Division of Surgical Research
Annual Report 2019/2020

Department of Surgery
University Hospital Zurich
Switzerland

University of Zurich[UZH]

USZ Universitäts Spital Zürich

Content

Preface

Dear Colleagues

Hard times create strong scientists - strong scientists create good science.

We all have challenging times behind us, the pandemic has influenced our lives and our work, but we have continued on our path and we can look back and see what amazing work we have done.

Despite the many obstacles created by the pandemic, we were still able to organize a number of online symposia and courses and the number of publications has once more increased over the past two years.

The Division for Surgical Research has grown beyond the borders of the surgical departments and is currently an appealing scientific interaction platform for other research groups not only within the USZ but for the entire scientific community in Zurich and abroad. We have invested many resources and effort to provide the Division's members with a versatile platform for continued success of our competitive research and for strengthening our already excellent reputation.

This success relies on the interaction between all our members and the highly professional and very efficient support of our core services. The histology and immunohistochemistry labs, small and large animal experimental surgery facilities, the photography/graphics services, and the MRI facility have once again supported a multitude of projects with outstanding motivation and dedication.

Despite the continuous financial cuts and increasingly complicated bureaucracy, we have begun to shape our future. We have successfully planned and realized our new small animal surgical and MRI facilities in Schlieren, which were inaugurated early 2021. Furthermore, we are actively planning the new large animal facilities on Irchel campus, as well as our new laboratories on the future Berthold-Areal.

We would like to thank all members of our Division for their excellent work, the fruitful collaborations and discussions, and the great atmosphere.

PD Dr. sc.nat.
Paolo Cinelli
Head Division of
Surgical Research

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

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Head Division of Surgical Research

Prof. Margarete Arras, DVM
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1. Organisation

Prof. Dr. med. Pierre-Alain Clavien, PhD, Director Clinic of Surgery and Transplantation

Prof. Dr. med. Hans-Christian Pape, Director Clinic of Trauma Surgery

Prof. Dr. med. Isabelle Schmitt-Opitz, Director Clinic of Thoracic Surgery

Prof. Dr. med. Paul Vogt, Director Clinic of Cardiac Surgery

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

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

Prof. Dr. med. dent. Harald Essig, Director a.i., Clinic of Cranio-Maxillo-facial Surgery

Prof. Dr. med. Reto Schüpbach, Head of Intensive Care Medicine

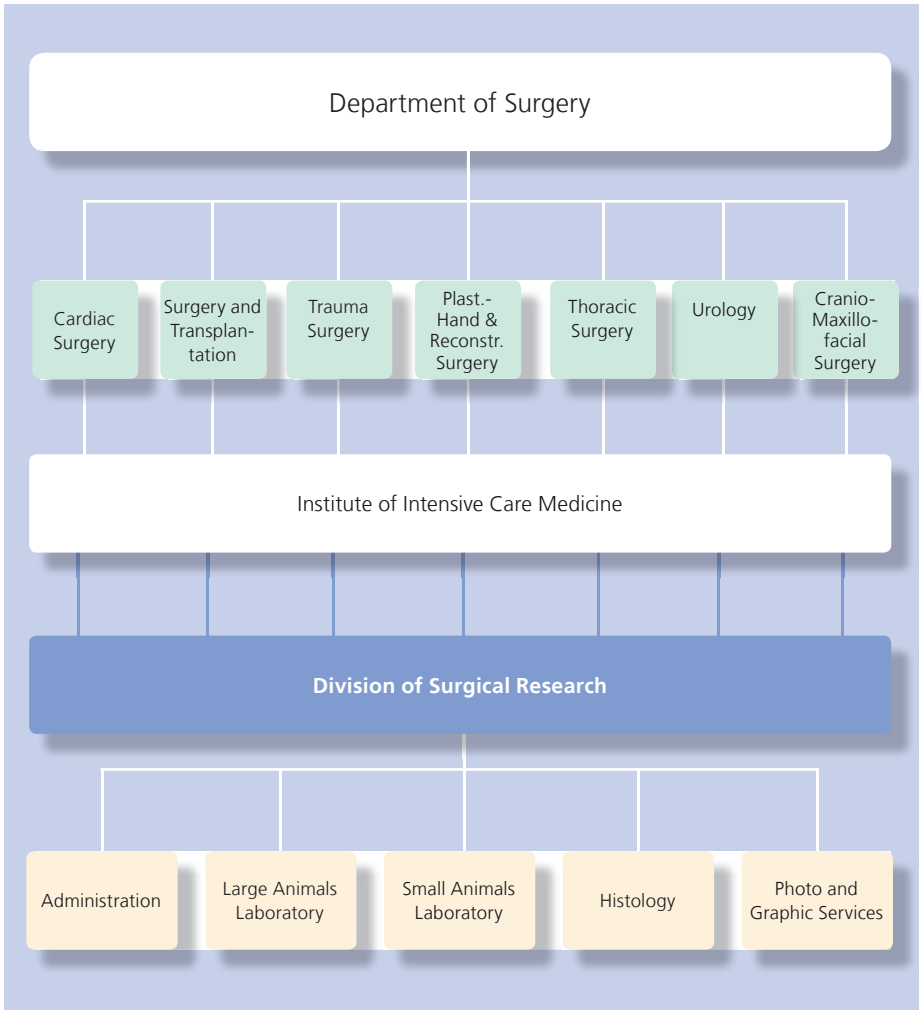
PD Dr. sc. nat. Paolo Cinelli, Head Division of Surg. Research

Prof. Margarete Arras, DVM Co-Head Division of Surg. Research

Tina Wentz Manager Division of Surgical Research

Donata Gröflin Teaching Coord. Division of Surg. Research

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



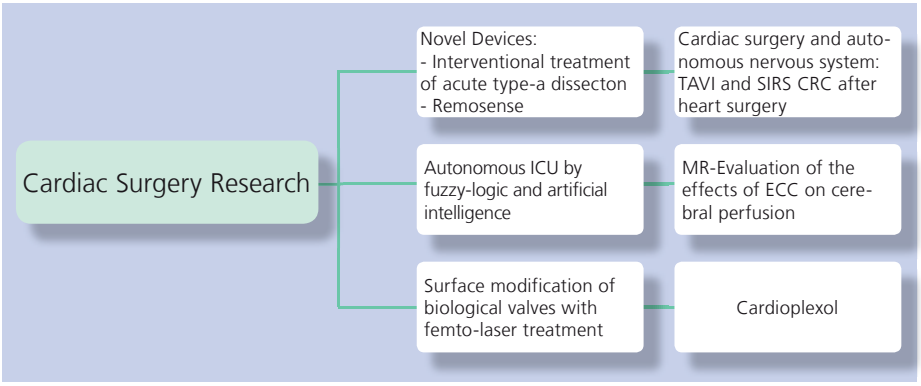
2. Research and Development

Cardiac Surgery Research

Prof. Dr. med. Paul Vogt, Director

Prof. Dr. med. Thierry Carrel

Prof. Dr. med. Robert Bauernschmitt



Novel devices: Interventional treatment of acute type-a dissection

M. Hofmann, M. Schmiady, G. Puippe (USZ, Interventional Radiology) P. Vogt, R. Bauernschmitt

Acute type-A dissection of the aorta is one of the most critical conditions in cardiovascular medicine, usually leading to immediate emergent surgery. Despite all improvements in surgical techniques, implant material and cardiopulmonary bypass, mortality and morbidity after surgery is high and did not change during the last decades.

Thus, the need for an interventional device has been claimed. Due to the frequently accompanying aortic valve insufficiency, the variable take-off of the coronary arteries and the anatomical variations of the ascending aorta and the location of the intimal tear several challenges have to be met to develop an immediately available graft meeting the needs of these patients in emergency conditions. To test various prototypes, a mock-circulation with the possibility to include biological tissues has already been realized.

Autonomous ICU by fuzzy-logic and artificial intelligence *(cooperation with Chair for robotics and Embedded systems, TU Munich)*

R. Bauernschmitt, A. Knoll (TU Munich)

At present, ICU-treatment depends on manual control performed by physicians and nurses. Many of these tasks can be transformed to a fuzzy-logic-based, autonomous and intelligent closed-loop control system. This may lead to a massive decrease oft he human workload. Control of inotropic medication and volume substitution can be transferred from former work of our group. Also automatic, intelligent control of extracorporeal pumps and oxygenatores has already been realized and published during earlier cooperrations. An addition, control of mechanical ventilators is the goal of the present project, which shall be achieved by a combination of a fuzzy-logic rule network together with machine learning through artificial intelligence.

The aim of the project is to improve proactive, individualized therapy for the patient, but also to unburden physicians and nurses to meet the demands of further pandemic situations.

Surface modification of biological valves with femto-laser treatment *(cooperation with NoviNano-institute, Lviv, Ukraine)*

P. Vogt, R. Bauernschmitt, I. Gnilitskyi, (Lviv, Ukraine)

While surgical repair is possible only in a minority of cases, implantation of heart valve prostheses is the only causal therapy in patients with advanced heart valve disease. Even state-of-the-art prostheses have a variety of shortcomings like thrombogenity (formation of blood clots on their surface), suboptimal hemodynamics and limited durability requiring additional operations or catheter interventions. The new generation of valve prostheses is supposed to be produced from biocompatible synthetic tissue, that, however, is treated by means of chemical and morphological modification of the surface towards a total blood- and cell repellent structure, thus preventing both blood clot formation and bacterial infection. The first step will be Developing and optimization of bloodphobic functional nano-microstructures on the surfaces of cardiac valves and stents by using femtosecond laser pulses.

- design bloodphobic laser-induced nano-micropatterning on metallic cardiac valves and stents. All experiment will be performed by using femtosecond laser system from Light Conversion “Pharos”.
- Laser-induced nano-microstructures will be optimized by means of tuning laser parameters (wavelengths, pulse duration, power). The laser parameters will be optimized to obtain high production of treated samples.
- The bloodphobicity of the samples will be tested by using tensiometer “Biolin Scientific”
- Subsequent small and large animal testing.

Cardiac surgery and autonomous nervous system: CRC after heart surgery *(cooperation with Humboldt-University, Berlin)*

R. Bauernschmitt, N. Wessel (HU Berlin)

The clinically available procedures for assessing the health and the prognosis of a patient during heart surgery are still too imprecise today and are only partially suitable for prognostic applications. The aim of the project is to characterise the health condition in the perioperative setting of cardiac surgery by the analysis of cardiorespiratory coupling (CRC). CRC investigates the mutual influence of cardiac and respiratory oscillations in their onsets, an increased CRC indicates an increased sympathetic tone. Preoperatively increased CRC values may be predictors for operation complications; a postoperatively increased CRC will show the stress due to the surgery but also inflammation.

The groups of the applicants already developed some methods for the detection and quantification of CRC, the pathophysiology however still is unknown. Therefore, different methods based on synchronisation and coordination, in time and phase space, will be developed for an advanced data analysis. Moreover, sophisticated models of cardiorespiratory dynamics will be developed to bring more insights into the physiology of this phenomenon.

The information obtained from CRC analysis is to be used in the future for preventive treatment, not least for the determination of the optimal time for treatment to prevent complications. In the context of a clinical study, the project will demonstrate for the first time, using methods of non-linear dynamics and biological physics, that the monitoring of the individual patients risk is possible and the basis for improved risk stratification during the perioperative setting of cardiac surgery.

MR-Evaluation of the effects of ECC on cerebral perfusion

M. Hofmann, M. Schmiady

The «Research Group Heart and Brain» of the Children–Hospital in Zurich works on brain damages caused by open heart surgery with heart-lung machine in children with congenital heart disease.The main focus is on neuropsychological and motor development. Optimizing the regimen of cardiopulmonary bypass in neonates has extensively been worked on, however, on-line-monitoring of cerebral damage by magnetic resonance imaging was not possible so far due to the incompatibility of both machines.

Thus, the goals of this project are the following:

- Development of an MRI-compatible heart-lung-machine
- Analysis of contemporary regimens of extracorporeal circulation and the detrimental effects on the central nervous system in a small animal experiment
- Optimizing these parameters and on-line control of their effects by imaging

Proof of concept has already been successfully finished.

