we also would like to thank.
Besides research the Division of Surgical Research has also organized last year many symposia and courses integrating basic and clinical science to inform both specialists and laypersons.
The success of our research and excellent reputation leads to a constant expansion of our research groups, which confronts our team daily with a number of organisational activities. The main challenges are the management of the limited lab space and the optimisation of the infrastructure to provide modern and functional facilities for performing competitive research.
We would like to thank all members of the Division of Surgical Research not only for their excellent work, but also for the great atmosphere, the stimulating discussions and fruitful collaborations, which are essential for our future.

We wish to everybody a successful 2018!

Prof. Dr.
Rolf Graf,
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Prof. Margarete Arras, DVM
Co-Head Division of Surgical Research

1. Organisation

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Donata Gröflin
Teaching Coord.
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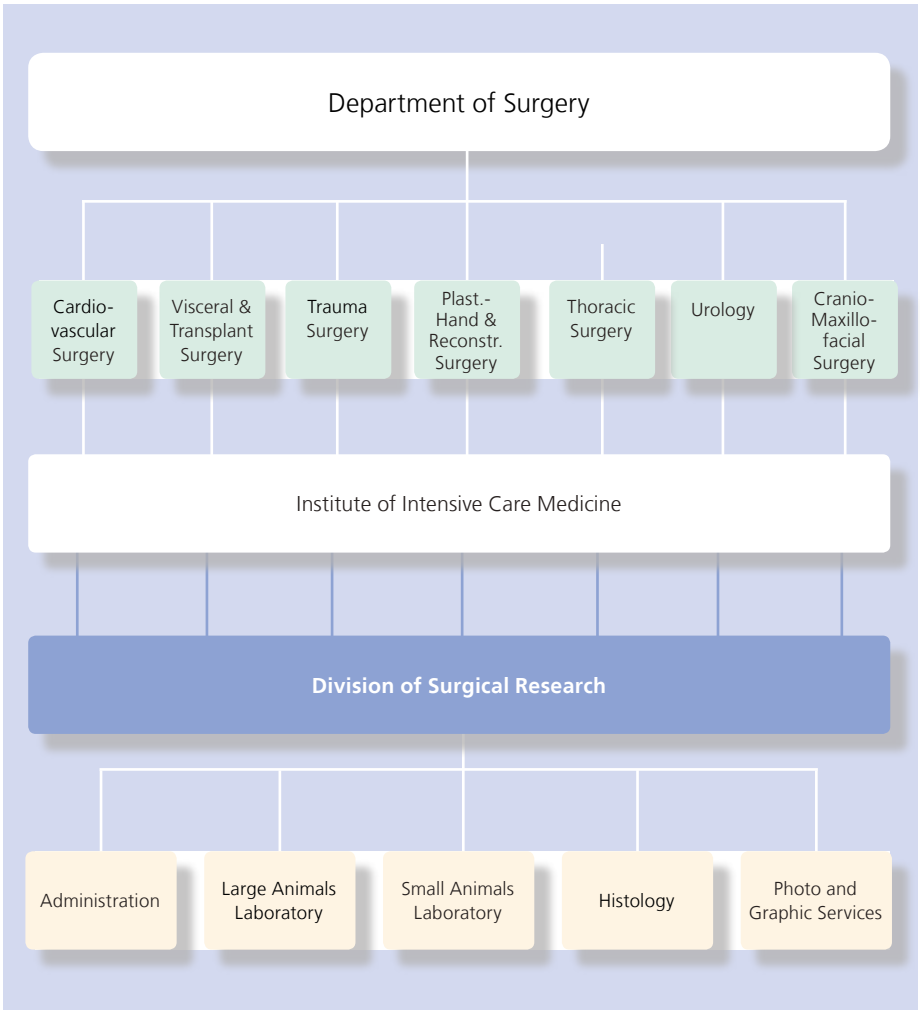
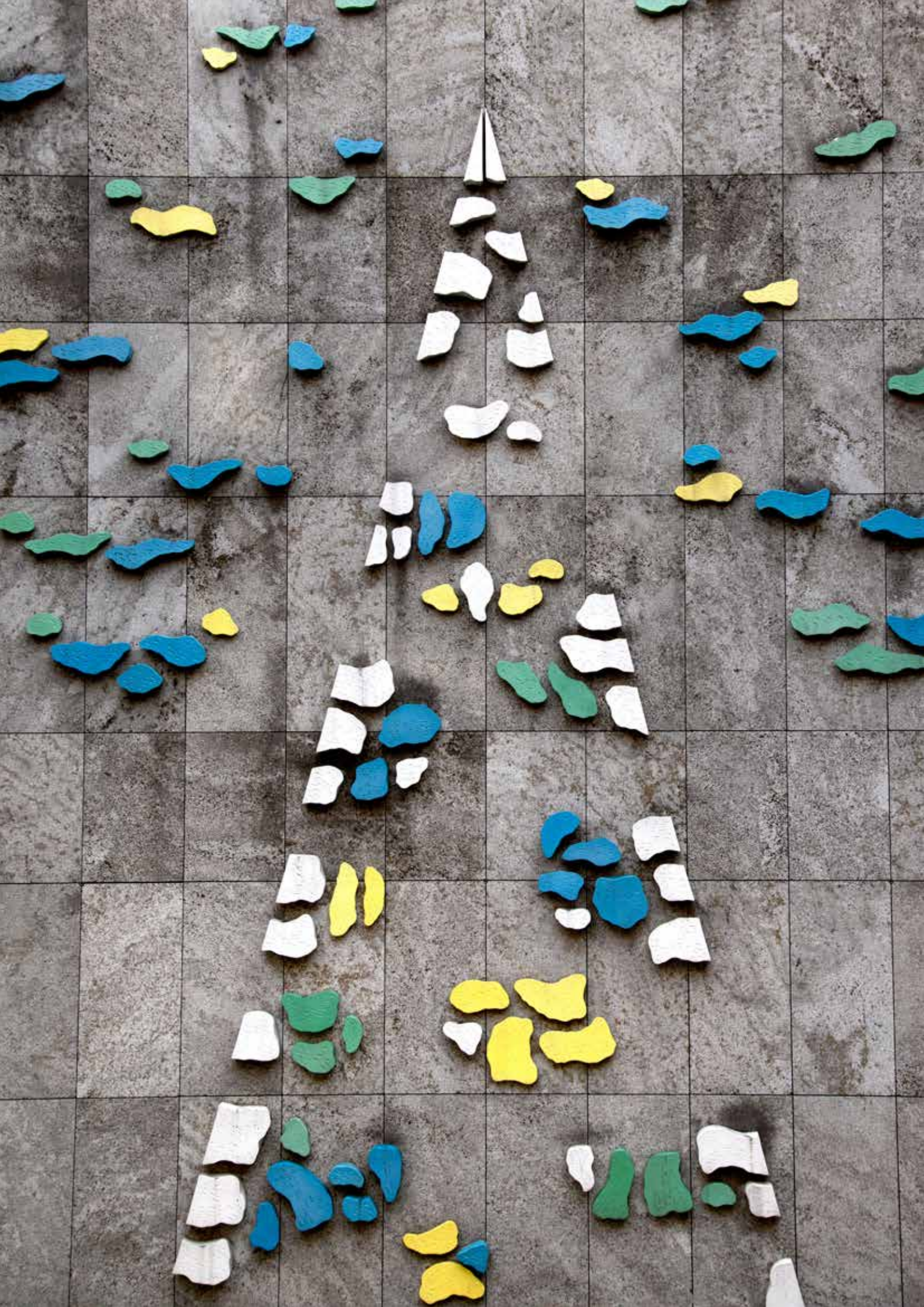
Position of the Division of Surgical Research
within the Department of Surgery



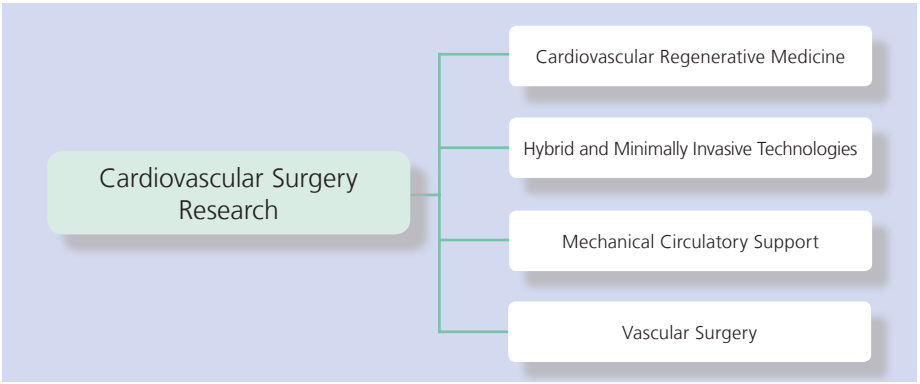


2. Research and Development

Cardiovascular Surgery Research

Prof. Dr. med.
Francesco Maisano,
Director

PD Dr. med.
Evelyn Regar, PhD



Valvular heart-disease and heart failure represent a major cause of mortality around the globe. Both entities are interdependent. The therapy options for affected patients with valvular heart disease are currently undergoing rapid changes and in addition to conventional, surgical valve replacement representing the standard of care since several decades, transcatheter techniques have entered the clinical-routine representing an efficient alternative for the treatment of elderly high-risk patients. Given sufficient long-term safety, it can be predicted that these minimally-invasive techniques may have a major impact on the treatment strategy of patients with VHD and will further be expanded to a broader and younger patient population.

On this background, the research of the department of cardiovascular surgery has a broad translational and multidisciplinary approach covering the ground from cellular and molecular biology to preclinical research to first in man and large scale clinical studies. Conceptually, we develop novel minimally invasive or transcatheter devices and treatment strategies for patients with valve and heart failure. To that end, our experimental research lines are as follows:

Novel Models for Heart Failure
Valve regurgitation is a pathological state where a unidirectional heart valve has become insufficient in its function and allows s blood to leak back. In consequence, the downstream blood ejection volume decreases, while the regurgitant blood volume causes overload in the upstream heart chamber. The upstream heart chamber undergoes morphological and cellular changes which can cause dysfunction and heart failure. The left ventricle undergoes thinning of the ventricular wall and remodeling of cardiac cellular structures attributed to prolonged stress caused by volume overload. These changes are believed to be irreversible and are involved in several features of heart failure. However, the exact mechanisms behind these adaptive phenomena of the left ventricle are still poorly understood. On this background, we develop and validate a novel murine animal model to study morphological and cellular changes in subacute left ventricular volume overload and afterload mismatch. This model allows to identify functional parameters and early biomarkers specific to left ventricular volume overload and remodeling; to investigate blood and tissue biomarkers known to be elevated in chronic left ventricular remodeling at early stages of left ventricular volume overload; to investigate early changes in myocardial fiber architecture as well as myocardial metabolism by means of Dynamic Nuclear Polarization and Diffusion Tension Imaging, to study cellular, subcellular and metabolic characteristics of early signaling and response.

Next generation bioengineered implants
Congenital heart defects represent a major cause of death around the globe. Although current therapy strategies have rapidly developed over the last decades, the currently used artificial prostheses are still considered to be suboptimal. They do not promote regeneration, physiological remodeling or growth (particularly important aspects for children) as their native counterparts. This leads to the continuous degeneration and subsequent failure of such substitutes which is associated to an increased morbidity and the need for multiple re-interventions. To overcome this problem, the concept of regenerative medicine comprising of tissue-, bio- engineering and hybrid technologies has been suggested as a next generation approach to enable native-like cardiovascular replacements with regenerative and growth capacities, amendable to young adults and children. However, despite promising data from preclinical and first clinical pilot trials, the translation and clinical relevance of such technologies is still very limited. The reasons for that are multifaceted and comprise of scientific, logistical, infrastructural and regulatory challenges that need to be systematically addressed in order to facilitate clinical translation of such next generation cardiovascular substitutes.

Development of Novel Devices
Development of novel devices is frequently performed in collaboration with industry partners and often based on own intellectual property. We investigate feasibility and safety in the porcine model, and work towards optimization of device characteristics, investigating hemodynamics, ventricular and device function in

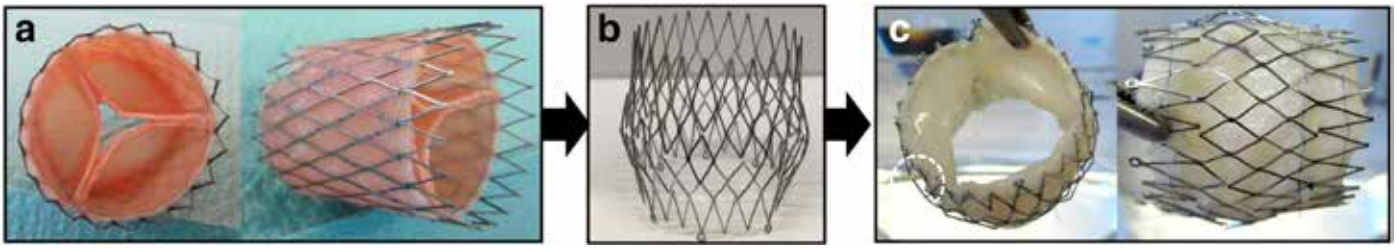


Figure 1: Manufacturing Tissue Engineered Transcatheter Sinus Valve (adapted from Motta & Emmert et al., Journal of Cardiovascular Translational Research, 2018)

detail and assessing long-term effects in order to prepare for translation into clinical application. Various devices designed to allow for minimally invasive or percutaneous treatment of mitral valve regurgitation, tricuspid valve regurgitation, chorda replacement and ventricular aneurysm were evaluated.

Development of novel strategies for procedural planning and guidance

A novel minimally invasive device typically asks for specific procedural planning and intra-operative, imaging based guidance. This is especially true as the heart is a 3D moving structure and many technologies,that allow for real-time imaging are restricted to 2D visualization, while others, such as MRI and CT are not available for the operator in the hybrid operation room and/or not suited to allow for direct manipulation with therapeutic devices. We focus on developing new approaches for the fusion of several imaging techniques, such as MRI, CT and echocardiography with fluoroscopy in real time in order to optimize catheter based procedures, to reduce X-ray contrast volume and radiation exposure.

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
- 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)
- Experimental Cardiology Unit, Department of Medicine, University of Lausanne Medical School, Switzerland
- 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)
- 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)

Awards:

M. Taramasso: TCT Linnemeier Young Investigator Award 2017
M. Taramasso: Habilitation “Transcatheter tricuspid valve therapies: the next frontier of structural valve intervention”
D. Reser: Habilitation “Minimally invasive cardiac surgery”

Figure 2: Multidisciplinary team during an experiment requiring open-chest heart surgery with heart-lung machine in the animal hybrid operation room, including cardiac surgeons, cardiac perfusionist, echocardiographer, veterinarian anesthesiologist, veterinarian specialized in porcine cardiac interventions and biomedical engineer.

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Dr. med.
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Dr. med.
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Study Nurse

Alice Birkner,
Study Nurse

Michael Stader,
Study Coordination,
Administration

Simone Frank,
Study Coordinator


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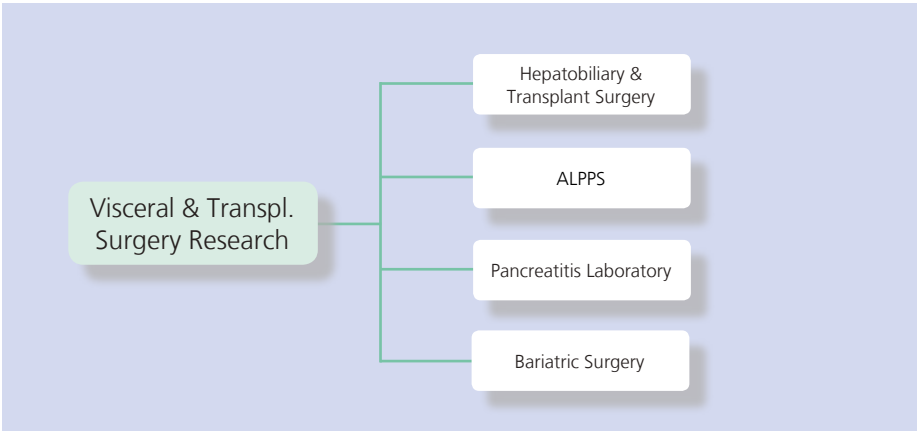
BINDER

Visceral & Transplant Surgery Research

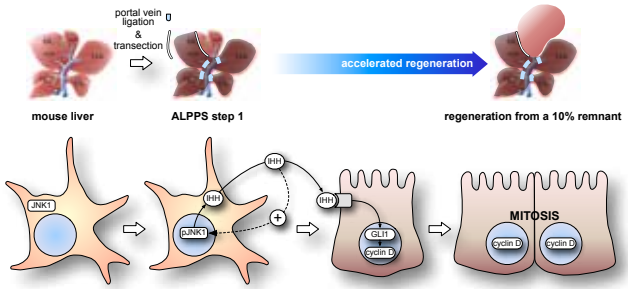


Prof. Dr. med. Pierre-Alain Clavien, PhD, Director

Prof. Dr. Rolf Graf

Surgeon scientists and basic scientists within the Department of Visceral & Transplant Surgery work together towards clinically relevant translational studies. The research teams are focused on multiple aspects of surgical research, such as designing novel surgical techniques (relevant to transplantation or liver regeneration), understanding the pathogenesis of pancreatitis, applying bariatric surgery to treat metabolic disorders, and developing strategies to enable the surgical treatment of visceral malignancies. Likewise, the identification of molecular mechanisms associated with above translational studies is explored using animal models.

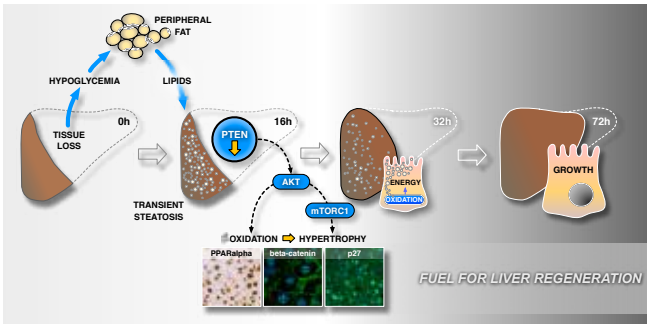
Multiple animal (mouse and rat) models have been developed to understand and explore clinically relevant surgical procedures, including arterialized orthotopic liver transplantation, transplantation of critically small grafts, normal liver regeneration (68%-hepatectomy), or failed (86%-, 90%-hepatectomy) and accelerated (ALPPS surgery) liver regeneration. Based on these, we identified the first molecular mechanism (paracrine JNK1-IHH signaling between stellate cells and hepatocytes) underlying the acceleration of regeneration through ALPPS. Furthermore, we discovered



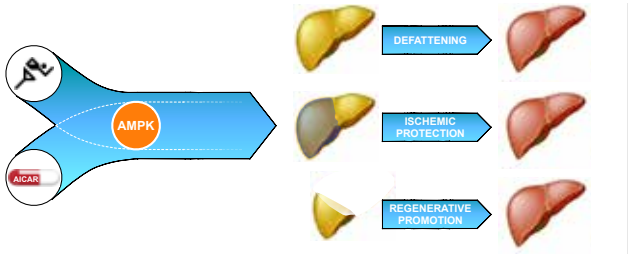
Parakrine JNK1-IHH signaling from stellate cells underlies the accelerated hepatocyte proliferation following ALPPS surgery

that lipids are the prime fuel of the regenerating liver and that the promotion of their catabolism can protect from liver failure. Combining our surgical models with dietary induction of fatty liver disease, we were able to show that fish oil is efficient in normalizing the metabolic state of fatty liver while improving its stress tolerance and its regenerative capacity.

In parallel, we have designed syngeneic orthotopic mouse models of metastasizing colorectal cancer, of liver metastasis, and of liver cancer. In these models, we demonstrated that oxygenation through the novel molecule ITPP counteracts metastasis and enhances efficacy of chemotherapy. Following our landmark discovery of serotonin for liver regeneration, we now deciphered novel immunomodulatory properties of the neurotransmitter that may be exploited for cancer therapy. Importantly, the results from our basic researched animated the initiation of novel clinical & outcome studies.

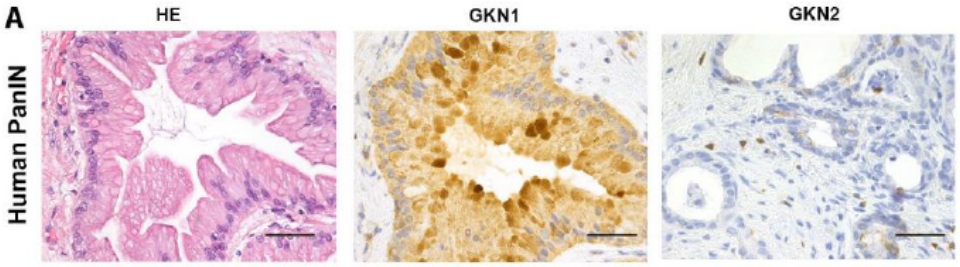


Peripheral lipids are oxidized in the liver to fuel hypertrophic regeneration in a PTEN-dependent way



Akin to exercise, the AMP analog AICAR improves metabolic function, stress tolerance and regenerative capacity of fatty liver.

The pancreas laboratory has explored molecular events involved in the pathogenesis of pancreatitis. Through mouse models of chronic, acute and autoimmune pancreatitis, we uncovered the epigenetic regulation of pancreatitis, and developed mouse models of gastric bypass to study molecular mechanisms responsible for changes in appetite, eating behavior, food preferences, and normalization of diabetic symptoms following metabolic surgery.



Gastrokine (GKN1 and GKN2) expression in human premalignant PanIN lesions

could dissociate acute from chronic pancreatitis in terms of pathobiology. Moreover, assessing the sequence of pancreatic metaplastic changes associated with cancer progression, we identified pancreatic gastrokine secretion as a potential disease modulator. Finally, longstanding clinical and experimental projects have established pancreatic stone protein (PSP) as a reliable marker of sepsis in the clinic.
Bariatric, or metabolic, surgery - performed to reduce obesity - meanwhile is known to lead to rapid resolution of type 2 diabetes. How this occurs mechanistically is unanswered. The recently established laboratory of bariatric surgery has

In recent times, the combination of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) has significantly enhanced survival of patients suffering from peritoneal carcinomatosis (PC). To understand the mechanisms behind HIPEC, a new research group was established. Using an original PC mouse model, we observed that HIPEC seems to lead to a better recognition of cancer cells by the immune system. These findings have stimulated a program for the study of HIPEC and cancer immunogenicity as to improve HIPEC efficacy.

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. Maries van den Broek (University of Zurich)
- Prof. Jean-Marie Lehn (University of Strasbourg)
- Prof. Gregory Gores (University of Minnesota Majo Clinics)
- Prof. Scott Friedmann (New York University Mount Sinai School of Medicine)
- PD Dr. Andreas Boss, Department of Radiology USZ
- PD Dr. Deborah Stroka (University of Bern)
- Prof. Dr. Mathias Heikenwälder, PhD, (TUM Munich)
- Prof. Dr. Adrian Hehl, MD, (University of Zurich)
- Prof. Dr. Achim Weber, MD, Department of Pathology USZ
- Prof. Aurel Perren (Universität Bern)
- Prof. Arnold von Eckardstein, Department of Clinical Chemistry USZ
- Prof. Thorsten Hornemann, Department of Clinical Chemistry USZ
- Prof. Martin Pruschy (University of Zurich)
- Dr. Daniela Lenggenhager (University of Zurich)
- Dr. Johannes vom Berg (University of Zurich)
- Prof. Philipp Rudolf von Rohr (ETH Zurich)
- PD Dr. Martin Hübner (CHUV, Lausanne)
- Various clinical collaborations

Awards:

Michael Linecker: ARS Preis SGC 2017 - Exercise improves outcomes of surgery on fatty liver and can be substituted through AMPK activation - an experimental study
Michael Linecker: Travel grant, International Congress of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) Mainz
Gitta Seleznik, Sabrina Steiner, Ermanno Malagola: Travel Grant, European Pancreas Club Meeting Budapest
Sabrina Steiner, Rong Chen: Travel Grant, Hartmann Müller Foundation
Anurag Gupta, Gitta Seleznik: Travel Grant, United European Gastroenterology Week Barcelona
Zhuolun Song: 16th Day of Clinical Research Prize USZ

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Joel Zvick,
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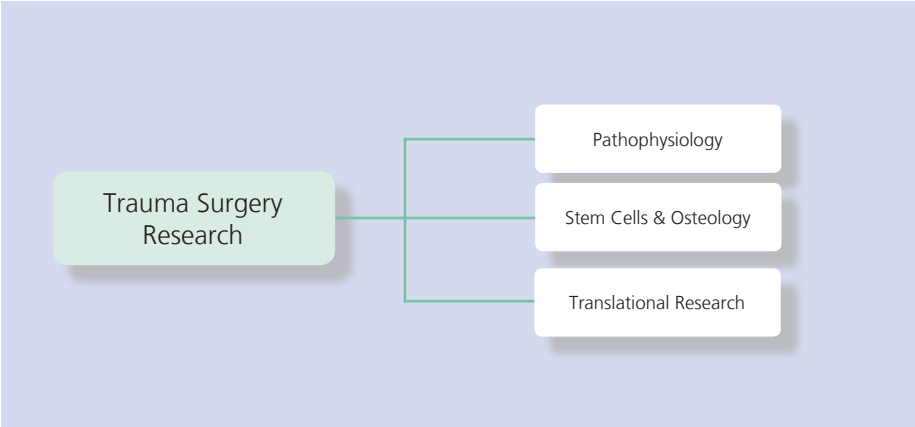
Trauma Surgery Research



Prof. Dr. med. Hans-Christoph Pape, Director

PD Dr. sc.nat. Paolo Cinelli

We are interested in all aspects of research that can improve treatment of severely injured patients at basic, translational and clinical levels. Our main interests are the study of the pathophysiology of trauma, the development of regenerative approaches for improving bone healing and the impact and treatment of fractures in older patients. To approach these clinically relevant challenges we have built a team of surgeon scientists and basic scientists that closely work together.

Pathophysiology of trauma

Traumatic injuries induce a complex host response that disrupts immune system homeostasis and trigger a systemic inflammatory response that predisposes patients to opportunistic infections and inflammatory complications leading 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 combining clinical data and gene expression changes (clinico-transcriptomics). This approach is useful to improve the prognostic performance and individual risk stratification in trauma patients. We could for example identify leukocytes, thrombocytes combined with the expression of sphingosine kinase-1 (SPHK1), complement C5, and haptoglobin (HP) as reliable prognostic markers. Patients with sepsis exhibit for example significantly higher leukocyte levels. 'Relative thrombocytopenia' can be associated with the risk of multi-organ dysfunction, the development of sepsis, and mortality, the latter of which can be predicted by our new approach within 3 days prior to the time point of death. C5-expression on day 1 after trauma correlates with an increased risk for the development of nosocomial infections during the later course, while HP was found to be a marker for the development of sepsis. We are further dissecting the molecular mechanisms underlying these physiological changes by using animal models. We have successfully developed a porcine polytrauma model and are analyzing locally, at the site of injury, and systemically how inflammation and immune response are initiated and how they are regulated.