Cardioplexol: a new form of cardioplegic solution on its way to clinical use

Th. Carrel

A Multi-Center, Open Label, Single Group, Observational Study to Investigate the Effects of Training on the administration of Cardioplexol

In a recently investigated RCT, Cardioplexol showed non-inferiority when compared to Buckberg blood cardioplegic solution. However, Cardioplexol was not administered as specified in the manufacturers protocol in 11.8% of the cases. This could indicate, that a training program may reduce the risk of incorrect administration.Primary and secondary Objectives: To explore the effects of a training program on the rate of correct application of Cardioplexol and to explore the effects of Cardioplexol on myocardial protection during ischemic period in on-pump cardiac surgery, and to evaluate the safety and tolerability of Cardioplexol. A multi-center, observational study was designed to evaluate the effects of a preparation and administration training program to cardio-

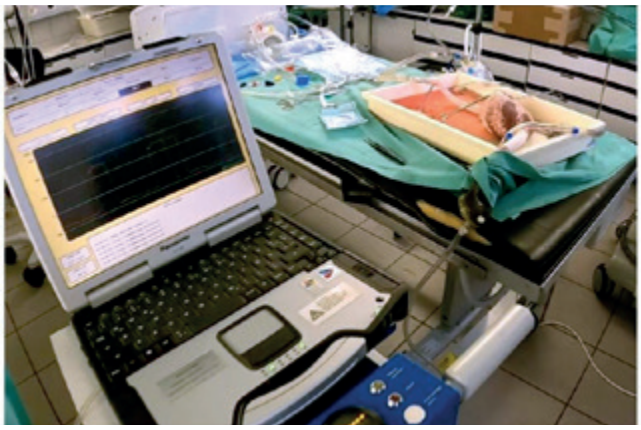


Figure 1: Preparation for analysis in the cadaver model (Extracorporeal pump and specimen)

technicians and cardiac surgeons inexperienced in the use of Cardioplexol. The training program consisted of a theoretical and one practical section. A short exam was taken by all participants in order to make sure that all aspects of Cardioplexol-Administration were fully understood. Each surgeon's first two surgeries with Cardioplexol were performed in the presence of a coach. Authorization for further use of Cardioplexol was only given when approved by the coach. After successful completion of the training program, each surgeon's next consecutive 4 cases were performed without the presence of the coach. Parameters regarding the primary efficacy endpoint were collected during the surgical procedure, patients were evaluated with respect to safety secondary endpoints from beginning of surgery up to 30 days after surgery. Male or female patients between 18 and 80 years of age requiring primary elective CABG or cardiac valve repair/replacement with an LVEV > 30% were enrolled in the study. A total of 25 surgeons were planned to be trained, account-

ing for a minimum of 150 patients to be operated in the study. Our study-center enrolled 5 active surgeons not familiar with the use of Cardioplexol. All surgeons successfully completed training and had two coached operations followed by 4 operations without further observation by the study designers/ Coaches. Data collection was completed in time. Study-results are not available yet

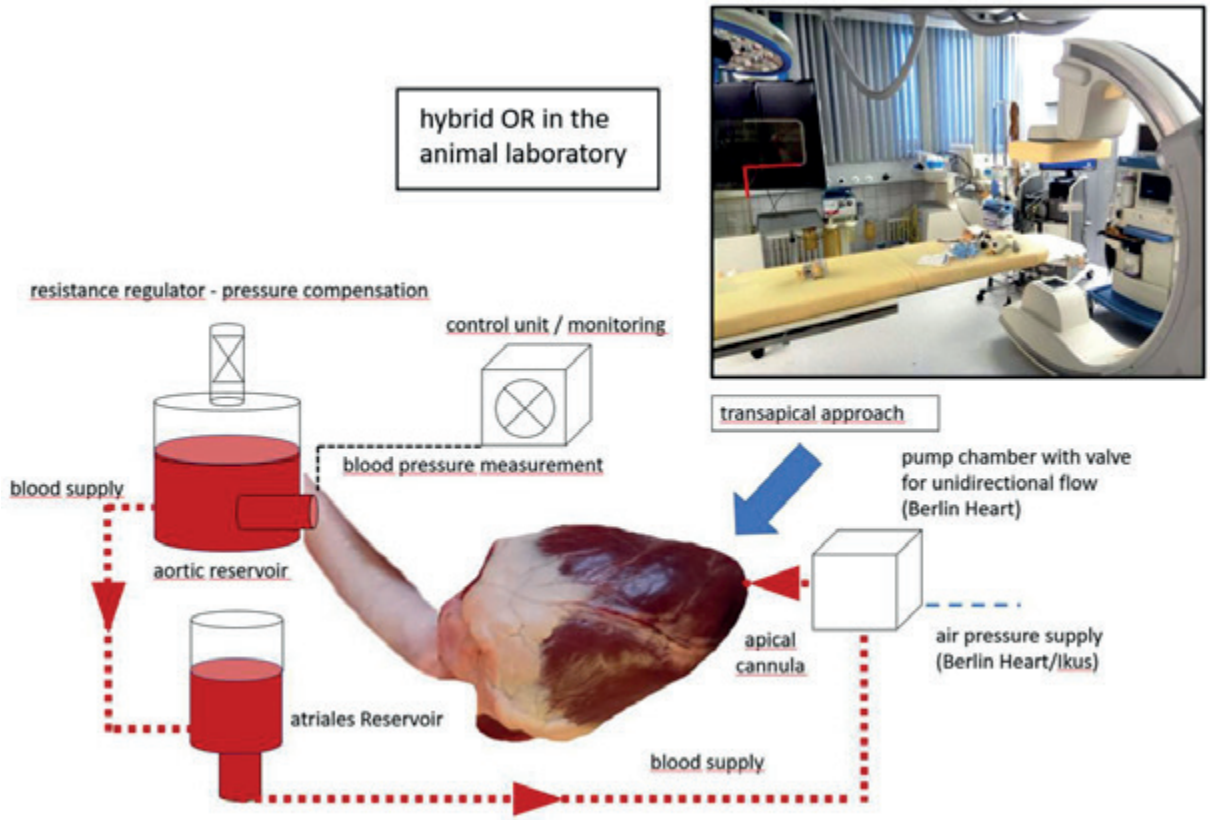


Figure 2: Schematic drawing of the artificial circuit giving us the possibility to examine different designs of TAAD-stents without sacrificing living animals

Collaborations / Sponsors:

- Dept. of Veterinary Surgery, Zurich
- Laboratory for tissue engineering, German Heart Center Berlin, Germany
- Division of Cardiology, University of Zurich
- Division of Radiology, University of Zurich
- NoviNano-institute, Lviv, Ukraine
- Institute of Physics, Humboldt-University Berlin, Germany
- Chair for robotics and Embedded Systems, TU Munich, Germany
- MEDIRA MedTech, Germany
- Telebionics, USA

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Surgery and Transplantation Research

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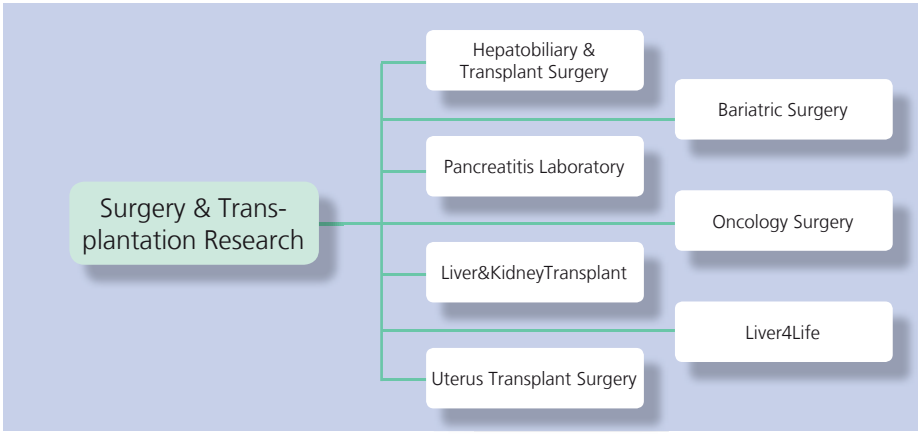
Prof. Dr.
Rolf Graf



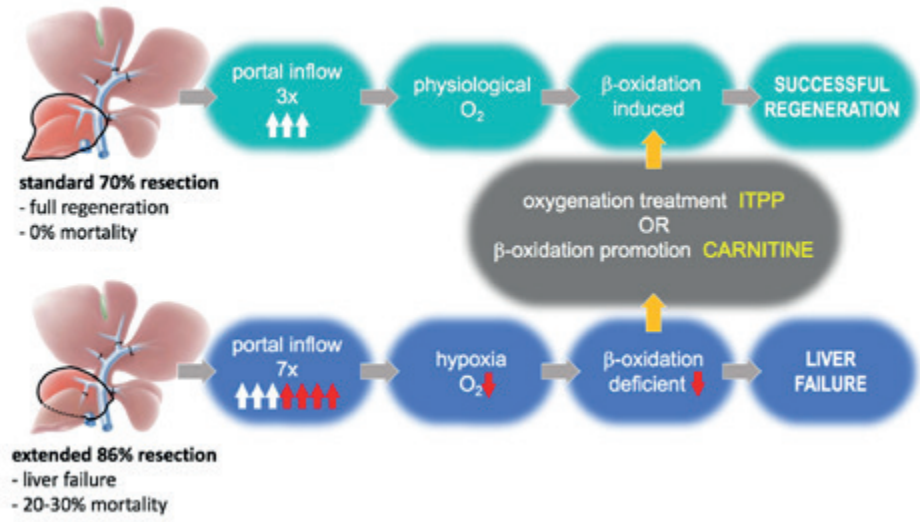
The research unit within the Department of Surgery and Transplantation encompasses several groups that all research novel options to improve surgery and its outcomes. Approaches range from developing new surgical techniques in appropriate animal models or studying the surgical consequences in patient populations to the exploration of fundamental research questions. Clinical translation remains the ultimate goal behind our research.

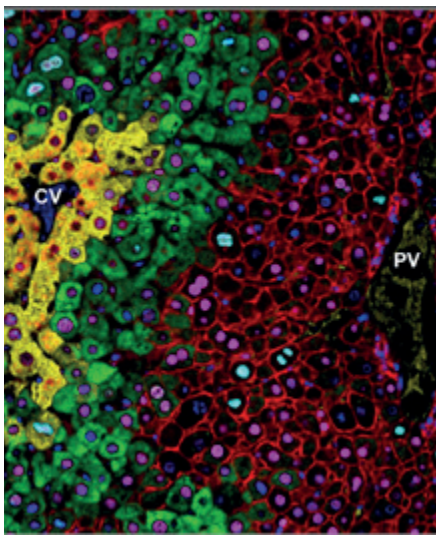
The core of our unit is the laboratory of the Swiss HPB Centre, which hosts the Hepatobiliary Research Group, the Pancreas Group, the Transplant Group, and the recent Uterus Transplant Group. Other recent additions have come through the Bariatric Group and the Surgical Oncology Group. A special branch of our research is provided by the Liver4Life Group, a joint-collaboration with machine engineers from the ETH-ZH funded through the Wyss Translational Zürich Institute (https://www.wysszurich.uzh.ch/projects/wyss-zurich-projects/liver4life).

Hepatobiliary Group

Surgical removal of hepatic tumors rests on the ability of the liver to regenerate. Understanding the principles behind liver regeneration therefore is one key prerequisite for the improvement of regenerative capacity and thus surgical success. We previously observed that fat is the principal energy source driving liver regeneration. Expanding these observations, we could show that the promotion of β-oxidation fosters regeneration sufficiently to prevent resection-induced liver failure. The latter is an entity that develops if the liver remnant left after surgery is too small in size to recover - indeed the most frequent cause of postoperative death in liver surgery. Fostering of β-oxidation may hence represent a clinically feasible and safe way to reduce surgical liver failure risks.

With the gain of a new SNF grant, we initiated a large project aiming at clarifying another fundamental question in liver regeneration: how can the liver grow and at the same time maintain vital metabolic function. The goal is to understand what sort of metabolic pressure acts during regeneration,





and whether such pressure is a physiological limit to the regenerative capacity of the liver. Such knowledge might enable us to enhance regeneration by easing the metabolic burden.
While surgery still offers the best chance of cure from liver malignancy, relapse is frequent after surgery. We now discovered that serotonin, a regeneration-promoting factor, also dampens immune responses against malignant cells - an unexpected finding for this neurotransmitter. Serotonin upregulates on cancer cells the expression of PD-L1, which then inhibits the activity of immune cells. Serotonin-lowering drugs in turn re-install normal immune activities and potentiate the efficacy of immune therapies. Importantly, we further observed that inhibition of PD-L1 has no effect on liver regeneration. Therefore, immunotherapy targeting PD-L1 should be compatible with regeneration and might hence represent a perioperative means to reduce recurrence risk - an important perspective given that radio- or chemotherapy both inhibit regeneration and cannot be applied perioperatively.

Pancreas Group
Research on the limited regenerative capacity of the pancreas has been completed. Focus of our 2019 activities were i) gastrokines as markers of pancreatic cancer risk, and ii) pancreatic stone protein (PSP) as a marker of sepsis. Considered as stomach-specific proteins, gastrokines are usually not expressed in the pancreas, however become so in benign precursors of pancreatic cancer. We could show that their expression modulates pancreatic disease progression in a way mostly consistent with a role as tumor suppressors. Given that gastrokines cease to be expressed in malignant pancreatic disease, and given they are secreted into circulation, these proteins may specifically mark the presence of pancreatic lesions that might progress to invasive disease.
Another protein released by the pancreas into circulation is PSP. Interestingly, we observed pancreatic PSP release under systemic stress conditions. Particularly in conditions of sepsis, PSP levels are highly elevated and thus may serve as an early indicator of systemic immune overreaction. Indeed, comparison of PSP against other established markers in burn patients confirmed its accuracy and its robustness in sepsis, indicating an upcoming, specific marker of sepsis in the clinic.