Stem Cells & Osteology

Fractures with "critical size defects", which are bone fractures producing a gap that is not able to heal completely from alone over a long period of time represents a major clinical orthopedic surgery. The gold standard treatment is the use of autogenous bone grafts in combination with alloplastic material. Usually the iliac crest is used as a donor site for bone harvesting. Nevertheless, this procedure has some drawbacks for clinical applications, such as limited availability of bone graft, morbidity, and donor site pain. Alternatively, biocompatible materials can be used but unfortunately, to date no single synthetic material offers all the benefits of the patient's own bone. Tissue engineering represents a very promising technique, which combines the use of stem cells with scaffold of synthetic or natural biomaterial together with molecular signals, such as growth or differentiating factors. Mesenchymal stem cells (MSCs) represent a good source of regeneration-competent cells. They can be isolated from a variety of tissues and are able to differentiate under the right culture conditions, into osteoblasts, chondrocytes, and adipocytes. The major problem with the use of MSCs isolated from bone marrow or fat tissue is that the isolated cells contain heterogeneous populations of stem and progenitor cells. Thus, for the clinical use of MSCs for regeneration purposes, it is urgently needed a better characterization of the cells and a standardization of the isolation and culture protocols. In our studies we test the possibility to enrich defined subpopulations of stem/progenitor cells for direct therapeutic application without requiring an *in vitro* expansion. The most promising enriched stem cells populations are tested for their regeneration capacity in mouse models. For the identification of new cell subpopulations we employ modern technologies like Cytometry by time-of-flight (CyTOF) allowing the real-time analysis of single cells in complex populations. Single cells, labelled with stable heavy metal isotopes are

analyzed by a combination of classical flow cytometry and mass spectrometry analysis. We are further interested in understanding the molecular mechanisms involved in stem cell maintenance and differentiation. We could for example recently identify a yet unknown factor, called Pramel7, which is essential for the establishment of pluripotent stem cells, which are cells able to produce all cell types of the body (Graf et al. Nature Cell Biology 2017). We are also developing new scaffolds for bone regeneration by combining synthetically produced scaffolds with extracellular matrix (ECM) produced by stem cells (collaboration with Prof. Wendelin Stark and Olivier Gröninger, ETH). Stem cells are first seeded on electrospun scaffolds. After cultivation, the cells deposit on the scaffold surface ECM components and hydroxyapatite. In further step the scaffolds are being decellularized thereby eliminating the cells from the scaffold surface but retaining the ECM components and hydroxyapatite (Figure 1).

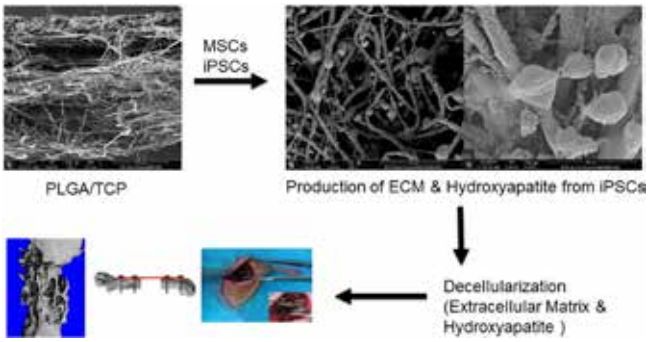


Figure 1: Preparation of scaffolds with extracellular matrix components (Simon Tiziani, Olivier Gröninger).

The scaffold can be then stored and used when needed. This approach allows the preparation of off-the-shelf bone graft substitutes with low risks for rejection promoting constructive remodeling of bone tissue and eliciting various biologic responses including angiogenesis and chemotaxis of bone forming cells. We finally test our scaffolds in a mouse model for critical size bone injury.

Geriatric Traumatology

The population worldwide is ageing and life expectance is steadily increasing. This demographic transition raises concerns about the growing incidence of age-related diseases, including osteoporosis. This disease is characterized by a decrease in bone density and quality, making it prone to sustaining fractures with low-energy injuries (osteoporotic fractures) often as consequence of a fall from a standing height. Osteoporotic fractures are associated with high rates of morbidity and mortality and the overall cost of treatment is very high. The role of trauma surgery in older patients is therefore of great importance. The main goal of treatment is to provide stable fixation that allows early weight bearing and mobilization. Our research focuses on one side in optimizing the surgical procedures by assessing through biomechanical testing the stability of different osteosynthesis devices. On the other side we aim at studying the cellular events underlying the development of osteoporosis. A current hypothesis is that a decrease in the number and function of bone and bone marrow derived MSCs is responsible of age-related bone loss. In a current clinical study, we are making use of our newly developed cytometry by time-of-flight technology to monitor at single cell level the changes occurring in MSCs isolated from osteoporotic bone upon fracture (Figure 2).

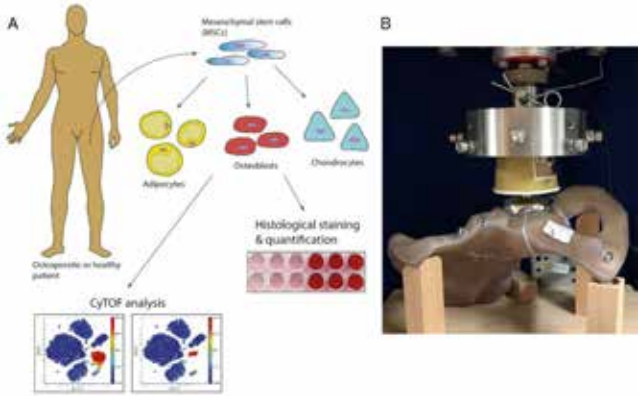


Figure 2: A. Strategy for the analysis of differences in differentiation potential in stem cells from healthy and osteoporotic patients (Benjamin Eggerschwiler). B. Example of measuring setup for measuring stability of screw fixation of ACPHT acetabular fractures (Georg Osterhoff).

Awards:

Hans-Christoph Pape: Dieffenbach-Büste Prize 2017, Deutsche Gesellschaft für Unfallchirurgie

Collaborations/Sponsors:

- Clinical Trials Center, University Hospital Zurich
- Orthopedic Research Laboratory, Biomechanics, University Hospital Balgrist, Zurich
- Jan Schwab, Klinik und Poliklinik für Neurologie & Experimentelle Neurologie, Charité Universitätsmedizin Berlin
- Institute for Biomechanics, ETH, Zurich
- Center for Applied Biotechnology and Molecular Medicine (CABMM), University of Zurich
- Markus Huber-Lang, Dept. of Traumatology, Hand-, Plastic and Reconstructive Surgery, University Hospital Ulm, Germany
- Michael Bauer, Institute for Anesthesiology and Intensive Care Medicine, University Hospital Jena, Germany
- Martijn van Griensven, Department of Experimental Trauma Surgery, Klinikum rechts der Isar, Technical University of Mu nich, Munich, Germany
- Armin Curt, Spinal Cord Injury Center, University of Zurich and University Hospital Balgrist
- Manfred Claassen, Institute for Molecular Systems Biology, Department of Biology, ETH Zurich, Switzerland
- Wendelin Stark, Olivier Gröninger, Institute for Chemical and Bioengineering, Department of Chemistry and Applied Bio-sciences, ETH Zurich, Switzerland.
- Todd McKinley, Indiana University, Purdue University, Indiana, USA
- Translational Large Animal Research Network (TREAT)

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Paolo Cinelli

PD Dr. med.
Roman Pfeifer

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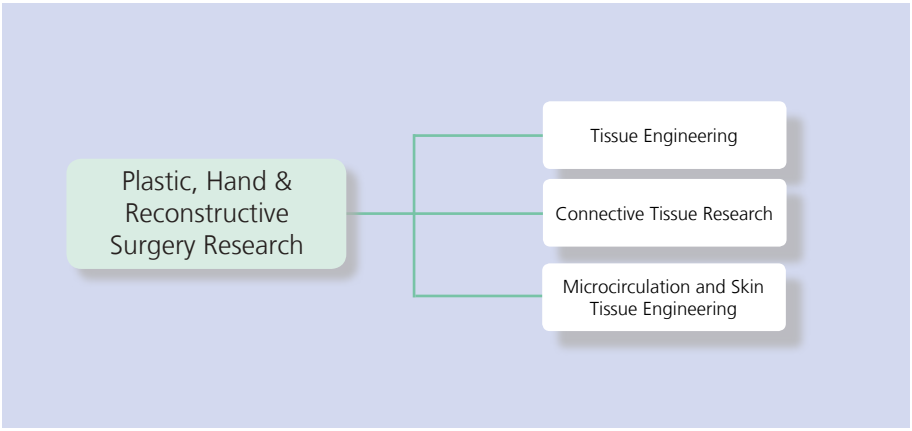
Plastic, Hand & Reconstructive Surgery Research



Prof. Dr. med. Pietro Giovanoli, Director

PD Dr. med. Maurizio Calcagni

Research activities in the Plastic Surgery and Hand Surgery lie in the fields of microcirculation, wound healing, connective tissue research, skin grafts, motion analysis, inflammatory biomarkers in burns, HLA sensitization in burns and vascularized composite allotransplantation:

Microcirculation and Wound Healing

For 2017, the Microcirculation and Skin Tissue Engineering group led by Prof. N. Lindenblatt has taken on new applications of the dorsal skinfold chamber mouse model. From the vascularization of biomaterials, to wound healing, and pre-clinical proof-of-concept of pharmaceuticals, they have shown that this classical model can be utilized for more than its traditional use.

In collaboration with Topadur Pharma AG and financed by the Commission of Technology and Innovation (CTI – Innosuisse), they are currently performing a preclinical study in diabetic mice to test the efficacy of a pro-angiogenic novel compound. The compound can be potentially used to treat diabetic foot ulcers. Furthermore, the Lindenblatt group is strongly involved in a multidisciplinary collaboration for the Hochschulmedizin Zurich Flagship 2016 Project “Skintegrity”, where innovative approaches for diagnosis and therapy of skin diseases and of wound healing will be investigated.

Finally, the group is investigating through mass spectrometry and molecular biology methods the underlying molecular mechanisms that contribute to the regenerative properties of autologous fat graftings (microfat and nanofat. Figure 1). The successful identification of factors involved in nanofat’s regenerative properties may lead to advantageous therapeutic benefits, resulting in direct clinical translation and research application in regenerative medicine.

Connective Tissue Research and Tissue Engineering

In collaboration with the ETH Zurich (Prof. Vogel) and the company ab medica, Italy, tendon rupture repair by an implant has been optimized: an emulsion electrospun and a coaxially electrospun DegraPol® tube that is biocompatible, biodegradable and very elastic, enabling the surgeon an easy handling during implantation has been developed and tested in the full transection rabbit Achilles tendon model. Biomechanical results are promising and further pre-clinical experiments are planned.

Furthermore, bone tissue engineering *in vitro* is performed and several new approaches including bioreactors are conducted (collaboration with Prof. Stark ETH Zürich). Two-dimensional and three-dimensional stem cell cultures were compared using the same materials and gene expression patterns were analyzed. Varying compression and perfusion regimen triggered different stem cell commitment.

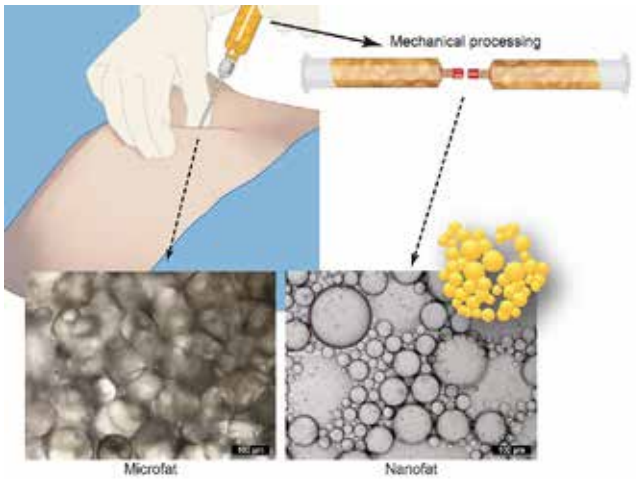


Figure 1: Microfat is harvested using 2.7 mm cannulas with 1mm holes and contains viable adipocytes as well as stromal vascular fraction. It is applied to achieve a volume effect, e.g. in soft tissue correction of the face. Nanofat is gained by further processing using mechanical shuffling and filtering through a titanium mesh with a predefined pore-sitze, which destroys the adipocytes. Nanofat can be used if no volume effect is intended to improve skin properties.

Kera-Sheet Innovation Project
The project's main aim is to produce reliable, safe and traceable autologous keratinocyte sheets (Figure 2, cultivated epidermal autograft, CEA) to treat patients in the burn unit of the USZ, all the while providing the surgeons with a window of flexibility in order to optimize the grafting date to the health of the patient.
The team of PD Dr. med. Maurizio Calcagni has established a method to produce cultured autologous keratinocyte grafts from human skin biopsies without the need for any xenogenic risk components such as feeder layer (murine or others) or bovine serum. The methodology has been reliable in over 100 biopsies processed to date. Furthermore, we have also established a protocol to produce a live graft as early as 18 days after biopsy harvest. We have also shown the stability of the graft up to 25 days after biopsy harvest. This, we anticipate, would give surgeons a much wider window to graft their patients.
Once our production protocol is validated in GMP, the impact on the health of burn patients is expected to be very important. Further expanding the range of autologous keratinocyte products produced in-house, within UZH/USZ, will impact a larger population of patients needing wound-healing enhancement.

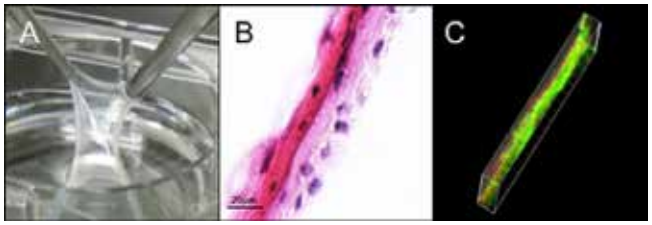


Figure 2: A) Cultivated Epidermal Autograft, CEA, B) Hematoxylin Eosin staining, C) Live (green)-Dead (red) staining

3-D motion analysis of the finger and wrist during activities of daily living
In assessing hand motion during daily activities, we aim to quantify hand function or recovery after a medical treatment. The three dimensional motion analysis sets the underlying methodology in order to achieve a high level of standardization and objectivity.
Within the motion analysis project we introduced a new marker set and three-dimensional data analysis routine for the kinematic measurement of fingers, thumbs and wrist joints. Test-retest repeatability was validated with positive outcome on a group of 20 healthy volunteers. Individual joint centers and orientations were mathematically derived by means of a set of basic motion tasks. Additionally, 10 selected activities of daily living were investigated focusing on range of motion and test-retest repeatability. The estimated accuracy and repeatability of the new measurement routine was better than normally accepted for studies of clinical relevance and outperformed the well established manual measurement with a goniometer.
Based on the positive results with the volunteering group, clinical measurements of patients with wrist pathologies could be started in November 2017. The application of the new three-dimensional motion analysis routine will continue in 2018 for patients with major injuries of the hand.

Regenerative and Reconstructive Plastic Surgery Group (Prof. Jan Plock)
The "Regenerative and Reconstructive Plastic Surgery Group" moved to the new facility in Schlieren. With an assistant professorship for group leader Jan Plock by UZH/USZ the group was able to establish the new laboratory. We are also very grateful for support from the motion analysis group in our department (PD Dr. Calcagni) with regards to establishing a motion analysis system for rodents.