Transplant Group
Our previous research has led to the development of the HOPE (Hypothermic Oxygenated Liver Perfusion) technology, which is applied on donor organs before their transplantation. Based on rat studies, we could demonstrate that HOPE markedly reduces ischemic injury of grafts, enabling the use of marginal organs for transplantation (e.g. steatotic ones, highly sensitive towards ischemia). These findings have been translated into a large multicentric trial to establish the use of HOPE for marginal graft transplantation. Meanwhile, these studies were extended to the kidney. Moreover, associated research identified the improvement of mitochondrial function as a mechanism behind the HOPE benefits; indeed, a specific mitochondrial serum marker is able to accurately predict the success of transplantations following HOPE treatment in the clinic. New projects on the potential anticancer effects of HOPE have been initiated, and continuous funding of HOPE studies through new SNF grants has been secured.

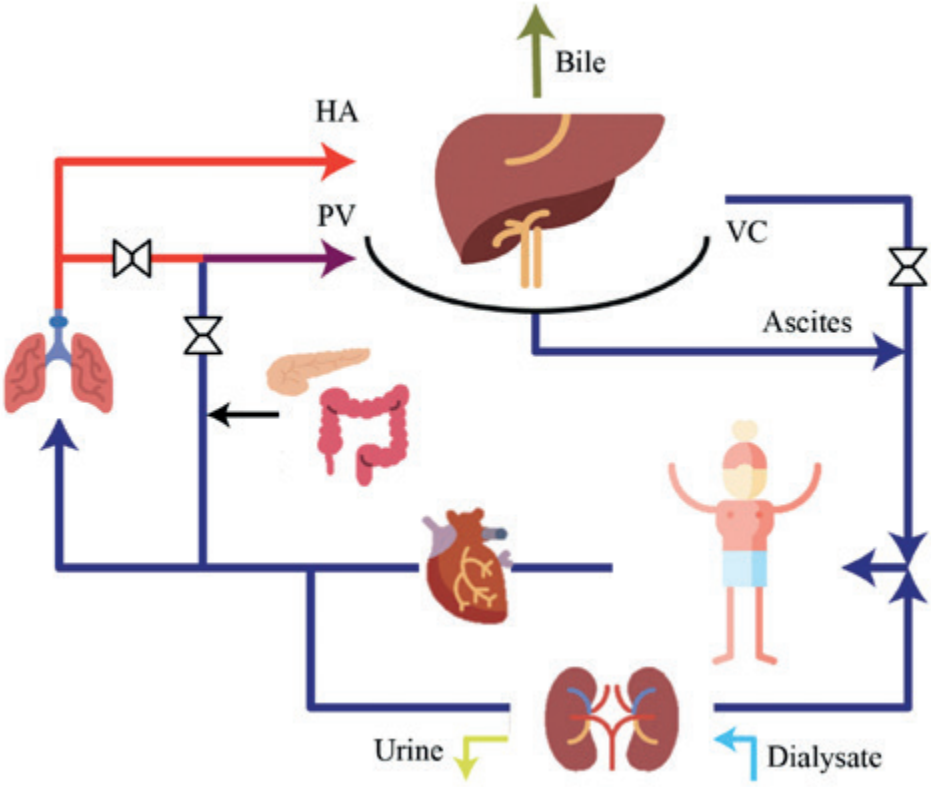
Uterus Transplant Group
Following the assembly of a multidisciplinary team, a research project has been started to advance the Swiss introduction of a clinical uterus transplant program for women with a dysfunctional uterus but a strong wish of motherhood. In a first step, we have developed a novel rat model of uterus transplantation and demonstrated that pregnancies following transplantation lead to normal offspring. This model now will be used to study the kind of ischemic injury that occurs to the uterus following harvest from deceased donors, and whether means such as HOPE can mitigate ischemic damage to a level compatible with later pregnancy.

S**urgical Oncology Group**
We are interested in a better understanding and the development of novel concepts for the treatment of metastatic disease, particularly peritoneal metastasis. Our main research goal is to improve the outcomes and treatment options for patients with metastatic cancer. In a collaboration with other European centres, we analyzed prognostic factors and created a novel prognostic score (BIOSCOPE) for patients with colorectal peritoneal metastasis treated with HIPEC (hyperthermic intraperitoneal chemotherapy). Current clinical projects focus on clinical differences of peritoneal versus hematogenous metastasis, a better understanding of the pathophysiology of surgical techniques (HIPEC), and the introduction and characterization of a novel concept of repetitive intracavitary treatment (PIPAC). In our experimental projects, we explore mechanisms and develop novel strategies for the treatment of peritoneal metastasis with the help of in vitro and in vivo models for peritoneal metastasis and local intracavitary treatment.

Bariatric Group
The spread of obesity has increased the demand for gastric bypass surgery. Following bypass, the metabolic deficiencies associated with obesity are largely reversed, however the underlying mechanisms are ill-understood. We have developed rodent models and designed exploratory clinical studies to better appreciate the physiological changes following Roux-en-Y gastric bypass. Investigated parameters range from ingestive behavior (e.g. microstructural organization of postoperative food/drink intake) or taste preferences to food reward and selection. We investigate these facets with the aim to sustain the benefits of bypass surgery over prolonged periods.

Liver4Life Group

The generous support of the UZH and ETH through Hans-Jörg Wyss has permitted the establishment of a surgical project joint with machine engineers from the ETH. Together, we developed a novel perfusion machine able to keep liver alive ex corpore for up to 10 days - an unprecedented achievement. Serial perfusion of donor livers discarded for transplantation has revealed that some poor-quality livers recovered function on the machine. Therefore, long-term perfusion may restore previously discarded organs to a transplantable status. According efforts in the clinic have been initiated. Likewise, the long perfusion time offers the opportunity to treat liver prior to transplantation (e.g. ex vivo defattening), or possibly even to regenerate smaller liver parts for multiple recipient transplantation. Thus, the machine provides us with a battery of new possibilities to ultimately expand donor pools or circumvent donor shortages.



Pump
- Blood transport
- Pulsation

Oxygenator
- Blood gas control
- pH control

Reservoir
- Buffer
- Mixing
- Filter

Dialysis
- Waste removal
- Volume control
- pH buffering

Infusions
- Nutrition
- Bile salts
- Flow control
- Artificial Pancreas

Other
- pO2 control in PV
- Diaphragm

Dr. med. Lilian Roth

Collaborations / Sponsors:

- Prof. Jean-Marie Lehn (University of Strasbourg)
- Prof. Gregory Gores (University of Minnesota Mayo Clinics)
- Prof. Scott Friedmann (New York University Mount Sinai School of Medicine)
- Prof. Alexander Galkin (Columbia University New York)
- Prof. Parry Guilford (University of Otago)
- Prof. David Meierhofer (Max Planck Institute for Molecular Genetics Berlin)
- Prof. Dr. Mathias Heikenwälder, PhD, (TUM Munich)
- Prof. Michelangelo Foti (University of Geneva)
- Dr. Jean-Rene Cardinaux (University of Lausanne)
- Prof. Aurel Perren (Universität Bern)
- PD Dr. Martin Hübner (CHUV, Lausanne)
- PD Dr. Deborah Stroka (University of Bern)
- Prof. Philipp Rudolf von Rohr (ETH Zurich)
- Prof. Sabine Werner (ETH Zurich)
- Prof. Maries van den Broek (University of Zurich)
- Prof. Dr. Adrian Hehl (University of Zurich)
- Prof. Dr. Achim Weber (University of Zurich)
- PD Dr. Andreas Boss (University of Zurich)
- Prof. Arnold von Eckardstein (University of Zurich)
- Prof. Thorsten Hornemann (University of Zurich)
- Prof. Martin Pruschy (University of Zurich)
- Dr. Daniela Lenggenhager (University of Zurich)
- Dr. Johannes vom Berg (University of Zurich)
- Various clinical collaborations

Awards:

Daniel Gero :Dr. Stierlin-Preis 2020
Christian Oberkofler: Swiss Transplantation Society Award 2020
Matteo Müller: Scientific Award Swiss Surgery Society 2020
Eshmuminov Dilmurodjon: Scientific Award Walter und Gertrud Siegenthaler Stiftung 2020
Matteo Müller: Transplant Center Zurich Award 2020
Pierre-Alain Clavien: Admittance to the National Academy of Medicine USA , 2020
Eshmuminov Dilmurodjon: Transplant Center ZH Award: An integrated perfusion machine preserves injured human livers for one week, 2019
Eshmuminov Dilmurodjon: American Society for Artificial Internal Organs - Best Abstract: A perfusion device to preserve liver function in an ex vivo environment for multiple days, 2019
Rong Chen: European Pancreas Club 2019 Travel Grant
Steiner Sabrina:European Pancreas Club 2019 Travel Grant
Steiner Sabrina: United European Gastroenterology Week 2019 Travel Grant
Seleznik Gitta: United European Gastroenterology Week 2019 Travel Grant
Petrowsky Henrik: Publon Peer Review Award 2019
Petrowsky Henrik: Outstanding Reviewer Award Hepatobiliary Surgery and Nutrition 2019

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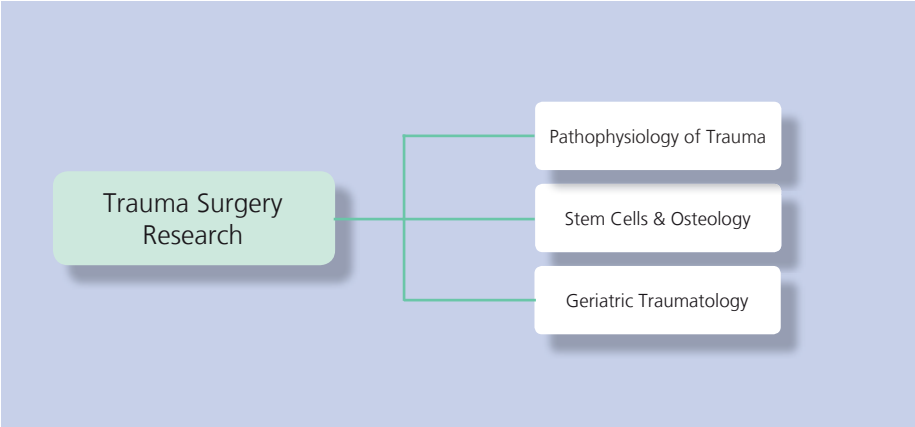
Trauma Surgery Research



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

PD Dr. sc.nat. Paolo Cinelli

As a leading trauma center, the Department of Trauma at the University Hospital Zurich provides help for severely injured patients. The Department is specialized in the surgical treatment of spinal, pelvic and extremity injuries as well as the use of artificial hip joints for fractures of the femoral neck. As an academic center, the clinic is actively involved in research and teaching. We are interested in all aspects of research that can improve treatment of severely injured patients at basic, translational and clinical levels. We have a team of surgeon scientists and basic scientists that closely work together to study the pathophysiology of trauma, the development of regenerative approaches for improving bone healing and the impact and treatment of fractures in older patients.

Pathophysiology of Trauma

Immunology of trauma

Severe trauma is an acute, often life-threatening situation that requires rapid management that is adapted to the overall injury pattern. In severe trauma, overwhelming systemic inflammation induces a complex host response that disrupts immune system homeostasis and triggers a systemic inflammatory response that predisposes patients to opportunistic infections and inflammatory complications, which can lead to nosocomial infections, sepsis or even multi-organ failure. We aim at identifying mechanisms associated with complicated courses after major trauma. To do this, we use systems biology approaches (transcriptomics, proteomics, lipidomics and metabolomics) and modern technologies like mass cytometry. The results are of importance to improve the prognostic performance and individual risk stratification in trauma patients.

In parallel to clinical studies on patients we have established 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. This standardized model allows studying the timely changes in local and systemic inflammation following multiple injuries. The combination of clinical and translational studies allows further dissecting of the molecular mechanisms underlying these physiological changes.

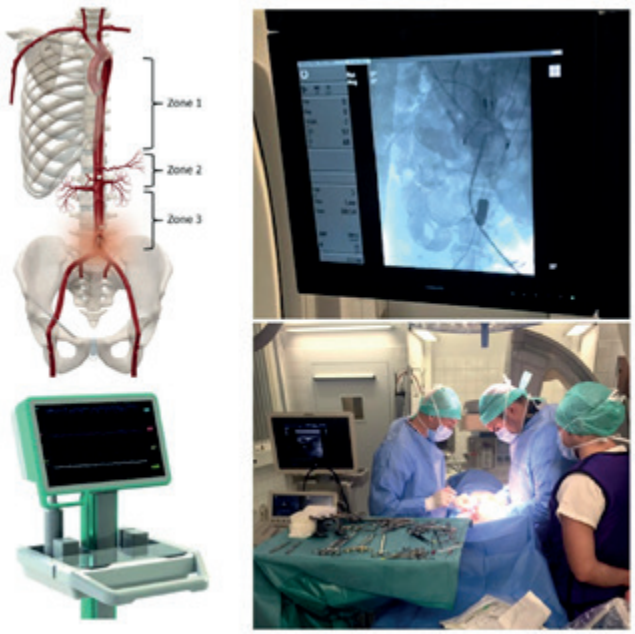


Fig.1: Surgical setup for REBOA experiments in a large animal model

Resuscitative endovascular balloon occlusion of the aorta (REBOA)

Hemorrhage is one of the main causes of early death, after severe blunt trauma. Although hemorrhagic control by external pressure, tourniquet, or open surgery are the commonly used interventions, endovascular the use of endovascular techniques for managing traumatic vascular lesions in solid organ injury is gaining greater popularity. The use of resuscitative endovascular balloon occlusion of the aorta (REBOA) as a modern clinical practice, adds a promising adjunct to the acute treatment of major blood loss in the abdomen or the pelvis. Depending on the bleeding source, REBOA may

be performed at three different zones: Zone 1 ranges from the left subclavian artery to the coeliac trunk; Zone 2 ranges from the celiac trunk to the most caudal renal artery, and Zone 3 extends from the most caudal renal artery to the aortic bifurcation (Figure 1). Even though REBOA may be used in severely injured patients with uncontrollable bleeding the zone-dependent effects of REBOA depending on the time of application are not yet fully studied. We compared the short-term zone- and organ-specific microcirculatory changes in abdominal organs and the extremity during occlusion of the aorta in a standardized porcine model. Microcirculation in the different organs was measured using an oxygen-to-see device. All abdominal organs showed significant changes in microcirculation during REBOA. The intra-abdominal organs reacted differently to the sameocclusion, whereas local microcirculation in extremities appeared to be unaffected by short-time REBOA, regardless of the zone of occlusion (Halvachizadeh et al. *Eur J Med Res 26:10*).

Visual-Based Analytics Tool for Outcome Prediction in Polytrauma Patients

Big data-based artificial intelligence (AI) is gaining importance in medicine and may be helpful in the future to predict diseases and outcomes. Our group recently used a big database to develop a new predictive visual analytics tool for polytrauma patients (IBM WATSON Trauma Pathway Explorer) that allows the assessment of individual risk profiles early after trauma. We could now validate this AI tool and compared it with the commonly used Trauma and Injury Severity Score (TRISS) scoring systems that has been developed to estimate survival probability in blunt and penetrating trauma. The new WATSON tool is capable of predicting different outcomes of patients who have sustained multiple injuries. The prediction of the WATSON-based visual analytics tool for early death corresponded to the effective clinical outcome in approximately 90% of the analyzed polytrauma patients, which was similar to the discriminative performance of TRISS. The WATSON Trauma Pathway Explorer, however, was better calibrated to the test data. Our findings show how big data-based systems have the potential to improve or replace established scores and to give us a deeper understanding of clinical relations in traumatology and provide in future the foundation for personalized medicine in polytrauma patients (Mica et al. *World J Surg.* 44(3):764-772; Niggli et al. *J Clin Med* 10(10):2115)).

Skeletal Stem Cells & Osteology

Surgical interventions for bone repair are required for numerous reasons, such as trauma-resulting non-union fractures, or diseases including osteoporosis and osteonecrosis. Unlike in other tissues, the majority of bony injuries (fractures) heal without the formation of scar tissue, and bone is regenerated with its pre-existing properties largely restored, and with the newly formed bone being eventually indistinguishable from the adjacent uninjured bone. Despite the fine degree of orchestration during fracture healing, the process may be impaired. Currently, 10–15% of the fractures that occur annually result in poor or unresolved healing, so called non-unions or critical size defects. These fractures, which cannot heal completely, from alone over a long period, represent a major clinical orthopedic surgery.

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 appropriate culture conditions, into osteoblasts, chondrocytes, and adipocytes. The major problem with the use of MSCs isolated from bone

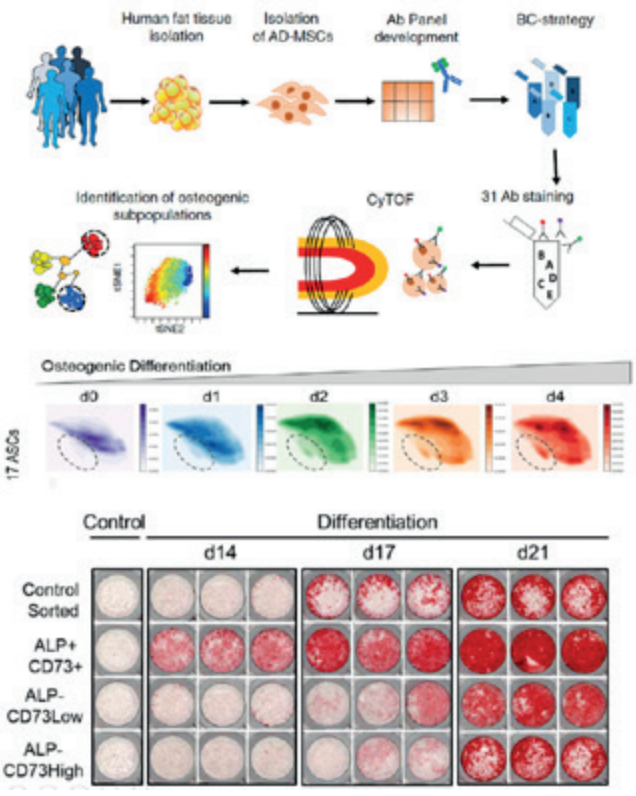


Fig. 2: Identification of ALP+/CD73low subpopulation of mesenchymal stem cells with enhanced osteogenic differentiation potential by mass cytometry.

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. Due to variations in the isolation, expansion and especially in the characterization of MSCs, it is difficult to interpret and

compare study results, for example on therapeutic efficacy. The development of standardized and reproducible analysis methods for predicting the differentiation potential of MSCs is therefore imperative. The quantification methods currently used to determine the differentiation potential of MSCs are based on absorption measurements, which are imprecise and prone to errors. We have therefore established a novel method to quantify objectively the differentiation potential of MSCs and to identify functional differences between different cell populations (Eggerschwiler et al. *Stem Cell Research & Therapy* 10:69).
We are also testing the possibility to enrich defined subpopulations of stem/progenitor cells for direct therapeutic application without requiring an in vitro expansion. 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. We could recently analyze with this technology the subcellular composition of 17 human MSC lines isolated from adipose tissue. We were able to identify a subpopulation of cells (ALP+/CD73low) that had an increased osteogenic differentiation potential (Figure 2). This combination of markers can be used both for the prospective isolation of selected cells from the stromal vascular fraction of adipose tissue and to determine the differentiation ability of the MSC kept in culture (Canepa et al. *Stem Cell Research & Therapy* 12:7).

Geriatric Traumatology

The elderly population increases worldwide and subsequently the number of geriatric trauma patients rises as well. Geriatric patients require special medical attention due to the higher risks for mortality and morbidity related to frailty, reduced physiological compensation mechanisms after trauma, polypharmacy and preexisting comorbidities, both in high-energy trauma cases as well as in low-energy trauma situations. Prediction-model based outcome scores are useful tools for judging the patients' status and for guiding medical decision-making. Especially in trauma, there is a need for adequate (mortality) prediction models to optimize post-resuscitation triage and the determination of initial therapy until transfer to the intensive care unit in severely injured patients. The existing scores are either not specifically developed and validated for mortality prediction of the elderly severely injured patients or highly rely on judgments, which are known for their suboptimal inter-observer reliability. We have developed a feasible and accurate novel score, the GERtality score, which combines simplicity with high accuracy for the prediction of in-hospital mortality in geriatric trauma patients. The score includes only five easily assessable patient variables, which makes it practical and simple to calculate (Schere et al. J. *Clin. Med.* 10, 1362).
An important clinical aspect of the ageing population is the occurrence of an imbalance between bone formation and resorption, which results in various diseases, such as osteopetrosis, osteopenia, and osteoporosis. The decrease in bone density and quality in osteoporotic patients leads often to 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.

Awards:

Benjamin Eggerschwiler, Best Poster Award, 18th Day of Clinical Research, Zurich

Collaborations/Sponsors:

- Clinical Trials Center, University Hospital Zurich
- Simone Schürle, Department of Health Sciences and Technology, Swiss Federal Institute of Technology
- Michael Krauthammer, Biomedical Informatics, University Hospital Zurich
- Thorsten Hornemann, Institute of Clinical Chemistry, University Hospital Zurich and University of Zurich
- Orthopedic Research Laboratory, Biomechanics, University Hospital Balgrist, Zurich
- Institute for Biomechanics, ETH, Zurich
- Institute for Regenerative Medicine (IREM), University of Zurich
- Translational Large Animal Research Network (TREAT)
- Center for Applied Biotechnology and Molecular Medicine (CABMM), University of Zurich
- Jan Schwab, Klinik und Poliklinik für Neurologie & Experimentelle Neurologie, Charité Universitätsmedizin Berlin
- Markus Huber-Lang, Dept. of Traumatology, Hand-, Plastic and Reconstructive Surgery, University Hospital Ulm, Germany

→

Collaborations/Sponsors (Continuation)

- 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 Munich, Munich, Germany
- Manfred Claassen, Institute for Molecular Systems Biology, Department of Biology, ETH Zurich, Switzerland
- Valerio Orlando, King Abdullah University of Science and Technology, Saudi Arabia
- Wendelin Stark, Olivier Gröninger, Institute for Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zurich, Switzerland.
- Todd McKinley, Indiana University, Purdue University, Indiana, USA

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Simon Tiziani

Lisa Stähli,
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Paola Nocchi,
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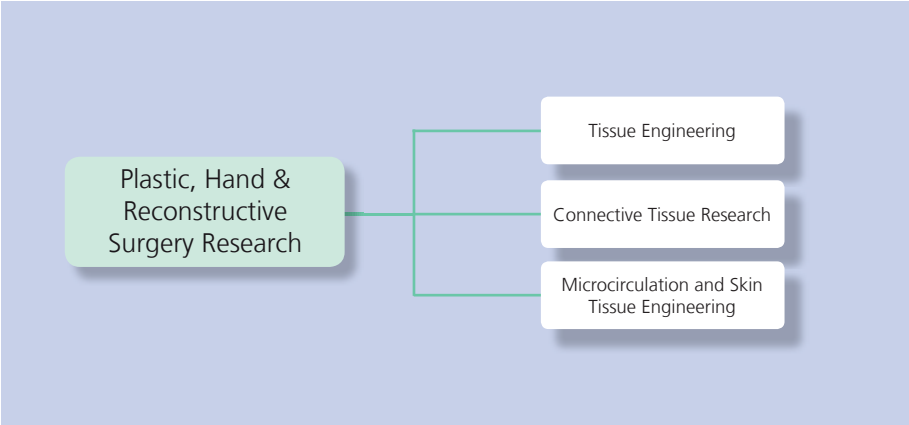
Clinical Science
PhD student

Plastic, Hand & Reconstructive Surgery Research



Prof. Dr. med. Pietro Giovanoli, Director

PD Dr. med. Maurizio Calcagni

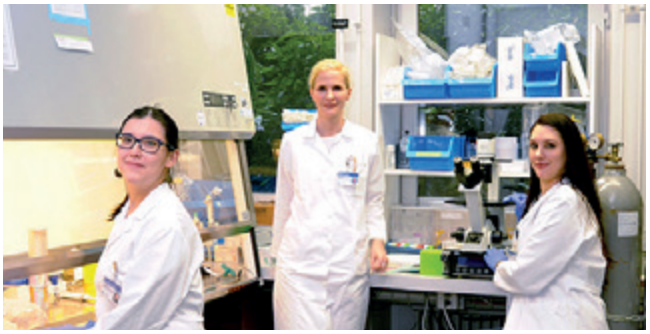
Research activities in the Plastic Surgery and Hand Surgery lie in the fields of microcirculation, wound healing, connective tissue research, tissue engineering, skin grafts, motion analysis, inflammatory biomarkers in burns, vascularized composite allotransplantation and lymphedema.

Prof. N. Lindenblatt has been engaged in several multidisciplinary projects in the fields of wound healing, preclinical drug development and tissue engineering.