The experimental focus of the group is on immunomodulatory and regenerative translational aspects of mesenchymal stromal cell application. The clinical studies are prioritizing regenerative therapies, reconstructive procedures and analysis of biomarkers in severe burns. Research in Prof. Plock's laboratory therefore targets the aspect of individualized treatment with an ultimate goal for personalized medicine.

Experimental Studies

Vascularized Composite Allotransplantation
On the basic science level, the group is investigating novel conditioning protocols to improve graft tolerance and possibly reduce the need for immunosuppressive drugs, combining modern immunosuppressants and tailored local or systemic cell therapy. Collaboration with the Department of Clinical Research in Berne (Prof. Dr. R. Rieben and Dr. Adriano Taddeo), Prof. V.S. Gorantla (Wake Forrest University) and Prof. J.P. Rubin (Univeristy of Pittsburg) has been productive in this regard.
Further, we investigate the potential of stem cell administration and their mechanisms for reduction of graft vasculopathy in acute and chronic rejection. Development of vasculopathy is hampering functional regeneration and jeopardizing graft survival.
To evaluate novel immunomodulatory therapies in terms of functional outcome, we have established dynamic testing by means of video-recorded swim tests for rodents. With the support of Prof. Martin Schwab's group (ETH) we have been able to build up a refined video motion analysis system.

Clinical Studies

Inflammatory biomarkers in burns
Severe burn injuries hold a special position in sepsis research due to vast wound surfaces inducing various inflammatory cascades. Differentiation between sterile inflammation induced by the burn injury per se in combination with subsequent surgical trauma and the state of sepsis sec-

ondary to infection often remains difficult, but is crucial for survival. Canonical biomarkers (CRP, leucocytes, PCT) often fail in that respect. Pancreatic stone protein (PSP) has recently emerged as promising diagnostic and prognostic marker. Our preliminary analyses of 26 post burn patients suggested serum PSP levels to be strongly associated with the presence of infection and mortality irrespective of the patients' age and total burned surface area. In that way, PSP might serve as helpful biomarker for timely identification of patients needing intensified medical care. So far, we have included nearly 100 patients giving rise to a comprehensive data-/biobank. As to that, future analyses will also address inflammatory biomarkers in burns beyond PSP in collaboration with the Center for Clinical Research (Prof. Dr. R. Graf) and the Department of Traumatology (Prof. H.-C. Pape and PD Dr. P. Cinelli). Comparing burns and polytrauma with distinctive molecular biomarker analysis will allow for improvements of individualized decision making. (ClinicalTrials.gov ID # NCT02537821)

HLA sensitization in burns
Since the inception of clinical reconstructive allotransplantation, burn victims have been identified as immunologically complex patients for these procedures due to preformed (HLA) antibodies. Yet it remains unclear whether detected HLA antibodies are the result of previous alloantigenic events or de novo formation of antibodies resulting from primary burn care. With support from the HLA laboratory at the University Hospital Zurich (Department of Immunology, Prof. Dr. O. Boyman and Dr. J. Nilsson) we have been able to show that the formation of HLA antibodies during acute burn care might be lower than previously expected. By using glycerol-preserved donor skin along with restrictive administration of blood products only 3 out of 37 patients demonstrated verified de novo sensitization during acute burn care in our cohort. Accordingly, modern concepts of burn care may contribute to a revised outlook on burn patients as potential candidates for VCA. (ClinicalTrials.gov ID #NCT02537821)

RE-ENERGIZE - A RandomizEd trial of ENtERal Glutamine to minimIZE thermal injury
More than in any other injury, the inflammation and catabolism associated with severe burns can exacerbate nutrient deficiencies, thereby predisposing patients to impaired immune function and increased risk of developing infectious complications, organ dysfunction, and death. Glutamine is thought to be vital for a number of key stress-response pathways in serious illness. As the largest burn center in Switzerland, the Division of Plastic Surgery and Hand Surgery is participating in an international multi-center trial that is double-blinded, pragmatic and randomized). The trial examines the effects of glutamine in burn patients, with the hypothesis that the administration of glutamine to burned critically ill patients is associated with improved survival and a quicker rate of recovery. The primary outcome is the 6 month mortality, and secondary outcomes comprise the time to discharge alive from hospital, ICU and hospital mortality and length of stay, health-related quality of life and the cost-effectiveness of glutamine administration. (ClinicalTrials.gov ID #NCT00985205)

Denovoskin (TBRU-dS-BA-PIIb)
In collaboration with the tissue biology research unit (Prof. Dr. E. Reichmann), the Pediatric Surgery team at Children's Hospital (Prof. Dr. M. Meuli and PD Dr. C. Schiestl) and Wyss Zurich we have started collaboration for two clinical trials on engineered autologous skin substitutes. In acute patients and for reconstructive purposes Denovoskin a dermo-epidermal skin graft is compared to split-thickness skin grafting as standard of care. (EudraCT Number 2017-002462-41)

Collaborations:

- Dr. Aldo Ferrari, PhD, Dr. Simone Bottan, PhD. Hylomorph AG and Laboratory of Thermodynamics in Emerging Technologies. ETH Zurich
- Prof. Dr. Sabine Werner, Laboratory of Tissue Repair and Cancer, ETH Zurich
- Topadur Pharma AG, Schlieren
- Ast. Prof. Dr. Tomás Egaña, PhD, Pontificia Universidad Católica de Chile, Santiago, Chile, and TUM Munich, Germany
- PD Dr. Andrea Banfi, PhD, Cell and Gene Therapy, Department of Biomedicine, University Hospital Basel
- Dr. Katrin Kerl, Department of Dermatology, University Hospital Zurich
- Prof. Dr. Brigitte Vollmar, MD, Institute for Experimental Surgery, University of Rostock, Germany
- Prof. V. Vogel, PhD, ETH Zurich
- Prof. W.J. Stark, PhD, ETH Zurich

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Anna Wang,
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Sonja Märsmann,
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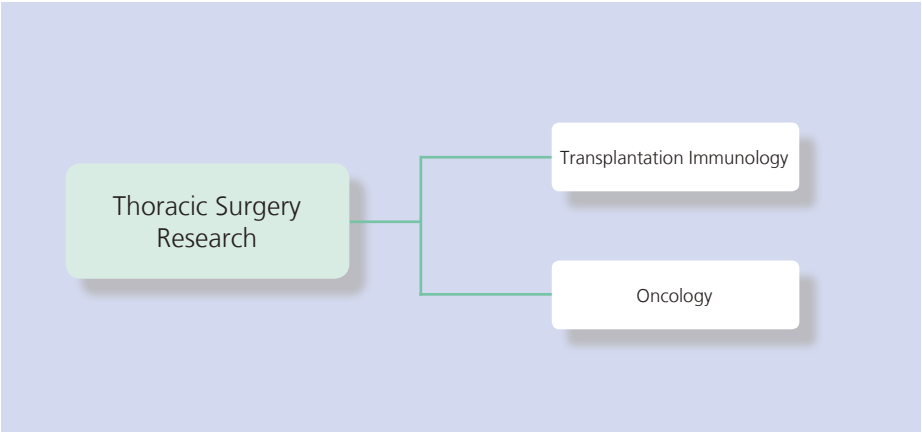
Thoracic Surgery Research



Prof. Dr. med. Walter Weder, Director

Prof. Dr. med. Isabelle Opitz

Research in thoracic surgery focuses on different areas, such as oncology and transplantation.

Malignant Pleural Mesothelioma (MPM)

One of the topics in cancer research is the development of therapeutic strategies for MPM, an incurable thoracic malignancy related to asbestos exposure. We currently apply intracavitarily cisplatin/fibrin after macroscopic complete resection in a phase II trial to prevent local tumor recurrence (NCT01644994). So far, we included 13 out of 20 patients in the protocol. In parallel, we are evaluating the combination of intracavitary cisplatin/fibrin with post-operative radiotherapy in a preclinical animal model. Various tumor biomarkers that can be useful for the prediction of disease aggressiveness and response to treatment are assessed in translational studies (protein expression, mutation profiles microRNAs). Apart from investigating these biomarker candidates in tumor tissue, our current projects particularly emphasize the identification of markers that can be detected in the blood of the patients, as these represent a very attractive tool for non-invasive diagnosis, outcome prediction, or disease monitoring. Besides, we are exploring novel targets for the treatment of MPM using *in vitro* cell models and pre-clinical animal models. Furthermore, we also assess the frequency germline mutation of BAP1 that predispose individuals to MPM.

Some of our pre-clinical studies are aimed at a better understanding of mesothelioma biology, allowing us to test targeted therapies. We also study the development of mesothelioma using experimental animal models. Finally, we are exploring how growth in 3D under different stiffness conditions promotes growth of specific cell populations, which could be particularly resistant to cancer therapy.

Lung cancer

Approaches to discover new prognostic biomarkers in lung adenocarcinoma (LAC) are based on the enzymatic activities present in the surgical resection specimens. The first approach is the development of a new mass spectrometry protocol for the quantitation of serine hydrolases enzymatic activities in order to validate the biomarkers previously discovered. The second approach is based on our 2017 publication (Arni et al., Oncotarget 2017) where we evaluated the tyrosine kinase activities as biomarker signatures to predict the outcome of early stage LAC patients. For this purpose, we developed a new strategy to overcome the problem of the embedding media OCT in proteomic approaches.

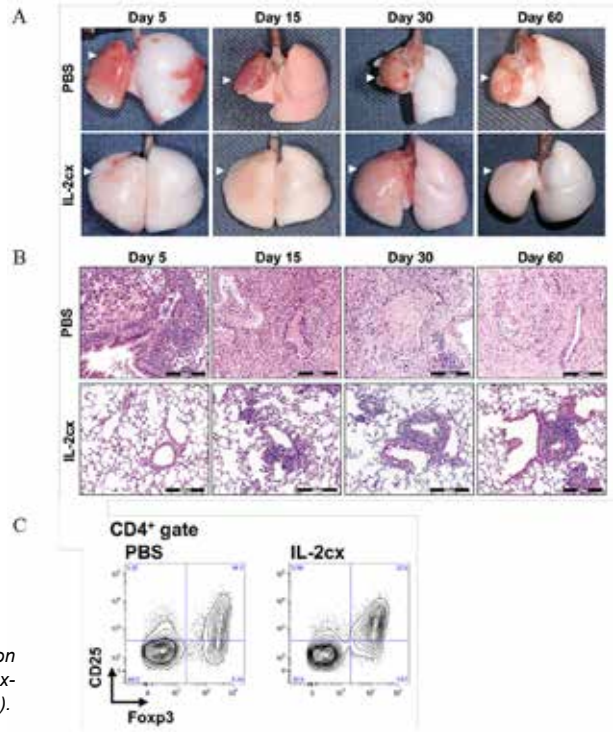


Figure 1: Macroscopic features on day 5, 15, 30 and 60 shows attenuation of damage on IL-2cx-treated allografts (A). HE histology shows attenuation of acute rejection on IL-2cx-treated allografts (B). FACS reveals promotion of Treg cells on IL-2cx treated recipients (C).

Lung transplantation
Novel strategies to overcome waiting list mortality have been implemented to overcome organ shortage. *Ex vivo* lung perfusion (EVLP) for re-evaluation of injured donor lungs provides future potential for the re-evaluation, treatment, and repair of injured donor lungs for transplantation by using alternative approaches. Recently, we are interested in using cytokine filters during EVLP. The results are encouraging and this strategy will be tested in future in a large animal transplant model.

Immunological interfaces
Another research interest focusses on immunological interfaces in experimental lung cancer and lung transplantation. Our previous research showed that the inhibition of CD26/DPP4 by (Vildagliptin) resulted in a reduction of incidence and growth of lung metastasis from colorectal cancer *in vivo*. In our ongoing work, we show that upon CD26/DPP4-inhibition, antitumoral macrophages and NK cells enrich within lung tumors and enhance their activity and cytotoxicity against the tumor thus leading to a significant reduction of lung tumor burden. Ongoing work in our experimental lung transplantation research explores the role of IL-2 stimulated and enhanced regulatory T cells, which leads to viable long term engraftment in a fully MHC-mismatched mouse lung transplantation model.

Further clinical research focuses on refinement of existing programs such as our pulmonary endarterectomy (PEA) and lung volume reduction surgery (LVRS) programs.