Effect of TOP-N53 on angiogenesis and vascular leakage in diabetic mice
Diabetic foot ulcers are a serious complication in diabetic patients, characterized with impaired wound healing and deficient blood supply. In collaboration with Topadur Pharma AG and financed by the Swiss Innovation Agency (Innosuisse), the group is currently performing a preclinical proof-of-concept study in diabetic mice to test the efficacy of TOP-N53, a pro-angiogenic novel compound. The compound can be potentially used to treat diabetic foot ulcers by promoting angiogenesis and reducing endothelial dysfunction.

Molecular profiling of autologous fat graftings
Investigation of the underlying molecular mechanisms that contribute to the regenerative properties of autologous fat graftings (microfat and nanofat) through mass spectrometry and molecular biology methods. Nanofat is prepared through mechanical shearing shearing and used successfully in the clinic to treat hyperthrophic scars and rejuvenate skin. The successful identification of factors involved in nanofat's regenerative properties may lead to advantageous therapeutic benefits, resulting in direct translation and research application in regenerative medicine.

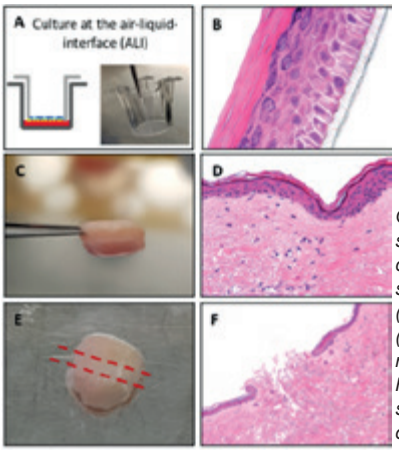
***In situ* bioengineered dressing for chronic wounds**
The Lindenblatt group is highly involved in the Hochschulmedizin Zurich Flagship 2016 Project "Skintegrity", where innovative approaches for diagnosis and therapy of skin diseases and of wound healing are being investigated. In collaboration with Prof. S. Ferguson and Prof. K. Würtz (ETHZ), the group is developing a personalized wound dressing that combines electrospun membranes and nanofat as a healing factor.



Group of Prof. Nicole Lindenblatt: from left; Nadia Sanchez-Macedo, Nicole Lindenblatt and Michelle McLuckie.

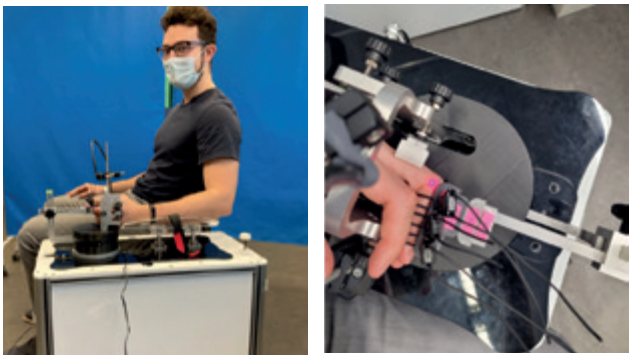
Wound healing by PD Dr. med. Maurizio Calcagni.
Wound healing disorders (hypercortisolemia) caused by chronic immunosuppressive treatment with glucocorticoids (GC) are investigated. There are indications that at the molecular level, a downregulation of the protein Nrf2 (nuclear factor (erythroid-derived 2) -like 2) could be involved in the wound healing disorder. For this purpose, three in vitro skin models using human keratinocytes with increasing complexity are used.
The study will provide essential insights into chronic GC-induced wound healing disorders as well as the effect of Nrf2 induction on wound healing. In addition, a possible treatment with a physiological compound is under investigation.

Kevin Arnke, PhD



Overview of the three in vitro skin models with increasing complexity: 3D epidermal skin model using Transwell® (A), skin organ culture model (C) and artificial "wound" model (E). The corresponding Hermatoxylin Eosin staining shows the tissue architecture of each model (B, D, F).

Motion Analysis by PD Dr. med. Maurizio Calcagni.
The aim of the motion analysis project is to quantify hand function based on biomechanical measurements. To assess the effectiveness of different surgical treatments and to be able to provide treatment recommendations, a quantitative and objective measurement technique is crucial. In 2019 and 2020, a new 3D motion analysis system consisting of 20 infrared cameras was installed, allowing us to study the effects of hand and wrist pathologies on daily activities more time-efficiently and with greater accuracy. The lab-internal motion analysis protocol was complemented with additional daily activities that are of interest with respect to finger injuries, and validated in healthy subjects.
Joint stiffness is common in patients after finger injuries and can severely impair hand functionality. However, objective clinical measurements of joint stiffness have been lacking. Therefore, to complement the kinematic analysis, a device for measuring the stiffness of the finger joints was developed in collaboration with the Institute for Biomechanics ETH and successfully tested in healthy volunteers. Measurements of patients after intra-articular finger fractures will be continued in 2021.



Typical equipment for motion analysis of fingers.

Connective Tissue Research and Tissue Engineering
Together with the ETH Zurich (Prof. Snedeker and Prof. Vogel) t**endon rupture repair** by a biodegradable polymer tube has been investigated. In order to facilitate the translation into clinics, the previously applied polymer tube has been tested with respect to storage and sterilization methods in order to confirm that bioactivity is retained after UV sterilization or storage at different temperature. Moreover, in vivo rabbit experiments showed the anti-adhesion effect after 12 weeks.
As for **artificial tendon tissue engineering**, novel stretching regimen of tissue engineered constructs seeded with adipose-derived stem cells have been developed and were applied to new piezoelectric scaffold materials developed at EMPA St. Gallen. Such strategies are applied to **bone tissue engineered constructs** in a collaboration with Prof. Wendelin Stark from ETH Zurich.
Finally, the impact of the secretome of differently sized spheroids is assessed, based on human adipose-derived stem cells in the chorioallantoic membrane of the chicken embryo (CAM assay) as well as in the chicken aortic ring assay on the **vascularization** (with Prof. Max Emmert).

Regenerative and Reconstructive Plastic Surgery Research Group (Group Prof. Jan Plock)
The research focus of our translational studies is on immunomodulatory and regenerative aspects of mesenchymal stromal cells. In the clinical spectrum we focus on tissue engineering and trauma immunology, especially in burn patients.Vascularized composite allotransplantation (VCA) is the transplantation of composite tissue as a single unit like face, hands and limbs. Transplant induced rejection is a major challenge in VCA and is usually associated with graft vasculopathy (GV). Thus, the aim of this project is to assess GV during VCA. Rat hind limb transplanted from Brown Norway into fully mismatched Lewis rats was used as an experimental model of VCA.

Understanding the molecular mechanisms underlying lipedema and lymphedema onset and development
The main interests of the group of **Dr. Gousopoulos, PhD**, lay on underlying mechanisms that contribute to the development of lymphedema and lipedema. Foundation of our research is the development of a lipedema and lymphedema biobank of skin and fat rest material, which is produced during the surgical process of lipedema or lymphedema treatment. Detailed histological, molecular and phenotypic analysis using cutting-edge techniques (incl. CyTOF, Aurora, lipid mass spectrometry, single cell RNA sequencing etc) are used to underpin the mechanisms underlying the pathology of these diseases.
Our work on lipedema has revealed an aberrant adipose tissue architecture in lipedema, as well as a specific immune cell composition, distinct to the one observed in obesity or

lymphedema. Our work is focused on understanding the role of specific immune components in the onset and progression of the disease, with a particular focus on how these may influence adipocyte growth, differentiation and metabolism. The immune cell infiltration as a key trigger and determinant of lymphedema and impaired lymphatic function presents the second main interest of the group. The initial phenotypic and molecular analysis will be followed by targeted animal studies to refine the mechanisms of action and evaluate novel pharmacological therapeutic solutions.

The Group of PD Dr. med. Bong-Sung Kim has worked on following topics:
Research on the MIF-protein familiy in the context of wound healing and fibroblast differentiation (Kooperation with LMU München and Yale Universität); Tissue Engineering Ansätze with innovative Hydrogels, mechanischer SVF und MIF-2 Delivery Systemen (Kooperation mit LMU München und ETH Zürich); Innovative regenerative Therapieansätze in der Verbrennungschirurgie
Erforschung eines neuen supermikrochirurgischen arteriovenösen Shunt Modells in der Ratte zur in vivo Vaskularisierung von mechanischer SVF (Kooperation mit Division of Reconstructive; Microsurgery des Chang Gung Memorial Hospitals Taiwan sowie dem Institute of Stem Cell and Translational Cancer Research, Chang Gung Memorial Hospital Taiwan); Evaluation of robot-assisted operations in reconstructive breast surgery (Kooperation mit Division of Reconstructive Microsurgery des Chang Gung Memorial Hospitals Taiwan)

Awards:

Group of Prof. J. Plock:
Winner Best Science Award, International Society of Vascular Composite Tissue Allotransplantation Society, New Delhi, 2019
Winner of the SGPRAC Award and Best Basic Science Presentation 2019
Group of PD Bong-Sung Kim:
2020 - Taiwan Scholarship Program der Ministry of Foreign Affairs, Ministry of Education Taiwan – Finanzierung des einjährigen Reconstructive Microsurgery Fellowships am Chang Gung Memorial Hospital Linkou, Taoyuan, Taiwan bzw. International Master in Science of Microsurgery an der Chang Gung University, Taoyuan, Taiwan
2020 - Hans Anderl Award der European Association of Plastic Surgery (EURAPS) – Zentraler Wissenschaftspreis der EURAPS
2019 - Erster Platz - Young Plastic Surgeons Scholarship 2019 der EURAPS – Finanzierung eines einmonatigen europäischen Fellowships
2019/2020 - Sachmittel „Die Rolle der Makrophagen migrationsinhibierenden Faktor (MIF)-Proteinfamilie in Wundheilung und Übergewicht“ durch die Deutsche Forschungsgemeinschaft (DFG) über drei Jahre

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
- 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
- Prof. Dr. med. Maximilian Emmert, Herzchirurgie USZ Zurich
- Wyss Center für Regenerative Medizin, Zürich
- Charité Berlin,

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Maurizio Calcagni

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Nicole Lindenblatt

PD Dr. med.
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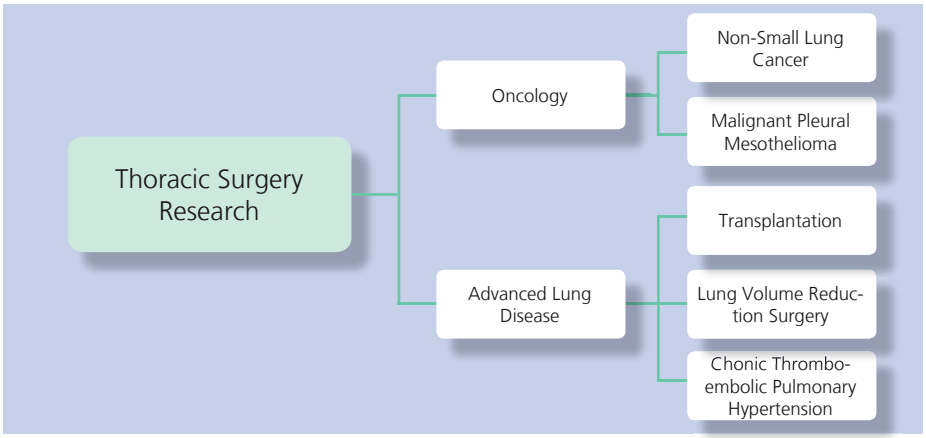
Michaela Kirschner



Research in the Department of Thoracic Surgery covers different lung pathologies.

Malignant Pleural Mesothelioma (MPM)
Research into MPM, an aggressive and incurable cancer related to previous exposure to asbestos, aims to improve diagnosis, prognosis and treatment options for MPM patients. Using our continuously growing comprehensive biobank, we assess the biomarker potential of protein and gene expression, mutation profiles and microRNAs, with a major focus on the identification of markers that can be easily detected in the blood of patients. Towards this end, in one of our projects, we are currently performing RNA and small RNA Sequencing on extracellular vesicles secreted by primary MPM and non-MPM cell lines. Preliminary comparison of the sequencing data has revealed a number of candidates, which are more abundant in extracellular vesicles secreted by MPM cells. These candidates are currently further validated, as they could represent potential novel diagnostic biomarker candidates.

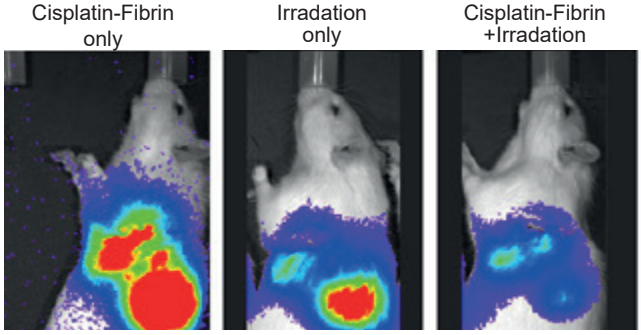


Fig. 1: Efficacy of cisplatin-fibrin followed by irradiation on tumor recurrence in an orthotopic MPM rat model. IL45-luciferase cell were implanted subpleurally, and resulting tumors were resected 9 days later. Intracavitary cisplatin-fibrin or placebo (NaCl-fibrin) was applied post resection. On day 12, 20 Gy CT guided local irradiation of the former tumor region, was applied. Tumor growth was monitored every 3 days by IVIS bioluminescence imaging. On Day 21 animals treated with the combination of cisplatin-fibrin showed significantly decreased tumor burden compared to the single modalities.