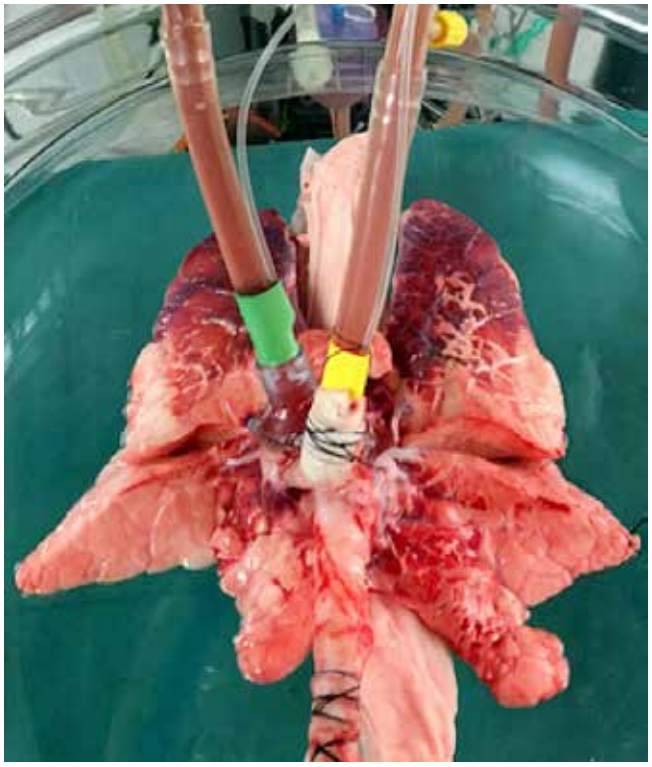


Figure 2: Pig lung during exvivo lung perfusion

Figure 3: Rat ex vivo lung perfusion system

Awards:

Ilhan Inci: Best experimental publication Swiss; Thoracic Surgery Association
Ilhan Inci: Best experimental publication Swiss; Zurich Transplant Center Price
Y. Yamada and W. Jungraithmayr: Best Abstract selected for the Caves Award; Annual Congress of the ISHLT 2017, San Diego
M. Niedzwiecki and W. Jungraithmayr: Best Master Thesis Award in 2017; Medical Faculty of the University Zurich
W. Jungraithmayr: Walter Brendel Award for the best scientific presentation; 52nd congress of the European Society of Surgical Research (ESSR) 2017, Amsterdam, Netherland

Collaborations:

- Institut klinische Biochemie der Universität Antwerpen, Belgien
- 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)
- 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
- Dr. Tatjana Sajic and Prof. Ruedi Aebersold, Department of Biology, Institute of Molecular Systems Biology (IMSB), ETH Zurich, Switzerland
- Dr. S. Gray, Translational Cancer Research Group, Trinity Center for Health Sciences, Institute of Molecular Medicine, St. James's Hospital, Dublin, Ireland
- Prof. Dr. H. Moch, PD Dr. A. Soltermann, Dr. B. Vrugt, Institut für klinische Pathologie, UniversitätsSpital Zürich
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- Dr. V. Serre Beinier, Département de chirurgie, Université de Genève
- Prof. Dr. W. Klepetko, Dr. M. Hoda, Division of Thoracic Surgery, Medical University Vienna
- Prof. Dr. R. Bueno, Department of Surgery, Brigham and Women's Hospital, Boston
- Dr. A. Jetter, Institut für Pharmakologie und Toxikologie, UniversitätsSpital Zürich
- Prof. Dr. D. Günther, Labor für organische Chemie, ETH Zürich
- Prof. Dr. B. Seifert, Department of Biostatistics, Epidemiology, Biostatistics and Prevention Institute, University of Zürich
- PD Dr. T. Frauenfelder, Dr. D. Nguyen-Kim, PD Dr. A. Boss, Institut für diagnostische und interventionelle Radiolgie, UniversitätsSpital Zürich
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- 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
- 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. Egbert Smit, NKI, Amsterdam
- Dr. Victor Van Beusechem, Department of Medical Oncology VUmc, Amsterdam

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Cordelia Bommeli,
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Urological Research

Prof. Dr. med.
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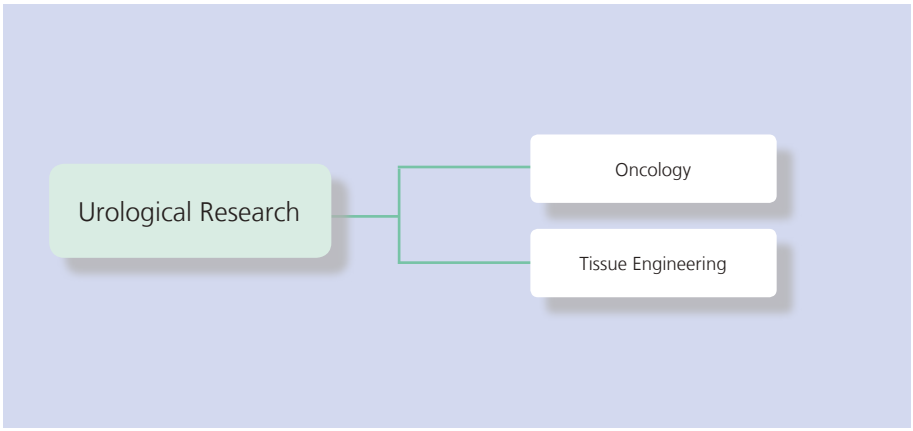


The department of Urology focuses its research interests on the two areas, which are Uro-Oncology and Tissue Engineering.

Novel immunological interventions relying on an active immune system

To study the complex interactions between the immune system and tumors we engage in three specific projects:

Banking of human antibody repertoires for therapeutic use: The main aim of this CTI project in collaboration with MEMO therapeutics is to establish a library ("antibody bank") of human antibody repertoires of individuals that have successfully mastered a disease. The comparison of the BKPyV-specific antibody repertoire in patients vs. healthy donors is expected to yield insights into the immune defense mechanisms that are required to control BKPyV-related diseases. We are currently detecting human derived monoclonal antibodies binding to BKPyV major capsid protein VP1 and covering all BKPyV serotypes.

Prostate cancer-specific bispecific antibodies (biAbs) to prevent and treat prostate cancer: We have recently established a collaboration with BriaCell. This company has conducted two phase I clinical trials with their tool "BriaVax" in metastatic (stage IV) breast cancer patients. Promising results have convinced BriaCell to conduct an additional phase IIa study in metastatic breast cancer patients. Our collaboration focuses on the combinatory use of STEAP1 x CD3 and EpCAM x CD28 bsAb with BriaVAx in either prostate and breast cancer. Co-incubation of BriaVax – which expresses high levels of EpCAM – with EpCAM x CD28 bsAb is expected to turn BriaVax cells into antigen-presenting cells (APCs). Addition of naïve T cells to the EpCAM coated BriaVax cells would lead to T cell activation by unspecific TCR binding to BriaVax pMHCs.

The indoleamine 2, 3-dioxygenase (IDO) as marker for prostate cancer diagnosis: IDO is an enzyme that degrades the essential amino acid tryptophan, thus inhibiting T cell proliferation and activity. It is predominantly induced in inflammatory environments. We were the first group proving the potential use of IDO as a marker in prostate cancer. We are currently studying the role of IDO as biomarker for diagnosis and prognosis in prostate cancer by the detection of the enzyme in urine of individuals undergoing first needle biopsy because at risk of developing prostate cancer (patent application PCT/EP2017/076169).

Focus Prostate Cancer Studies

Our department participates in several academic international randomised controlled trials (REDUSE, IMPROVE, PEACE III) to improve outcomes in patients with advanced prostate cancer. We are currently gathering funding for a phase I and II trial on bipolar androgen therapy (BAT) with a new medical compound in advanced prostate cancer patients. The aim is to identify which prostate cancer subtypes may respond to BAT and find predictive markers. For future biomarker discovery we established the two biobanks proCOC (Prostate cancer outcome study) and metaPROC (metastatic prostate cancer).

Multiple androgen receptor (AR) dependent and independent resistance mechanisms limit the efficacy of current treatment modalities for castration resistant prostate cancer (CRPC). Autophagy is a survival mechanism in cells exposed to anti-cancer treatment. We hypothesized that also a promising N-terminal targeting-AR treatment may lead to up-regulation of autophagy, which can be targeted by a combination therapy with autophagy inhibitors.

Focus Testis Cancer Studies

Our institution is enrolling patients in the Swiss Austrian German Testicular Cancer Cohort Study (SAG TCCS) to study the quality of life and follow-up schedules in patients with testis cancer. Furthermore our group has recently received a grant from the Swiss Cancer League to define the role of microRNAs in the management of testis cancer patients.

Additionally our group contributes clinical patient data to several international collaborations to optimize clinical care.

Urologic Tissue Engineering

Targeting urologic diseases such as urinary incontinence, the Tissue Engineering group is following different approaches to grow stem cells and initiate tissue regeneration. In a first approach, we use human skeletal muscle precursor cells (MPCs) for tissue (re)generation. The use of MPCs for tissue regeneration has been internationally recognized and we joined forces in an international consortium of the Horizon 2020 EU program to fight urinary stress incontinence in a project entitled **Multisystem Cell Therapy for Improvement of Urinary Incontinence (MUSIC)**. In this first phase clinical trial, we will treat 40 patients with their autologous muscle precursor cells. Patient-specific cell batches will be produced in clean room facilities under good manufacturing practice conditions. In combination with post injection electromagnetic stimulation, we expect a better regeneration of the sphincter muscle.

A second approach uses adipose derived stem cells (ADSC) as a key instrument to bioengineer contractile bladder tissue. The ADSCs differentiated to smooth muscle cells (SMC) under natural conditions. However, it is uncertain whether these cells maintain their cell fate long term *in vivo*. One of our aims is to evaluate different combinations of cells to improve the bladder tissue formation by modification of the microenvironment and the enhancement of cell-to-cell interactions. As autologous SMC cannot be harvested from organs with end-stage disease and tissue regeneration requires large amount of functional SMC, there is an urgent need for other cell sources. ADSC are a suitable cell source for SM tissue engineering. We investigate the functional role of autophagy during differentiation and remodeling of ADSCs to SMC *in vitro*. Another aim is to develop a functional substitute for the improvement of the bladder wall function for patients suffering from end-stage bladder disease. We are currently investigating the regenerative capabilities of primary bladder smooth muscle cells and pre-differentiated, smooth muscle-like adipose-derived stem cells in compressed collagen hydrogel scaffolds.

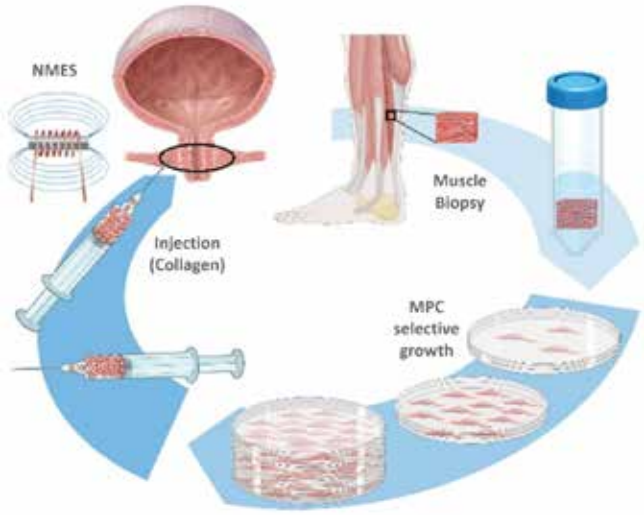


Fig 1.
Multisystem Cell Therapy for Improvement of Urinary Incontinence (MUSIC)

A central concern associated with the use of any cell source for tissue engineering is the non-invasive monitoring of *in vivo* tissue formation. We therefore apply magnetic resonance imaging to directly assess stem cell differentiation and skeletal muscle fiber formation. Since the regenerated tissue quality after stem cell therapy is crucially important for its proper function, we apply neuromuscular electromagnetic stimulation (NMES) to support *in vivo* tissue development, cell survival and innervation.

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
- Dr. Christoph Esslinger, Neurimmune Holding AG, Schlieren
- Dr. Laura Luberto, Takis srl, Rome, Italy
- PD Dr. med S. Santourlidis, Heinrich-Heine University, Düsseldorf (Germany)
- Prof. Dr. Michael Detmar, Institute of Pharmaceutical Sciences, ETHZ
- Prof. Dr. Peter Wild, Institute of Surgical Pathology University Hospital Zurich
- Proteomedix AG
- University of Applied Science North Western Switzerland (FHNW)
- Prof. Dr. Arnold von Eckardstein, Institute of Clinical Chemistry
- Dr. Andrew Vickers, Memorial Sloan Kettering Cancer Center, New York, USA
- Prof. Dr. Donna Ankerst, Technical University, Munich
- Prof. Rita Gobet, Division of Pediatric Urology, University Children's Hospital Zurich
- Dr. Maya Horst, Division of Pediatric Urology, University Children's Hospital Zurich

- Prof. Hans Uwe Simon, Pharmacology Institute; Bern
- Prof. Dr. Simon M. Ametamey, Dpt. Pharmaceutical Sciences, ETHZ, Zurich, Switzerland
- Prof. Dr. Christoph Handschin, Biozentrum Basel, Basel, Switzerland
- PD Dr. med. Andreas Boss, Institute for Diagnostic and Interventional Radiology, USZ
- Dr. sc. nat. Martin Ehrbar, Division of Obstetrics, University Hospital Zurich

Awards:

Christian Fankhauser: Poster Prize of the Swiss Urology (SGU 2017) for: “Diagnostic value of frozen section examination (FSE) during inguinal exploration in patients with inconclusive testicular lesions”.
Thomas Hermanns, Christian Fankhauser and Prof. Dr. J. Beyer (Oncology): Q-Award 2017 USZ for «Interdisziplinäre Hodentumor-sprechstunde».


Prof. Dr. med.
Tullio Sulser,
Director


PD Dr. med.
Maurizio
Provenzano,
PhD


PD Dr. med.
Daniel Eberli,
PhD


PD Dr. med.
Cédric Poyet


PD Dr. med.
Thomas Hermanns


Souzan Salemi,
PhD


Rosa Angelica Alves
de Sousa,
M.sc.


Sarah Kedzia,
M.sc.


Damina Balmer,
M.sc.


Alexandra Veloudios,
Study Nurse


Deana Mohr,
PhD


Mykhailo
Razumenko,
PhD


Abdou Alleyeh,
PhD


Jenny Prange,
PhD

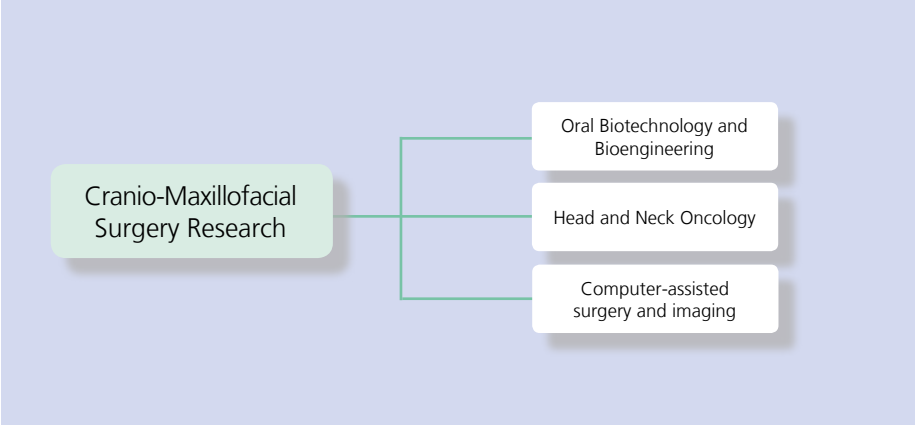

Dr. med.
Christian
Fankhauser


Dr. med.
Benedikt Kranzbühler


Jakub Smolar,
PhD Student


Daniel Keller,
PhD Student

Cranio-Maxillofacial Surgery Research



Prof.
Dr. med. dent.
Martin Rücker

Prof. Dr.sc.nat.
Franz E. Weber,
PhD

Research in the Department of Cranio-Maxillofacial Surgery covers head and neck oncology, computer assisted surgery, oral biotechnology & bioengineering, and photodynamic therapy. The focus of the latter one is the treatment of medication-related osteonecrosis of the jaw (MRONJ). MRONJ is a severe adverse drug reaction, manifested in a progressive irreversible bone destruction in the maxillofacial region. MRONJ-patients suffer from pain, loosening of teeth, poor mucosal healing and exposed necrotic bone in the oral cavity.