In another project, we are currently evaluating the role of microRNAs in the response of MPM cell to chemotherapy. Here we could show that overexpression of certain microRNA can lead to a sensitization of the cancer cells to the chemotherapeutic drug cisplatin, as well as to the current gold-standard of cisplatin-pemetrexed doublet therapy.
Furthermore, in preclinical small animal models, we are evaluating novel potential therapeutic targets, as well as innovative treatment strategies such as intracavitary application of chemotherapy in combination with radiotherapy. In our orthotopic rat mesothelioma model, we could show that a combination of surgical resection, followed immediately by intracavitary application of cisplatin bound to the natural glue fibrin, and sequential adjuvant irradiation results in improved local tumor control (Fig.1). In addition, patient recruitment for a phase II clinical trial to prevent local tumor recurrence (NCT01644994) by intracavitary application of cisplatin-fibrin after macroscopic tumor resection was completed in 2019, and the follow-up phase will end this summer.
In further projects, we evaluate if the loss of function of BRCA1 associated protein 1 (BAP1), which is observed in ~50% of MPM cases, could be exploited for targeted therapy. For this, a genetically engineered model was established expressing either functional or non-functional BAP1 and whole-genome siRNA synthetic lethality screens were performed assessing differentially impaired survival between the two cell lines. The screen unexpectedly revealed 11 hits that were more cytotoxic to BAP1-proficient cells. Two actionable targets, ribonucleotide reductase (RNR) catalytic subunit M1 (RRM1) and RNR regulatory subunit M2 (RRM2), were validated. This revealed e.g. that gemcitabine and hydroxyurea were more cytotoxic in BAP1-proficient cell line-derived spheroids compared to BAP1-deficient. Taken together, we found that BAP1 is involved in the regulation of RNR levels during replication stress. Our observations reveal a potential clinical application where BAP1 status could serve as predictive or stratification biomarker for RNR inhibition-based therapy in MPM (Fig. 2).

Fig 2: Schematic representation of the potential role of BAP1 in the regulation of RRM2 on transcriptional level under normal and replicative stress condition. Upon replicative stress, in the absence of BAP1, E2F-1 is stabilized as a consequence of DNA-damage-induced ATM activation, leading thereby to RRM2 up-regulation (left panel). Upon replicative stress in the presence of BAP1, E2F-1 level decreases, therefore up-regulation of RRM2 upon replicative stress is reduced (right panel).

Lung cancer

Lung cancer is the most fatal disease compared to other malignancies. Accumulated data shows that the transmembrane exopeptidase CD26/dipeptidyl peptidase 4 (DPP4) is expressed on lung cancer. We showed before that inhibition of CD26/DPP4 reduced the size of lung tumors mainly via enhanced NK cell activity. In a next step, we aimed at improving the effect of CD26/DPP4-inhibition by combining CD26-inhibition with a PD-L1 antagonist, and developed an ex vivo culture system using primary lung cancer cell lines generated by ourselves or obtained through international collaborations. First results show that PD-L1 expression is boosted in the presence of INF-γ (Fig. 3), and, given the high expression of IFN-γ from enhanced NK cell activity after CD26-inhibition, we expect that a combined inhibition of PD-L1 and CD26 will synergistically enhance the anti-tumoral effect against lung cancer.

In another project, we are using proteomics-based approaches for the identification of prognostic biomarkers. In order to validate previously discovered prognostic biomarkers in lung adenocarcinoma (LAC) and in collaboration with a group in ETHZ, we established an ABPP-SWATH/DIA-MS method for the quantitation of serine hydrolases (SH) enzymatic activities. With this newly established strategy and starting with 24 OCT-embedded biopsies of stage IIIA LAC, we reproducibly and precisely quantified the active hydrolases depletion while incorporating measurements of the proteome composition and abundances. We also introduced a new protease activity index, expressed as the Relative Activity-Dependent Depletion index (RADDi), that can separate tumors from non-tumor samples and stratify survival subtypes. Additionally, the contextual information generated using our approach (e.g., enzyme quantity, active versus non-active fraction, and levels of endogenous inhibitors) can be used to integrate enzyme data with the available computational machine learning approaches and to formulate hypotheses regarding the mechanisms that regulate SH activity. Our ultimate goal is now to measure the proportion of “inactive SHs” from the “total” SHs and potentially follow 400 enzymes activities of the SH superfamily in our lung resection specimens.

Another area of lung cancer research is the establishment of representative primary cell culture models, which can in future be used for biomarker studies, as well as for high through-put drug screening approaches to identify novel treatment options. In lung cancer, our current focus is on the establishment of 3D organoid/tumoroid models as these are better suited to reflect the primary tumor including its intratumoral heterogeneity. So far, following establishment of a suitable work-flow and culture protocol, we have established 15 organoid cultures from 34 patients (success rate: 44%). Immunohistochemical staining have confirmed that the organoids retained the intratumoral heterogeneity of the primary tumor. In a next step, we will use sequencing approaches in order to also confirm the molecular identity between primary tumor and tumor organoid.

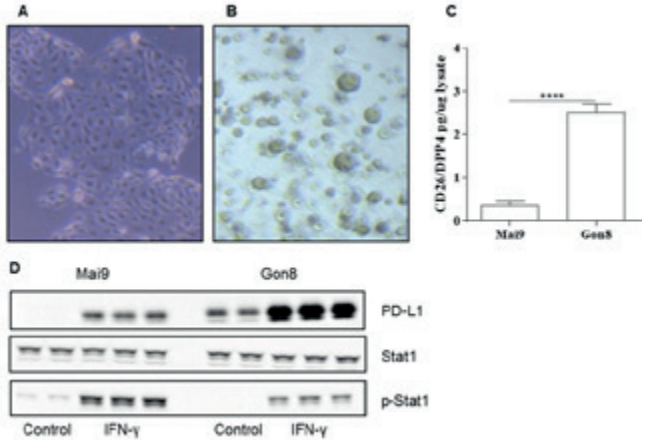


Fig. 3: 3D organoid culture of primary lung cancer cells. Lung cancer cells in conventional 2D culture (A) and a 3D organoid model comprising different types of cells and surrounding extracellular matrices that typically mimics lung cancer (B). Gon8 lung cancer cells express significantly higher CD26/DPP4 levels compared to Mai9 cells (C). Over expression of PD-L1 in the presence of IFN-γ via phosphorylation of Stat1 (D) in cancer cells from lung adenocarcinoma (Mai9 and Gon8).

Lung transplantation

To overcome organ shortage for lung transplantation and reduce waiting list mortality, we tested several original hypothesis in both porcine and rat models.

With the rat ex vivo lung perfusion (EVLP) model, we used drugs to 1) modulate specifically plasma membrane or mitochondria specific ATP sensitive potassium channels and reduce oedema formation, or 2) drugs such as nicotinamide adenine dinucleotide to modulate pulmonary vasoconstriction during EVLP or in a mismatch model of rat lung transplantation to attenuate acute and chronic allograft rejection. We also applied gene therapy related methods and rat EVLP for the delivery of adeno associated viruses into the bronchus and tested for the transfection efficacy of 4 different serotypes. We screened for optimal EVLP perfusion temperature since subnormothermic temperatures have proven beneficial for other solid organ transplants. We evaluated the effects of subnormothermic temperatures on EVLPs with subsequent left lung transplantation and recorded significantly higher lung oxygen-

Itzel Shantal Martinez Lopez, PhD Student

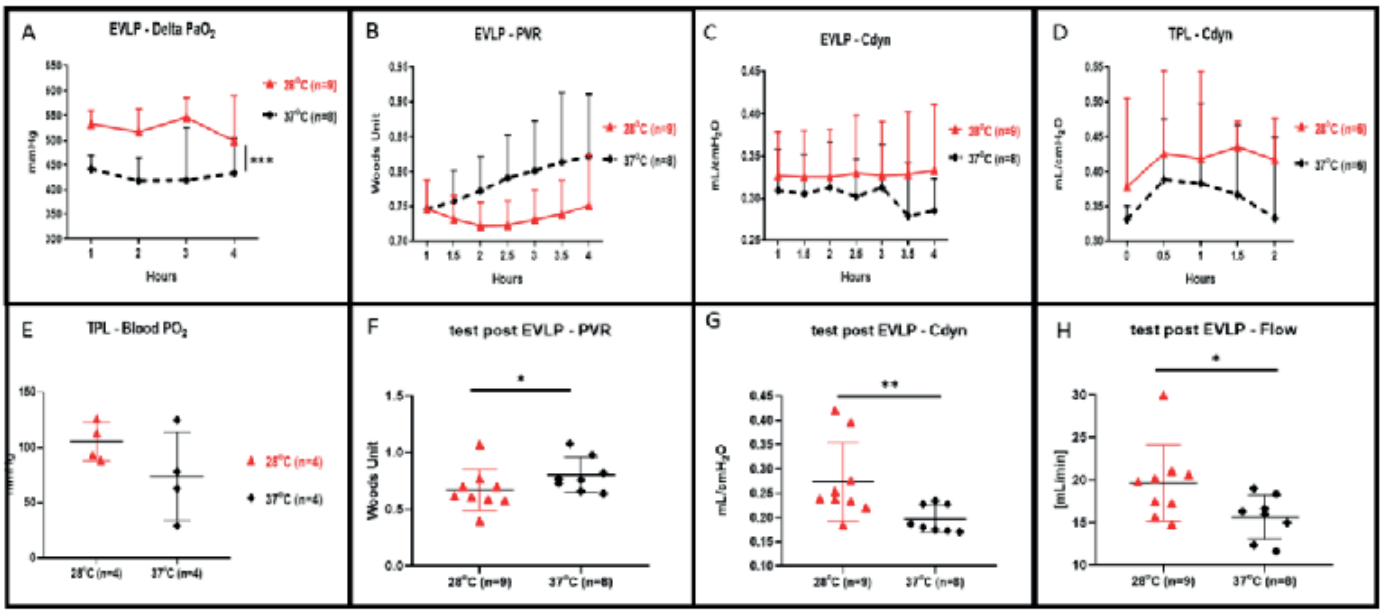


Fig. 4: Effects of subnormothermic temperatures on EVLP and lung transplantation. Lung oxygenation in (A, E), pulmonary vascular resistance (PVR) in (B, F), dynamic compliance (Cdyn) in (C, D, G) and flow in (H) during ex vivo lung perfusion (EVLP) in (A, B, C, F, G, H) and after 2 h of left lung transplantation in (D and E). Perfusate oxygenation was significantly improved, pulmonary vascular resistance was lower and dynamic compliance was higher during the 28◦C EVLP. After 2 h of post EVLP transplantation reperfusion time, the compliance measured from the rat allocated to the 28◦C EVLP group was higher and the oxygenation from the pulmonary vein was higher. (F) In the 28 ◦C EVLP group and during the 5 min end of EVLP stress test we recorded a significant lower PVR, and (G) a significantly higher Cdyn and (H) a significantly higher flow when compared to the normothermic group.

ation, lower pulmonary vascular resistance (PVR) and higher dynamic compliance (Cdyn) when compared to the 37°C EVLP (see also Fig. 4). After the left lung transplantation, the Cdyn and oxygenation were also improved in the 28°C group as were the tissue related parameters. Lung pro-inflammatory cytokine levels were greatly reduced at 28°C both during EVLP and after lung transplantation. We also reported, during both EVLP and after left lung transplantation, these beneficial effects on cytokine levels and improved physiological and biochemical lung parameters with the use of 1) perfluorocarbon-based oxygen carrier during EVLP and 2) in a porcine EVLP model of perfusate particle size filtration.

In our hands, future promising tracks for the improvement/handling of injured lungs are the use of 28°C EVLP, the use of different drugs (nicotinamide adenine dinucleotide ATP-sensitive potassium channels), but also the use of oxygen carriers (PFOB) and the application of perfusate size filtering which were all shown to be non-inferior settings in comparison to the clinically approved 37°C EVLP.

Lung Volume Reduction Surgery (LVRS)

In the field of lung volume reduction surgery, focus is on patient selection criteria and outcome. Several international collaborations for a European LVRS database and joint research were created. Furthermore, in 2020 we have initiated and started an international multi-centric randomised clinical trial "Surgical Compared to Bronchoscopic Lung Volume Reduction in Patients With Severe Emphysema" (SINCERE, ClinicalTrials.gov Identifier: NCT04537182), in which we randomize LVRS versus BLVR (bronchoscopic lung volume reduction) with valves.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

CTEPH is a rare, chronic and debilitating disease characterized by pathological changes to both sides of the pulmonary arteries. In order to be able to perform research aiming to gain a better understanding of the underlying pathophysiological mechanisms of CTEPH, we have established a biobank of resected tissue from pulmonary endarterectomy (PEA), blood samples and primary cell cultures. For our primary cell culture efforts, we are using both the obstructing material removed during the PEA surgery, as well as intima (the inner layer of the pulmonary arteries) tissue. From this material, over the course of the last 2 years we have successfully established 50 primary cell lines from 25 patients. At present, in collaboration with the Department of Pathology, these cell lines undergo a thorough histopathological characterisation, which not only serves as a way to characterise the cells we are growing, but also helps us to understand the composition of the obstructing lesions. Furthermore, as a first step in our multiomics NGS (genomic and transcriptomic) profiling approach aiming to identify the different players involved in CTEPH's microenvironment disruption, we have performed whole genome sequencing on PEA-derived tissue from 50 patients. The resulting sequencing data is currently being analysed.

Prof. Dr. med.
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Awards:

M. Patella and I. Opitz
Award of the Schweizerische Gesellschaft für Thoraxchirurgie (SGT) for the best clinical paper 2020 for the work «Prognostic factors of oligometastatic non-small-cell lung cancer following radical therapy: a multicentre analysis»

M. Kirschner
Award „Best Thoracic Surgery Video“ of the Schweizerische Gesellschaft für Chirurgie (SGC) and the Schweizerische Gesellschaft für Thoraxchirurgie fort he project „Efficacy of irradiation combined with intracavitary cisplatin-fibrin after lung-sparing surgery in an orthotopic rat model of mesothelioma“

N. Enz and W. Jungraithmayr
B. Braun Award at the 54th Annual Meeting of the European Society for Surgical Research for the work “The co-expression of CD26 and TGF-b1 renders lung cancer targetable to CD26-inhibition”

I. Inci
Award of the Schweizerische Gesellschaft für Thoraxchirurgie (SGT) for the best clinical paper 2019 for the work
“Lung Transplantation with controlled Donation after Circulatory Death Donors”

W. Jungraithmayr
Award of the Schweizerische Gesellschaft für Thoraxchirurgie (SGT) for the best experimental presentation 2019 for the project
“The co-expression of CD26 and TGF-b1 renders lung cancer targetable to CD26-inhibition”

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- Prof. Onur Boyman, Klinik für Immunologie, Universitätsspital Zürich, CH
- Centre Hospitalier, Department of Thoracic Surgery, Strasbourg, France (Gilbert Massard)
- Dr. Yoshito Yamada, Department of Thoracic Surgery, Kyoto University Hospital, Japan
- 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
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- Prof. Dr. D. Günther, Labor für organische Chemie, ETH Zürich
- PD Dr. T. Frauenfelder, Dr. D. Nguyen-Kim, PD Dr. A. Boss, Institut für diagnostische und interventionelle Radiolgie, UniversitätsSpital Zürich
- Prof. Dr. M. Pruschy, Fabienne Tschanz, Institut für molekulare Radiologie, UniversitätsSpital Zürich
- Prof. Dr. M. Carbone, Prof. Dr. H. Yang, Prof. Dr. G. Gaudino, University of Hawai'i, Cancer Center, Honolulu
- Dr. G. Reid, Prof. Department of Pathology, University of Otago, Dunedin, New Zealand
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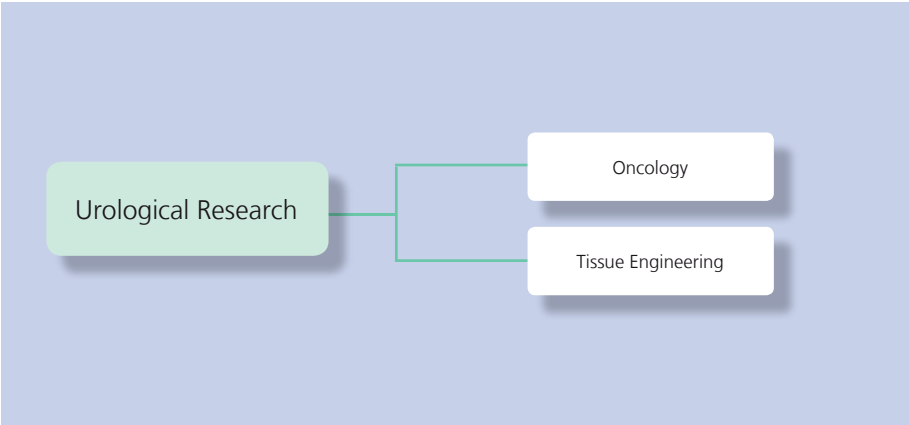
- Dr. Kunyoung Kwon, Dongkang Hospital, South Korea

Urological Research



Prof. Dr. med.
Tullio Sulser,
Director

Prof. Dr. med.
Daniel Eberli, PhD

Research at the Department of Urology is centered around the two areas Uro-Oncology and Tissue Engineering/Regenerative Medicine.

Focus Prostate Cancer Studies

Prostate cancer is the second most frequently diagnosed cancer in men worldwide and represents the third leading cause of cancer-related death among men in developed countries. Precise visualization and therapy of primary and recurrent PCa foci is one of the prominent challenges in these tumor patients. Prostate-specific membrane antigen (PSMA) based imaging and therapy is increasingly used for targeted PCa management. However, a low PSMA surface expression in patients with low-volume and low-grade cancer can limit accurate imaging and therapy. In vitro and in vivo data has demonstrated that androgen deprivation therapy (ADT) induces PSMA surface expression. However, ADT might negatively influence disease progression in certain patients. We hypothesize that upregulation of PSMA expression can also be induced by other commonly used FDA-approved compounds indirectly targeting the AR pathway. We aim to identify these pharmacological compounds inducing the PSMA expression in vitro and in vivo.
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. Recently we have demonstrated that treatment with Apalutamide, Abiraterone acetate and Epi-001 activates autophagy as a cytoprotective mechanism in PCa cells and targeting of autophagy enhances the antitumor effect of the compounds. Therefore, combination therapy with autophagy inhibitors can provide a new therapeutic approach potentially translatable to patients.

The early detection and clinical management of prostate cancer (PCa) has become a controversial subject in the past decades. The screening for PCa is based on the measurements of the prostate specific antigen (PSA) in blood. Men with elevated PSA levels have an increased risk of harboring a prostate tumor and are therefore eligible for a prostate biopsy. However, PSA testing has a high rate of false positives, leading to unnecessary biopsies in 50 - 75% of cases, and consequently exposes a relevant number of patients to potentially severe side-effects. We have therefore focused on the development of a non-invasive test relying on novel urine biomarkers, that can complement PSA testing and increase screening specificity. A mass spectrometry-based proteomic analysis on urine samples from 45 patients identified biomarker candidates, which have been validated with ELISA immune-assays and show promising performances in predicting PCa. We are now in the process of developing our own antibodies targeting the biomarkers, for the development of a more sensitive and multi-plex immune-assay.

As an alternative biomarker type we explore for PCa diagnostics, extracellular vesicles (EVs) are particularly intriguing. EVs, which are membrane-bound nanoparticles secreted by cells into the blood or media, are known to carry essential specific to their cell of origin. Using advanced in vitro models, we harvested EVs produced by PCa cells and analyzed them with proteomics (LC-MS/MS) to determine which cargo are related to disease progression. Candidate proteins are being validated in retrospective analysis of patient samples from the proCOC (prostate cancer outcome study) biobank.

We participate in several academic international randomized controlled trials and prospective studies (REDUSE, IMPROVE, PEACE III, PBCG) to improve outcomes in patients with advanced PCa. Beside the established risk calculator from PBCG, new studies are focusing on prostate cancer imaging prior biopsy and its predictive value for the detection of significant PCa.

Focus Testicular Cancer Studies

Our testis cancer research team focuses on discovering new tumor markers and updating prediction models to improve clinical care. In our first research project funded by

Krebsforschung Schweiz we are defining the role of microRNAs during follow-up after curative treatment. Despite newly discovered tumor markers, so called miRNAs, their use has not translated into the clinic. Therefore, we are currently gathering funding for a method exploring novel tumor markers in collaboration with the ETHZ. Additionally, our patient data to update the current prediction models for metastatic disease was presented at ASCO 2020.

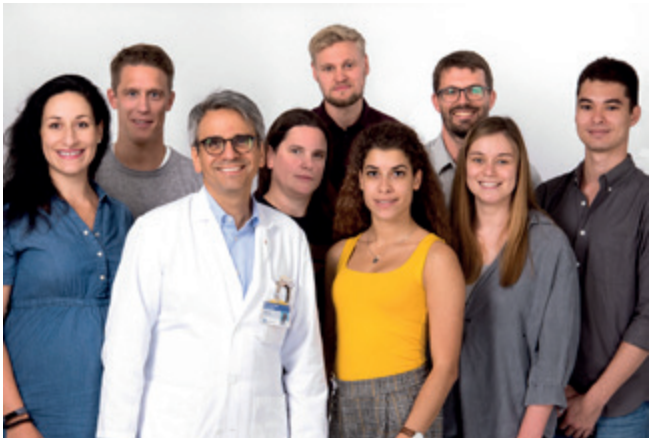
Focus Bladder Cancer Studies

In a multicenter study on muscle invasive bladder cancer (n=389) with neoadjuvant chemotherapy prior to cystectomy, with could show the prognostic relevance of the histopathologic tumor regression grade (TRG) as simple additional histopathological test in addition to the classical TNM grading. The combination of both TRG and TNM showed a significantly improved prognostic stratification of the overall survival after cystectomy as compared to TNM alone. Further studies focusing on BCG response and treatment outcome are planned.

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. We coordinate an international consortium of the Horizon 2020 EU program and a project entitled Multisystem Cell Therapy for Improvement of Urinary Incontinence (MUSIC) (www.music2020.ch). In this first phase clinical trial, we treated 9 patients patients with their autologous muscle precursor cells. Patient-specific cell batches are produced in clean room facilities under GMP conditions. In combination with post injection electromagnetic stimulation, we expect an improved regeneration of the sphincter muscle.

As autologous smooth muscle cells (SMC) cannot be harvested from organs with end-stage disease and tissue regeneration requires large amount of functional SMC, there is an urgent need for other cell sources. Therefore, we selected adipose derived stem cells (ADSC) as an alternative cell type to bioengineer contractile bladder tissue. The ADSCs can efficiently differentiate to smooth muscle cells (SMC) under special conditions. However, their long-term cell fate in vivo is uncertain. Therefore, we aim to develop a functional substitute for the improvement of the bladder wall function for patients suffering from end-stage bladder disease. We are investigating the regenerative capabilities of primary bladder derived SMCs and pre-differentiated, smooth muscle-like ADSCs in compressed collagen hydrogel scaffolds. In addition, we established a novel three-dimensional cell culture system for primary bladder derived SMCs. This approach using so-called spheroids showed promising features for future bladder tissue engineering projects. We expect improved functionality and regenerative potential in smooth muscle cell spheroids compared to traditional two-dimensional cell culture. The next approach is to determine the impact of myostatin, (negative regulator of muscle growth) inhibition on smooth muscle growth and functionality. Our ultimate goal is to bioengineer contractile bladder tissue that can mimic the mechanical properties and functionality found in the native bladder.



Group MUSIC.From left; Deana, Haralampieva, Florian Schmid, Daniel Eberli, Jenny Prange, Steve Kappenthuler, Iliana Mebert, Lukas von Tobel, Rosa Angelica Alves de Souza, Nicolas Steinke.

A next approach aims to investigate differences in extracellular matrix composition in healthy and diseased human bladder derived smooth muscle cells (SMC). The gained information will help us to understand disease related cell changes and might allow us to generate new treatment strategies. This project is another step on the way to developing a functional substitute for the improvement of the bladder wall function for patients suffering from end-stage bladder disease.