Figure 1 MRONJ lesion in the maxilla.

The treatment of MRONJ is generally difficult and the optimal therapy strategy has still to be established. Since MRONJ is associated with a high bacterial load on exposed bone in the oral cavity, we are investigating the potential of antimicrobial photodynamic therapy (aPDT) for the inactivation of MRONJ-associated bacteria. aPDT, by using a non-toxic dye (photosensitizer) and laser light, results in the production of reactive oxygen species which act locally and highly toxic for bacteria. We propose that reduction of the bacterial burden on exposed bone and in oral wounds is of vast importance for mucosal healing and will massively reduce the risk of MRONJ. So far, we could show that key bacterial species involved in the development of MRONJ can be killed by aPDT *in vitro*. Soon we start an animal trial to investigate the effectiveness of aPDT in preventing MRONJ in a mouse model of the disease. The goal of the project is to establish aPDT as the new gold standard for the prevention of MRONJ. Due to its effectiveness and the use of a technique already established in dental medicine, this project has great potential for a translation into the clinics in the near future.

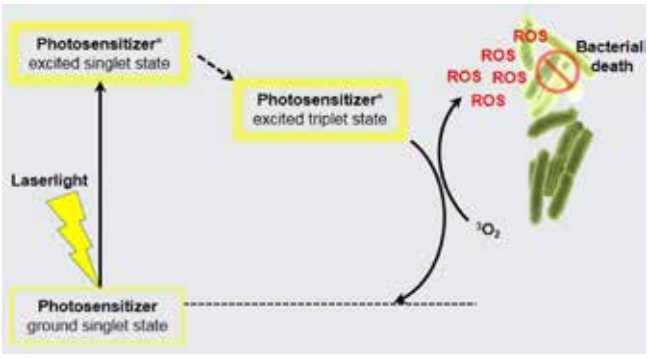


Figure 2 Simplified principle of antimicrobial photodynamic therapy (aPDT).

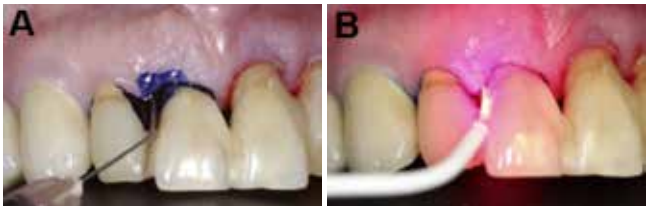


Figure 3 aPDT for the treatment of periimplantitis. A) Application of the photosensitizer. B) Illumination with laser light (from Scuelan et al. Dental Clinics of North America 2015)

Topics in Oral Biotechnology & Bioengineering are epigenetic active small chemicals for bone regeneration and additive manufacturing of bone substitutes with the final aim to provide our patients with osteoconductive bone substitutes from calcium phosphate and Bioglass. The project on additive manufacturing of bone substitutes is funded by the Swiss National Science Foundation and includes partners from the University of Applied Science (Muttenz, Switzerland) and the PolyU (Hong Kong). Another project is funded by a Bundesstipendium and deals with the preservation and regeneration of the pulp to keep teeth alive.

Computer assisted surgery is another focus in our department. Here we want to optimize the digital planning of operations and move on towards automation of planning and quality control. Finally, we want to offer our patients patient-specific implants and osteosynthesis materials.

Head and Neck Oncology is partner in a University project (KFSP) to study and provide new tools for the monitoring of oxygenation of tumors and the prognostic and therapeutic impact of this parameter. Funding of this project finished in 2017 but the clinical trial is still ongoing.

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)
- ETH Zurich, Cartilage Engineering + Regeneration (Prof. M. Zenobi-Wong)
- Universität Hongkong, Prof. R. Zwahlen
- UZH, Biochemistry, Prof. Amedeo Caflisch
- Biolitec research GmBH, Jena, Germany
- Orcos Medical, Küsnacht, Switzerland
- University of Zurich, Center of Dental Medicine, Division of Preventive Dentistry, Periodontology, and Cariology, Zurich, Switzerland (Prof. T. Attin, Dr. T. Thurnheer)
- University of Zurich, Institute of Anatomy (Prof. C. Maake)
- ETH Zurich, Department of Health Sciences and Technology, Institute for Biomechanics, Laboratory for Bone Biomechanics Zurich, Switzerland (Prof. R. Müller)
- University of Zurich, Department of Chemistry, Zurich, Switzerland (Prof. G. Patzke)
- University Hospital of Zurich, Department of Infectious Disease and Hospital Epidemiology, Zurich, Switzerland (Prof. A. Zinkernagel)

Prof. Dr. med. dent.
Martin Rücker

Prof. Dr.sc.nat.
Franz E. Weber,
PhD

Chafik Ghayor, PhD

PD Dr. med. dent.
Harald Essig

Dr. med. dent.
Paul Schumann

Dr. med. dent.
Thomas Gander

Dr. med. dent.
Daniel Zweifel

Bhattacharya
Indranil, PhD

Kathrin Schumann,
Scient. Administration

Alexander
Tchouboukov,
Lab. Technician

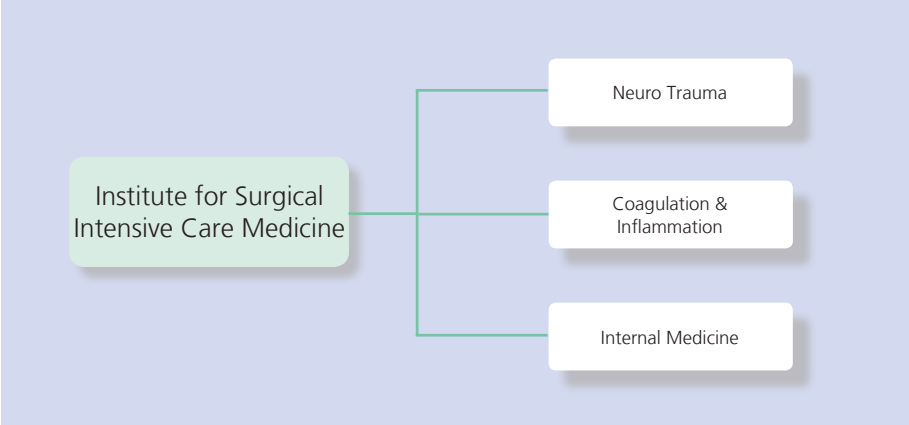
Ana Perez,
Lab. Technician

Tse-Hsing Chen,
PhD Student

Nurpur Khera,
PhD Student

Anja Ivica,
PhD Student

Institute for Surgical Intensive Care Medicine



Prof. Dr. med. Reto Schüpbach, M.Sc.

KD Dr. med. Peter Steiger

Prof. Dr. med. Marco Maggiorini

Intensive medicine (IS) provides a platform allowing almost all specialties in medicine to offer advanced invasive or surgical procedures and therapies and promotes therapies of syndromes, typically seen in critical care (ICU) patients.
The institute for intensive care medicine is undergoing a vast change process by consolidating different intensive care divisions. In a first step, the science team of Prof. Dr. Med Marco Maggiorini has joined the surgical intensive care science team.

Intensive care medicine research separates into clinical and basic research, where the following core areas are covered:

- Clinical studies with brain injury and patients with neurological issues
- Basic research of Sepsis (partially via anaesthesia or heart surgery research)
- Basic research of clotting with inflammations
- Clinical studies in hemodynamic and device applications

The institute for intensive care medicine pursues a quick consolidation of its structure by building up a joint basic and clinical research team, collectively training new staff and leading a conjoint concept for data collection across all intensive care stations – together with all intensive care stations in Swiss university hospitals.

Presently active research groups are to be linked in form and content in order to facilitate them as the following research focus points:

- Core area neurotraumatology and neuro intensive care medicine
- Core area of systematic inflammation (Sepsis, infection, vascular intra-vascular barrier dysfunction)
- Core area of intensive care improvement

Thanks to the Swiss Personalized Sepsis Study (SPHN call), where a first co-authored research is conducted (first author Prof. Adrian Egli, Universität Basel) - simultaneously combined with a USZ- internal installation of a fully electronic patient documentation system – the focus of creating a superordinate research platform increased fundamentally.

Simultaneously – and according to the UZH mission statement of promotion of innovation – a second research and development collaboration with an industrial partner was established. The aim of this partnership is (1) an improvement in ventilation strategies with critically ill patients, (2) an improvement in machine / user interaction and (3) a development of new tools and features of ventilation machines.

Collaborations:

- ECKS: Indikatoren / Kontraindikatoren – Berliner Charité & Universitätsmedizin Göttingen
- Visus: Visual behaviour of intensivists in usual daily situations – Kinderspital Zürich - Eleonorenstiftung
- ECMO: factorial survery – Berliner Charité & Univer sitätsmedizin Göttingen

Prof. Dr. med.
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M.sc.

Prof. Dr. med.
Marco Maggiorini

KD Dr. med.
Peter Steiger

Dr. med.
Christoph Ganter

Dr. med.
Karl Philipp Bühler

Dr. med.
Giovanna Brandi

Dr. med.
Stephanie Klinzing

Dr. med.
Matthias Hilty

Alessandro
Franchini,
PhD

Dorothea
Heuberger,
PhD Student

Ozlem Altintas,
PhD Student

Catharina Giese
Head Development
and Administration

Animal Welfare in Biomedical Research

Prof.
Margarete Arras,
DVM

Nikola Cesarovic,
DVM, PhD

Anesthesia and peri-operative Pain Research

An important reason for suffering in experimental animals is pain induced by invasive procedures, diseases and injuries. But pain management is more than an animal welfare concern, as it has important scientific and methodological implications for the design of experiments and the quality of the resulting data. To ensure high-quality scientific outcomes and humane treatment of laboratory animals sufficient anesthesia, reliable alleviation of pain and supporting experimental housing conditions are essential.

In the past, we have developed and evaluated physiology and behavior based pain assessment tools for laboratory mice.

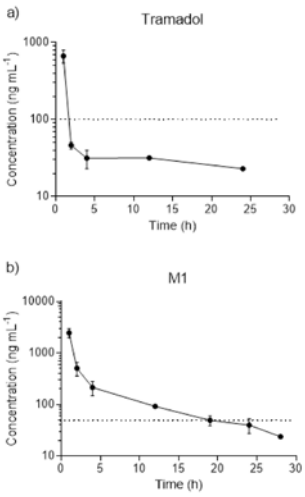


Figure 1: Serum concentrations after oral Tramadol administration. *a) Semi-log plots of mean serum tramadol concentrations over time (h) after subcutaneous administration of 25 mg kg-1 tramadol followed by 25 mg/kg of tramadol in drinking water for 24 hours. The horizontal line represents the minimal analgesic concentration of tramadol (100 ng mL-1) in humans.*
b) Semi-log plots of mean serum M1 concentrations over time (h) after subcutaneous administration of 25 mg kg-1 tramadol followed by 25 mg kg-1 of tramadol in drinking water for 24 h. The horizontal line represents the minimal analgesic concentration of M1 (40 ng mL-1) in humans.

Reference: Evangelista R, Bergadano A, Arras M, Jirkof P (2018) Evaluation of the analgesic efficacy of a 25 mg/kg Tramadol s.c. injection-oral combination in a surgical model in C57BL/6J mice. JAALAS, accepted.

Since 2017 we focus our work also on the development of tools for the legally required severity assessment in animal experimentation. Therefore, we combine well-established severity assessment methods with new approaches like cognitive bias testing to detect changes in the animal's affective state. This work is conducted as part of the research consortium DFG FOR2591 in collaboration with 15 different research groups in Germany and Switzerland. Within the consortium we are collaborating with several research groups to establish remote and automated systems to grade severity fast, objectively and in a non-invasive way (e.g. Automated Mouse Grimace Scale). The overall aim is the assessment of severity in different animal models with validated and easy-to-use parameters. With the implementation and evaluation of refinement measures (e.g. improved housing conditions or local anesthesia) we aim to minimize severity and to contribute to the 3R principles.

These tools are also used to improve analgesia protocols for the treatment of pain in mice without affecting experimental read-out. We characterized for example the opioid Tramadol (Fig. 1) as well as Tramadol-Paracetamol combinations in abdominal surgery (Fig. 2) and in orthopedic models and the antipyretic Paracetamol in embryo transfer surgery. In a collaboration with the University of Basel we are currently developing a new sustained release buprenorphine formulation for stress-free and continuous analgesia administration in rodents.

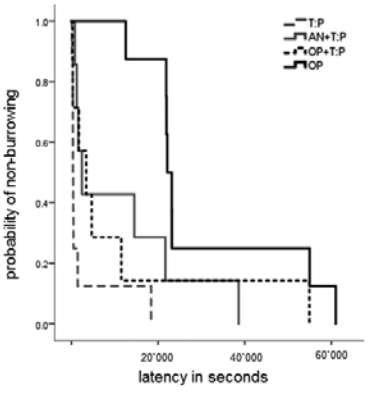


Figure 2: Burrowing Test. *A prolongation of burrowing latency indicates post-surgical pain in mice. Oral Tramadol:Paracetamol treatment results in comparable burrowing latencies as control treatments. Burrowing latencies differed significantly between T:P and An + T:P (p= 0.024) and OP compared to all other groups: OP vs T:P (p < 0.0001), OP vs. An + T:P (p= 0.032) and OP vs. OP +T:P (p=0.019). T:P = TP in drinking water only, An +T:P = anesthesia and T:P in the drinking water, OP+ T:P =anesthesia and surgery with T:P in the drinking water; OP =anesthesia and surgery only. Reference: Jirkof P, Arras M, Cesarovic N (2018)Tramadol:Paracetamol in drinking water for treatment of post-surgical pain in laboratory mice. Applied Animal Behaviour 198: 95-100, doi.org/10.1016/j.applanim.2017.09.021*

Photo: M. Durst

Collaborations:

- Alessandra Bergadano, Comparative Medicine, F. Hoffmann-La Roche
- Andre Bleich, Institute for Laboratory Animal Science, Hannover Medical School
- Brianna Gaskill, Animal Sciences, Purdue University
- Micheal Czaplik, Department of Anesthesiology, RWTH Aachen University
- Jörg Huwyler, Pharmazeutische Technologie, University of Basel
- Annemarie Lang, Clinic for Rheumatology and Clinical Immunology, Charité Berlin, Germany
- Dorit Mehrhof, Institute of Imaging and Computer Vision, RWTH Aachen University
- Heidrun Potschka, Institute for Pharmacology, Toxicology and Pharmacy, Ludwig-Maximilians-University Munich
- Petra Seebeck, Zurich integrative Rodent Physiology, University of Zurich
- Rene Tolba, Institute for Laboratory Animal Science & Experimental Surgery and Central Laboratory for Laboratory Animal Science RWTH Aachen University

Awards:

Paulin Jirkof
Felix Wankel Junior-Animal Welfare Research Prize, Ludwig-Maximilians-University Munich

Prof.
Margarete Arras,
DVM

Nikola Cesarovic,
DVM, PhD

Flora Nicholls,
Dipl. biol.

Miriam Lipiski,
DVM

Paulin Jirkof,
PhD

Thea Fleischmann,
DVM

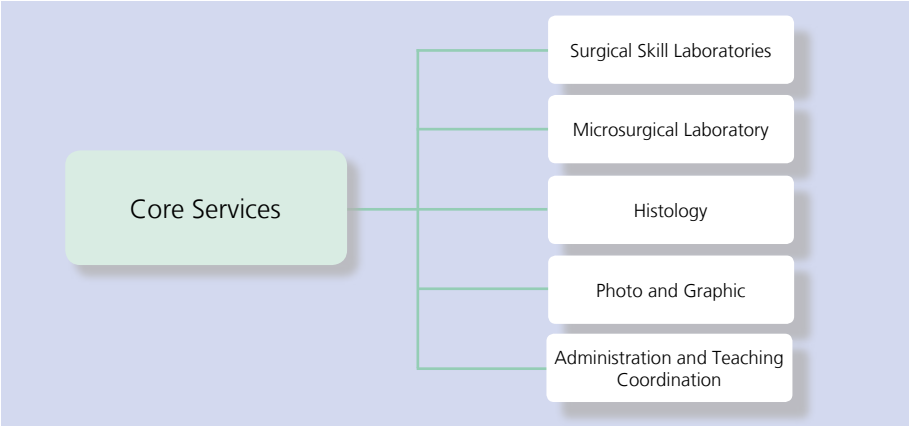
Mareike Sauer,
DVM

Marko Canic,
DVM

Mattea Durst,
PhD Student


Super Tag

3. Core Services



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.

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.

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.

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

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.

Prof.
Margarete Arras,
DVM

Nikola Cesarovic,
DVM, PhD

Nico Wick,
Photographer

Lea Schütz,
Photographer

Carol De Simio,
Scientific
Illustrator

Pia Fuchs,
Lab. Technician
(till March 2017)

Ursula Süss,
PhD
(till August 2017)

Andrea Garcete-
Bärtschi,
Lab. Technician

Ines Kleiber-
Schaaf,
Lab. Technician

Tina Wentz
Administration
Division of
Surgical
Research

Donata Gröflin,
Teaching
Coordination
Division of
Surgical
Research

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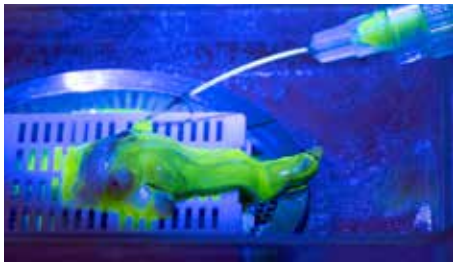
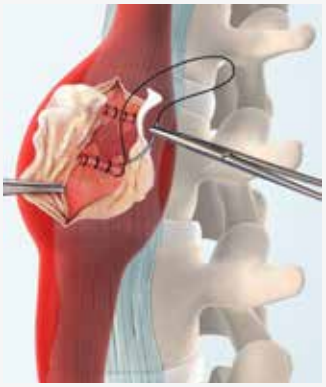
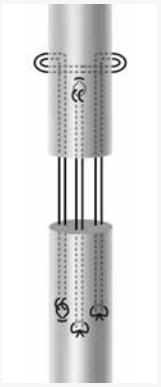
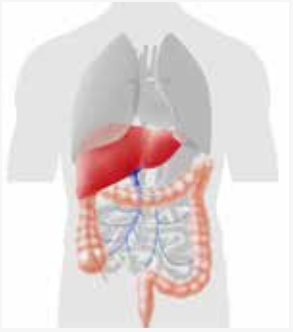
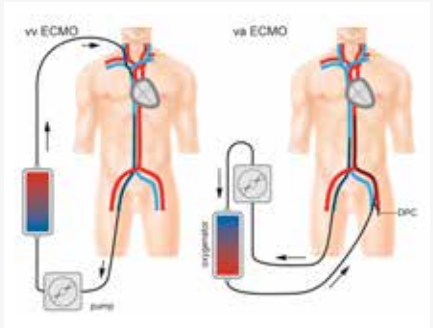
- cutting and converting of video-files for presentation and web
- construction and maintainance of websites
- maintainance of the digital image archives

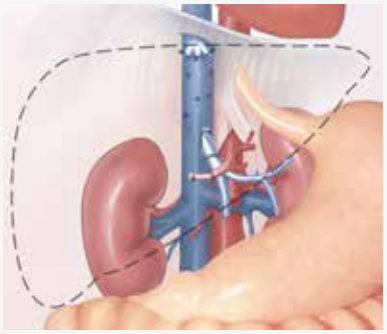












4. Events and Workshops at the Division of Surgical Research 2017








16th Day of Clinical Research, February 9, 2017

Surgical Suture Skills Course, Winterthur, May 31 - June 01

Lab Retreat, Stoos, January 13 - 15

Christmas Lecture and Apéro, December 21

Farewell of Pia Fuchs, March 30, and Ursula Suess, August 25

5. Grants

Cardiovascular Surgery Research:		
EU FP7	Intelligent Materials for *in situ* heart valve tissue engineering	M. Emmert
SNF	Interlacing magnetic resonance velocity encoding and computational fluid dynamic for mapping wall shear stress in the cardiovascular system	S. Benussi, S. Kozerke
Swiss Heart Foundation	Transcatheter aortic implantation of “off-the-shelf” tissue engineered heart valves in a translational adult sheep model	M. Emmert
Swiss Heart Foundation	Safety and efficacy of transcatheter transplantation of human GMP grade next-generation cardio poietic stem cell based 3D microtissues in a translational post-infarction heart failure pig model	M. Emmert
Swiss Heart Foundation	Role of LV volume overload and afterload mismatch during progression and treatment of functional mitral regurgitation	H. Rodriguez
Swiss Heart Foundation	Impact of mitral valve replacement on intracardiac fluid dynamics and left ventricular efficiency	F. Maisano
Stiftung für Herz-und Kreislauferkrankheiten	EpiPhrenic POrcine Study (EPOS) - Physiologie Mechanism Behind Cardiac Enhancement Therapy, a Novel Implantable Therapy Concept for Heart Failure Patients with Narrow-QRS and/or no Evidence of Mechanical Intra-Ventricular Dyssynchrony	F. Maisano
USZ Innovationspool	Nahtfreier (Sutureless) Aortenklappenersatz	A. Ouda
USZ Innovationspool	Interkardiale Verwendung vom AngioVac Aspirationssystem	A. Ouda
USZ Innovationspool	Cerebral protection in transcatheter aortic valve replacement procedures	F. Maisano
Industry Grant	Development of minimally invasive and transcatheter therapeutic approaches	F. Maisano
Industry Grant	Development multimodality-imaging guided minimally invasive interventions	F. Maisano

Visceral & Transplant Surgery Research:		
SNF Project grant	Molecular strategies for improved outcomes after major liver resection	Clavien P.-A.
SNF Project grant	HOPE for Human Liver Grafts obtained from Donors after Brain Death	Dutkowski P.
SNF	Serotonylation promotes pancreatic cancer by regulating cytoskeletal dynamics	Graf R.
SNF	Improving local clinical excellence, research methodology, and promoting dissemination of specialist knowledge in Hepato-Pancreato-Biliary and Oncologic Surgery between Switzerland - Russia and Kazakhstan	Clavien P.-A.
SNF Sinergia grant	Metabolic control of hepatocyte proliferation in regeneration and cancer	Humar B., Clavien P.-A.
SNF Investigator Initiated Clinical Trials programme	Hypothermic oxygenated perfusion (HOPE) for human livers - a prospective randomized European liver transplant trial	Dutkowski P.
FOUNDATIONS:		
SNF/Stiftung Krebsforschung Schweiz, MD-PhD Fellowship	The role of Kupffer cell polarization and GPR120 agonism in mediating the beneficial effects of fish oil and exercise in fatty liver	Frick L.
Vontobel Stiftung	Gastrokine as an early marker for pancreatic carcinogenesis	Graf R., Seleznik G., Reding T.
Novartis Foundation	Exogenous melatonin promotes graft regeneration in small-for-size liver transplantation	Tian Y.
Liver and Gastrointestinal Disease Foundation	ITPP und Krebs	Graf R.

Olga Mayenfisch Stiftung	Behavioral mechanisms underlying changes in food selection and intake in humans after Roux-en-Y Gastric Bypass	Bueter M.
Olga Mayenfisch Stiftung	Benchmark Research in Surgery	Staiger R.
Amelie Waring Stiftung	Role of deoxy-sphingolipids in acinar cell pathobiology following diabetes mellitus	Sonda S.
INSTITUTIONAL GRANTS:		
Clinical Research Priority Program	Non-resectable liver tumors – from palliation to cure Clinical Research Priority program	Clavien P.-A.
Wyss Translational Center Zurich	Liver4Life	Clavien P.-A., von Rohr P. (ETHZ)
Novartis Foundation	Exogenous melatonin promotes graft regeneration in small-for-size liver transplantation	Tian Y.
Edoardo R.-, Giovanni, Giuseppe und Chiarina Sassella-Stiftung	ITPP as a radiosensitizer in the treatment of liver metastasis	Borgeaud N.
Edoardo R.-, Giovanni, Giuseppe und Chiarina Sassella-Stiftung	The role of LINE1-mediated genome transformations in tumor and metastasis development	Schneider M., Gupta A., Borger P.
Forschungskredit Candoc, Universität Zürich	Uncovering the role of Serotonin in the interaction between cancer & the immune system	Schneider M.
Innovationspool UZH	Geschlossenes Perfusionssystem für die hyperthermale intraperitoneale Chemotherapie	Lehmann K.
Innovationspool UZH	Routinemässiger Einsatz einer oxygenierten Perfusion von humanen DED und ECD Lebern vor Transplantation	Dutkowski P.

Trauma Surgery Research:		
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
Gottfried und Julia Bangerter-Rhyner-Stiftung	Identification of subpopulation of adipose derived stem cells for bone bioengineering by CyTOF analysis	P. Cinelli
AO Research Fund	Effects of standard reaming and RIA techniques on local soft tissue and systemic homeostasis in a porcine trauma model	M. Teuben, HC Pape
Olga Mayenfisch Stiftung	From pluripotency to differentiation: the role of Pramel7 in murine embryonic stem cells	P. Cinelli
USZ INOV00040	Visual Analytics in Trauma Surgery WATSON Health	L. Mica
USZ INOV00049	Telemedizin	HC Pape

Plastic, Hand & Reconstructive Surgery Research:		
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
Novartis Stiftung für Biologisch-Medizinische Forschung	Mass spectrometry of Nanofat: a novel systems biology approach to identify tissue regeneration factors	N. Lindenblatt
Commision for Technology and Innovation/Innosuisse	*In vivo* proof of concept for TOP-N53, a highly potent topical drug for acceleration of wound healing	N. Lindenblatt
Hochschulmedizin Zürich	Skintegrity - An interdisciplinary approach to understand, diagnose and treat skin diseases and wounds-P6	N. Lindenblatt
Werner-Siemens Stiftung	Center for artificial muscles in reconstructive medicine` (Co-applicant, PI: Yves Perriard, EPFL, 2. Co-applicant: Thierry Carrell, Inselspital Bern)	N. Lindenblatt
Hartmann-Müller Stiftung, Zürich, Schweiz	Molecular profiling of nanofat: a systems biology approach to understand tissue regeneration	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
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	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

La Colline PhD Fellowship	Skin Engineering Platform	M. Calcagni
Innovationspool USZ	Adipose derived stromal vascular fraction for the treatment of finger contractures in patients affected by systemic sclerosis	M. Calcagni, O. Distler, P. Giovanoli
Innovationspool USZ	Skin Engineering Platform	P. Giovanoli, M. Calcagni
Heubergstiftung	Investigating the effect of hypothermal conditioning on the quality and growth potential of *in vitro* cultured keratinocytes for skin grafting	M. Calcagni, S. Darwiche

Thoracic Surgery Research:

Zürcher Krebsliga	Prognostic Marker for MPM	I. Opitz
SNF Overhead		I. Opitz
Vontobel Stiftung	MikroRNAs als prognostische und prädiktive Tumormarker für die multimodale Behandlung des malignen Pleuramesothelioms	I. Opitz
Lunge Zürich	MicroRNAs as prognostic and predictive tumour markers assisting the selection of patients with malignant pleural mesothelioma for multimodality treatment	I. Opitz
SNF Professorship	MPM – an integral approach for better outcome	I. Opitz
Krebsforschung Schweiz	Mesoscape 001-pS6: Construction of a multi-institutional European Tissuebank	I. Opitz
Polianthes Foundation	Comprehensive Investigation of Predictive Biomarkers for Chemotherapy Response and Novel Drug Targets in Patients with MPM by Next Generation Sequencing	I. Opitz
SAKF Foundation	Multi-omics profiling for identification of novel circulating biomarkers for malignant pleural mesothelioma	I. Opitz
SNF	Improving Mesothelioma Patients Outcomes by Early Non-Invasive Diagnosis	I. Opitz
Polianthes Foundation	Next Generation Sequencing of Malignant Pleural Mesothelioma for Therapy Response Prediction	I. Opitz
Swiss National Science Foundation Sinergia grant	From asbestos exposure to cancer: a systemic approach to detect loss of homeostatic control in the mesothelial environment	E. Felley-Bosco
Walter Bruckerhoff Stiftung	Targeting epigenetic deregulation	E. Felley-Bosco
Polianthes Foundation	Mechanisms underlying development of resistance and progression to mesenchymal phenotype in mesothelioma	E. Felley-Bosco
Stiftung für Angewandte Krebsforschung	“Overcoming development of resistance and progression to mesenchymal phenotype in mesothelioma” and “Alternative splicing in BAP1: implications in DNA damage response and drug sensitivity in mesothelioma”	E. Felley-Bosco
CTI	Entwicklung einer Matrix-basierten Technologieplattform für die Hochdurchsatz-Analyse von 3D Zellkulturen	E. Felley-Bosco
Innovationspool	Implementierung der „Synapse 3D®“ Software von Fujifilm zur Planung und Simulation von (minimal-invasiven) anatomischen Lungenresektionen, Lungenvolumenreduktionschirurgie und minimal-invasiven Zugängen	C. Caviezel
Hartmann Müller Stiftung	The role of cytokine filtration during *ex vivo* lung perfusion	I. Inci
Hermann Klaus Stiftung	*Ex vivo* reconditioning of donor lungs with Trimetazidine after prolonged cold ischemia	I. Inci
Lungen Liga Zurich	The effect of lung volume reduction surgery on outcome after lung transplantation in patients with emphysema	I. Inci

Innovationspool	Assessment and reconditioning of donor lungs with *ex vivo* lung perfusion system	I. Inci
Swiss National Fond	Reconditioning of marginal donor lung in *ex vivo* lung perfusion system using Perfluorocarbon based oxygen carrier	I. Inci
Foundation A. P. Naef (Lausanne)	Inhibition of ischemia-reperfusion injury using ATP sensitive potassium channel modulators in *ex vivo* lung perfusion system in lung transplantation	I. Inci
Lungenliga Graubünden	Inhibition of ischemia-reperfusion injury using ATP sensitive potassium channel modulators in *ex vivo* lung perfusion system in lung transplantation	I. Inci
Swiss Lung Foundation	A small animal model for reconditioning marginal donor lung in *ex vivo* lung perfusion system using an advanced perfluorocarbon emulsion before transplantation	I. Inci
Hartmann Müller Stiftung	A small animal model for reconditioning marginal donor lung in *ex vivo* lung perfusion system using an advanced perfluorocarbon emulsion before transplantation	I. Inci
Schweizerischer Nationalfonds	Suppression of lung tumor growth by CD26 /DPP4-inhibition	W. Jungraithmayr
Helene Bieber Fonds	The CD26-costimutatory pathway is critical for Th17-mediated lung transplant improvement	W. Jungraithmayr
Hartmann-Müller Stiftung	The protective effect of local anesthetics on primary graft dysfunction after experimental lung transplantation	W. Jungraithmayr
Kurt und Senta Herrmann-Stiftung	Blockade of CD26/DPP4 - co-stimulation to improve lung transplant survival	W. Jungraithmayr
Stiftung für wissenschaftliche Forschung	Ein neues Therapiekonzept zur Bekämpfung des Lungenkarzinoms durch Hemmung der CD26/DPP4	W. Jungraithmayr
Forschungskredit, University Zurich	The protective role of CD26/DPP4-inhibition in lung transplantation – a preclinical study	W. Jungraithmayr
Assistant Professorship, University Zurich	Lungentransplantation	W. Jungraithmayr
Development program “Filling the Gap”	The protective role of CD26/DPP4-inhibition in lung transplantation – a preclinical study	W. Jungraithmayr
Hermann Klaus-Stiftung, University Zurich	A new therapeutic concept against lung cancer through inhibition of CD26/DPP4	W. Jungraithmayr
Stiftung für Krebsbekämpfung, University Zurich	Ein neues Therapiekonzept zur Bekämpfung des Lungenkarzinoms durch Hemmung der CD26/DPP4	W. Jungraithmayr
Stiftung für Angewandte Krebsforschung (SAKF) Zurich	Targeting human lung cancer by synergistic CD26- and checkpoint inhibitor	W. Jungraithmayr
„Clinical Scientist”, Medizinische Hochschule Brandenburg (MHB)	A new concept against lung cancer	W. Jungraithmayr (Mentor, co-applicant)
Sophien-Stiftung, Zurich	A new therapeutic concept against lung cancer by inhibition of CD26/DPP4	W. Jungraithmayr
Internal Research Fund from the MHB	Expression of CD26/DPP4 on human cancer as biomarker and target against lung cancer	W. Jungraithmayr
SAKF Foundation	Biomarkers with enzymatic activities for improved risk stratification of lung cancer patients	S. Hillinger

Urological Research :		
Max & Hedwig Niedermayer Stiftung	N-terminal androgen receptor targeting and autophagy inhibition to overcome resistance development during the evolution of prostate cancer treatment	B. Kranzbühler
Horizon 2020 Förderung, Staatssekretariat für Bildung, Forschung und Innovation	MUSIC: Multisystem Cell Therapy for Improvement of Urinary Continence	D. Eberli
Kurt und Senta Hermann Stiftung	N-terminal androgen receptor targeting and autophagy inhibition to overcome resistance development during the evolution of prostate cancer treatment	B. Kranzbühler
Unitectra	Proof-of-Concept Funding {PoC) “Novel Urine Biomaker for Prostate Cancer”	M. Provenzano
Commission for technology and Innovation (CTI)	Banking of human antibody repertoires for therapeutic use	M. Provenzano
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
Institutional Grant from Baugarten Stiftung, Zürich	MPCs for the treatment of urinary incontinence	D. Eberli, T. Sulser
EDAP TMS	HIFU Prostate Treatment and the use of focal HIFU	D. Eberli
Baugarten Stiftung, Zürich	Neuro-elektromagnetische Stimulation und menschliche Muskelstammzellen zur Behandlung von Urininkontinenz	D. Eberli
Commission for technology and Innovation CTI	Biomarker discovery engine for novel cancer diagnostics based on liquid biopsy	D. Eberli
Institutional Grant from Baugarten Stiftung, Zürich	MPCs for the treatment of urinary incontinence	D. Eberli, T. Sulser

Cranio-Maxillofacial Surgery Research:		
Schweizer National Fond	Osteoconductive and osteoinductive customized implants for large mandibular defects	F. E. Weber
Bundesstipendium	Pulp Regeneration	F. E. Weber

Surgical Intensive Care Medicine:		
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
SPAN	Swiss Personalised Sepsis Study	R. Schüpbach

Animal Welfare in Biomedical Research:		
Swiss National Science Foundation	International short visits	P. Jirkof
Purdue University Honors College visiting scholar grant		P. Jirkof
DFG Project funding in FOR 2591 Forschungs-verbund	Severity assessment in animal based research	P. Jirkof, M. Arras
Bf3R, Berlin, Project Funding	Integration of a refinement project on pain management in the mouse osteotomy model in a basic research study on bone healing (Refine-MOMo 1328-54) Project Funding	P. Jirkof, M. Durst

6. Publications 2017

1. Abdelghani, M., Spitzer, E., Soliman, O.I.I., Beitzke, D., Laggner, R., Cavalcante, R., Tateishi, H., Campos, C.M., Verstraeten, L., Sotomi, Y., et al. (2017). A simplified and reproducible Method to Size the Mitral Annulus: Implications for Transcatheter Mitral Valve Replacement. European Heart Journal Cardiovascular Imaging 18, 697-706.

2. Adank, J.-P., and Mortezavi, A. (2017). Diagnostik und Therapie der Harninkontinenz. Praxis-Depesche, 67-71.

3. Al-Jazairi, M.I.H., Klinkenberg, T.J., Van Putte, B.P., Mariani, M.A., and Benussi, S. (2017). Totally thoracoscopic pulmonary vein isolation a simplified technique. Innovations : Technology And Techniques In Cardiothoracic And Vascular Surgery 12, 493-495.

4. Allemann, F. (2017a). Radiuskopffraktur – wie weiter? Praxis 106, 285.

5. Allemann, F. (2017b). Wir planen Stunden, Tage und Wochen….entscheiden tun aber Sekunden - Unfallchirurgie im Zentrumspital. Informationsschrift KSD (Swiss Review of Military and Disaster Medicine) 2, 47-48.

6. Ancona, F., Stella, S., Taramasso, M., Marini, C., Latib, A., Denti, P., Grigioni, F., Enriquez-Sarano, M., Alfieri, O., Colombo, A., et al. (2017). Multimodality Imaging of the Tricuspid Valve with Implication for Percutaneous Repair Approaches. Heart 103, 1073-1081.

7. Auffret, V., Webb, J.G., Nietlispach, F., and et al. (2017). Clinical Impact of Baseline Right Bundle Branch Block in Patients Undergoing Transcatheter Aortic Valve replacement. JACC Cardiovascular interventions 10, 1564-1574.

8. Banzic, I., Brankovic, M., Maksimović, Ž., Davidovic, L., Markovic, M., and Rancic, Z. (2017). Parkes Weber syndrome-diagnostic and management paradigms: a systematic review. Phlebology 32, 371-383.

9. Barman-Aksözen, J., C Wiek, P., Bansode, V.B., Koentgen, F., Trüb, J., Pelczar, P., Cinelli, P., Schneider-Yin, X., Schümperli, D., and Minder, E.I. (2017). Modeling the ferrochelatase c.315-48C modifier mutation for erythropoietic protoporphyria (EPP) in mice. Disease Models & Mechanisms 10, 225-233.

10. Barth, B.K., De Visschere, P.J.L., Cornelius, A., Nicolau, C., Vargas, H.A., Eberli, D., and Donati, O.F. (2017). Detection of clinically significant prostate cancer: short dual-pulse sequence versus standard multiparametric MR imaging-a multireader study. Radiology 284, 725-736.

11. Beaume, M., Köhler, T., Greub, G., Manuel, O., Aubert, J.-D., Baerlocher, L., Farinelli, L., Buckling, A., van Delden, C., and Study, S.T.C. (2017). Rapid Adaptation Drives Invasion of Airway Donor Microbiota by Pseudomonas after Lung Transplantation. Scientific Reports, 40309.

12. Becker, A.S., Cornelius, A., Reiner, C.S., Stocker, D., Ulbrich, E.J., Barth, B.K., Mortezavi, A., Eberli, D., and Donati, O.F. (2017). Direct comparison of PI-RADS version 2 and version 1 regarding interreader agreement and diagnostic accuracy for the detection of clinically significant prostate cancer. European Journal of Radiology 94, 58-63.

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14. Beckmann, S., Nikolic, N., Denhaerynck, K., Binet, I., Koller, M., Boely, E., De Geest, S., and Psychosocial Interest Group, S.T.C.S. (2017b). Evolution of body weight parameters up to 3 years after solid organ transplantation: The prospective Swiss Transplant Cohort Study. Clinical Transplantation 31, e12896.

15. Bezan, A., Posch, F., Ploner, F., Bauernhofer, T., Pichler, M., Szkandera, J., Hutterer, G.C., Pummer, K., Gary, T., Samonigg, H., et al. (2017). Risk stratification for venous thromboembolism in patients with testicular germ cell tumors. PLoS ONE 12, e0176283.

16. Bhindi, B., Jiang, H., Poyet, C., Hermanns, T., Hamilton, R.J., Li, K., Toi, A., Finelli, A., Zlotta, A.R., van der Kwast, T.H., et al. (2017). Creation and internal validation of a biopsy avoidance prediction tool to aid in the choice of diagnostic approach in patients with prostate cancer suspicion. Urologic oncology 35, 604.e617-604.e624.

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18. Boege, Y., Malehmir, M., Healy, M.E., Wolf, M.J., Böhm, F., Frick, L., Maire, R., Moch, H., Heikenwalder, M., Weber, A., et al. (2017). A Dual Role of Caspase-8 in Triggering and Sensing Proliferation-Associated DNA Damage, a Key Determinant of Liver Cancer Development. Cancer Cell 32, 342-359.e310.

19. Bonani, M., Frey, D., de Rougemont, O., Mueller, N.J., Mueller, T.F., Graf, N., and Wüthrich, R.P. (2017). Infections in de novo kidney transplant recipients treated with the RANKL inhibitor denosumab. Transplantation 101, 2139-2145.

20. Bouaicha, S., Cunier, M., Scheyerer, M.J., Wanner, G.A., Simmen, H.-P., and Werner, C.M.L. (2017). Does Sagittal Spinopelvic Configuration Influence Vertebral Fracture Type or Localization in Trauma Patients?: A Retrospective Radiologic Analysis. Clinical Spine Surgery 30, E265-E269.

21. Bramstedt, K.A., and Plock, J.A. (2017). Looking the world in the face: the benefits and challenges of facial transplantation for blind patients. Progress in Transplantation 27, 79-83.

22. Brüstle, K., Calen, C., Kuwata, S., Nietlispach, F., Zuber, M., Maisano, F., and Taramasso, M. (2017a). How to Treat Tricuspid Valve Disease What's New on the Horizon. Current Treatment Options in Cardiovascular Medicine, 19: 18.

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1. Abdelghani, M., Spitzer, E., Soliman, O.I.I., Beitzke, D., Laggner, R., Cavalcante, R., Tateishi, H., Campos, C.M., Verstraeten, L., Sotomi, Y., et al. (2017). A simplified and reproducible Method to Size the Mitral Annulus: Implications for Transcatheter Mitral Valve Replacement. European Heart Journal Cardiovascular Imaging 18, 697-706.

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26. Burkhardt, M.A., Gerber, I., Moshfegh, C., Lucas, M.S., Waser, J., Emmert, M.Y., Hoerstrup, S.P., Schlottig, F., and Vogel, V. (2017). Clot-entrapped blood cells in synergy with human mesenchymal stem cells create a pro-angiogenic healing response. Biomaterials Science 5, 2009-2023.

27. Burn, F., Schirpenbach, C., Bidlingmaier, M., Reincke, M., Vetter, D., Weishaupt, D., Brockmann, J.G., Müller, M.K., Weber, M., Dahm, F., et al. (2017). Left-Sided Living Kidney Donation Leads to Transiently Reduced Adrenocortical Responsiveness. American Journal of Transplantation 17, 1879-1884.

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