Jenny Ann Prange, Dr. sc. nat

Collaborations:

- PD Dr. med S. Santourlidis, Heinrich-Heine University, Düsseldorf, Germany
- Prof. Dr. Michael Detmar, Institute of Pharmaceutical Sciences, ETHZ
- Prof. Dr. Peter Wild, Senckenberg Institut für Pathologie, Universitätsmedizin Frankfurt, Germany
- Proteomedix AG, Schlieren
- 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 & PD Dr. Maya Horst Division of Pediatric Urology, University Children's Hospital Zurich
- PD Dr. med. Andreas Boss, Institute for Diagnostic and Interventional Radiology, USZ
- Dr. sc. nat. Martin Ehrbar, Division of Obstetrics, University Hospital Zurich

Awards:

Marian Wettstein: René Küss Prize 2019 EAU, Section of Transplantation Urology.
Marian Wettstein: Best poster award, EAU 2019, Management of end-stage renal disease patients diagnosed with active surveillance-eligible prostate cancer during pre-transplantation work-up: A decision analysis.
Marian Wettstein: Best Poster award, Canadian Urologic Association (CUA) 2019 in Québec, Bladder Cancer Session, Effectiveness for novel therapies in BCG-unresponsive non-muscle invasive bladder cancer: a decision analysis.
Christian Fankhauser: 2. Place at EAU guideline cup in Barcelona 2019
Daniel Eberli et al.: Swiss Urology Scientific Prize, Extensive histological sampling following focal therapy of clinically significant prostate cancer with high-intensity focused ultrasound

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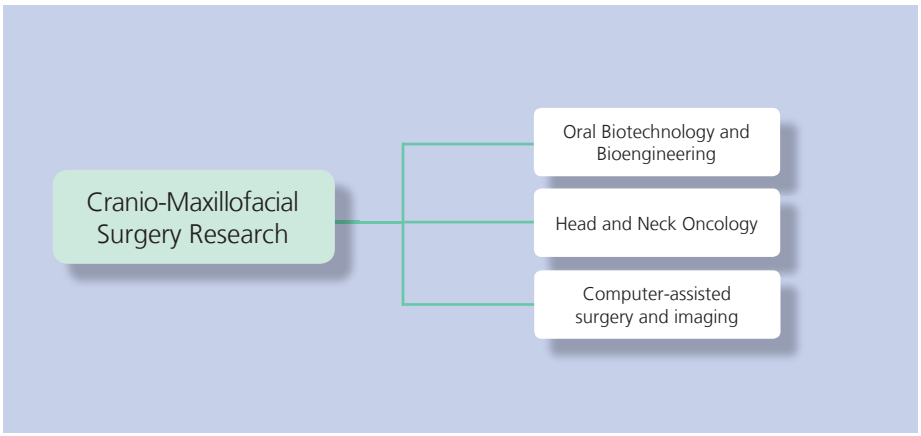

Research in the Department of Cranio-Maxillofacial Surgery covers head and neck oncology, computer assisted surgery, photodynamic therapy, and oral biotechnology & bioengineering. The focus of the latter one is the development and realization of osteoconductive patient specific bone substitutes. Guided bone regeneration is another research topic and a methodology mainly used in the dental field to augment bone defects needed for dental implant placement. Over the last decades we developed and characterized the first biodegradable, bioactive guided bone regeneration membrane. The bioactivity of these membranes was owed to the fact that the membrane served as delivery system for small chemicals (Fig. 1). More recently we showed that

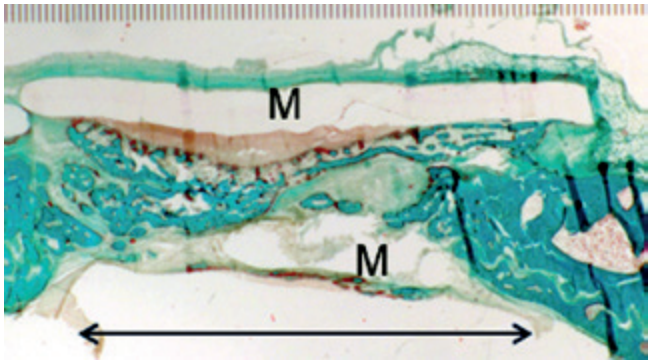

Figure 1: Bone defect regeneration facilitated by a DMA-releasing guided bone regeneration membrane (M). Bone in blue. Original defect margin is indicated by the arrow (Siegenthaler et al. Materials (2020).

these small chemicals, like dimethylacetamide (DMA), are epigenetically active and can be used as drugs to treat and prevent osteoporosis, adiposity, inflammation (Fig. 2), and can even be used for male contraception (Fig. 3).

A third project of oral biotechnology & bioengineering is supported by a Swiss Government Excellence Scholarship and a research grant from the Swiss Society for Endodontology. It deals with the preservation and regeneration of the

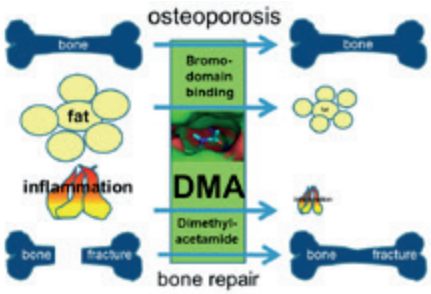

Figure 2: Effect of the excipient dimethylacetamide (DMA) on osteoporosis, adiposity and inflammation
(from: Ghayor et al Scientific Report (2017).

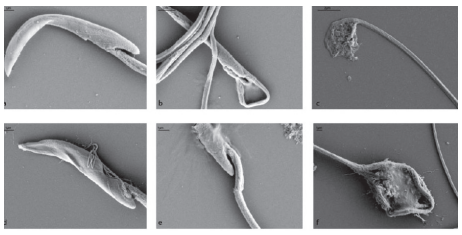

Figure 3: Reversible distortion of sperms by DMA treatment (from Khera et al. Chemosphere (2020)

pulp by growth factors, dentin conditioning, and exosomes to keep teeth alive, to postpone tooth loss and their replacement by dental implants. 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.

Photodynamic therapy is a promising treatment for medication-related osteonecrosis of the jaw (MRONJ). Such medications are often prescribed to inhibit bone destruction in osteoporosis or cancer patients. MRONJ is a severe adverse drug reaction, manifested in progressive irreversible bone destruction in the maxillofacial region, associated with discomfort and pain for the patients.

Collaborations:

- University of Applied Sciences Northwestern Switzerland, School of Life Sciences, Institute for Medical and Analytical Technologies (Prof. Michael de Wild).
- 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).
- Division of Obstetrics (Prof. R. Zimmermann, Dr. Martin Ehrbar)
- UZH, Biochemistry, Prof. Amedeo Caflisch
- ETH Zurich, Department of Health Sciences and Technology, Institute for Biomechanics, Laboratory for Bone Biomechanics Zurich, Switzerland (Prof. R. Müller)

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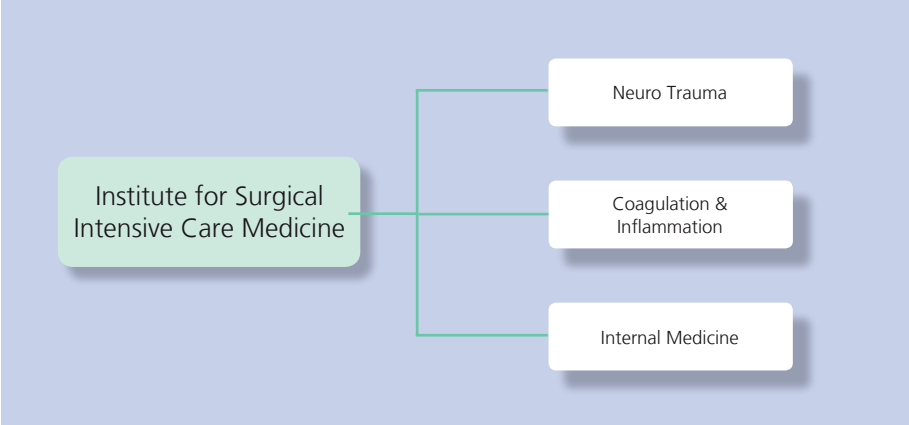
Institute for Surgical Intensive Care Medicine



Prof. Dr. med. Reto Schüpbach, MSc

KD Dr. med. Peter Steiger

Last year the institute of intensive care medicine made a major development step forward. On one hand, the appointment of Prof. Dr. med. Sascha David as chief physician of our intensive care unit HOER D with focus on internal medicine brought an esteemed and valuable colleague in our department. On the other hand, the whole team contributed to an extensive research effort nationally and internationally during the difficult and hectic pandemic time. Various cooperations with other clinics and institutes were established and intensified on a national and international level.
Prof. Dr. Sascha David brings an extensive research background into our department with world-class work in experimental and clinical research. Below is a small overview over his research scope covering his work in ARDS and sepsis. We are delighted to welcome Prof. Dr. med Sascha David to our team!

Overview study focus Prof. S. David:
Experimental Focus
Breakdown of the vascular barrier - or in clinical terms the “capillary leakage syndrome” - is a hallmark of diverse critical illnesses that contribute to the pathophysiology of multiple organ failure. The overall goal of our group is to study the molecular mechanisms regulating endothelial permeability and to develop novel therapeutic strategies against barrier breakdown.
We have been focusing on the so-called Angiopoietin (Angpt)/Tie2 ligand receptor system. Tie2 is a transmembrane receptor tyrosine kinase that is essential for embryonic vessel development. In mature organisms, its function shifts toward maintenance of endothelial homeostasis and reaction to insults. Angpt-1 (the good guy) is the major agonist of the Tie2 receptor that promotes protective anti-permeability signals, whereas Angpt-2 has antagonistic properties and induced permeability (the bad guy) (Figure 1). Our group was the first to proof in a murine knockout model of sepsis that Angpt-2 directly contributes to morbidity and mortality by inducing leakiness of the vasculature.

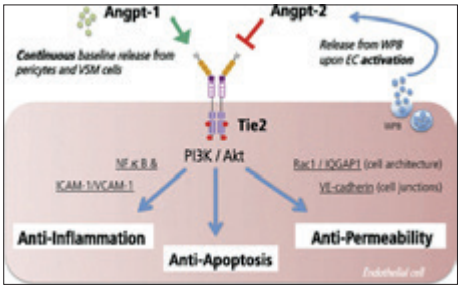


Fig 1

Based on this finding, we have conducted a series of experiments exploring potential therapeutic strategies (antibodies, siRNA, etc.) to eliminate or block the injurious Angpt-2 protein in sepsis models. We are also conducting drug-repurposing screens to identify potential off-target Angpt-2 regulators.
Recently, we have gained attention in the regulation of the Tie2 receptor expression per se not just its activation and we were fortunate enough to find a novel mechanism of MMP14 driven Tie2 cleavage. With this knowledge, we plan to develop a small molecule together with researcher from the ETH to treat Tie2 driven vascular leakage in mice (and ultimately men).
Another focus lies in the investigation of the endothelial glycocalyx both in vivo (SDF imaging) and in vitro (endothelial microperfusion chip model). As injury of the endothelial glycocalyx can be found early in critical illness and substantially contributes to endothelial dysfunction we investigate the regulation of enzymatic glycocalyx degradation (by lack of heparanase-2, Hpa-2) both in septic shock as well as severe COVID-19.

Clinical Focus
Having observed that both the excess of injurious molecules (e.g. Angpt-2) and the consumption of protective ones (Angpt-1, Hpa-2) can trigger pathological vascular leakage we have extensively focused on a technique termed therapeutic plasma exchange (PEX) in clinical research projects. In a

prospective non-randomized pilot study, we could demonstrate that early PEX improves hemodynamics and endothelial permeability as well as reduced inflammatory cytokines in patients with severe septic shock (EXCHANGE I, NCT04231994). Stimulation of endothelial cells with septic patients' blood ex vivo induces a characteristic phenotype

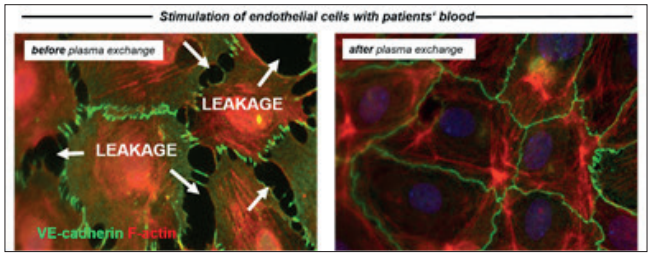


Fig 2

with actin stress fibers and junctional disassembly that ultimate leads to the formation of gaps between adjacent cells (Figure 2, left panel, white arrows). Stimulation of ECs with blood from septic patients' after a single PEX was performed does not induce any morphological changes of barrier breakdown anymore (Figure 2, right panel).
PEX can also restore the degraded endothelial Glycocalyx. We have planned a large international multicenter randomized controlled trial (23 centers) powered for mortality as primary endpoint that we expect to start in early 2022 (EXCHANGE II).
Barrier breakdown of the alveolo-capillary membrane of failing lung is also the pathophysiological hallmark of ARDS (acute respiratory distress syndrome). In order to better understand ARDS we are collecting human biomaterials (BAL fluids and blood) and clinical characteristics of ARDS patients. This ARDS Register has been started at Hannover Medical School and already contains more than 200 patients and is currently being expanded to our institute at the USZ. The register will help to translate experimental findings of our basic research group from bench to bedside. Another clinical focus is the support of ARDS patients with ECMO with and without mechanical ventilation (termed awake ECMO).
In light of the key position of the endothelium in severe cases of Covid-19 we are involved in numerous clinical and translational projects analyzing endotheliopathy and coagulopathy in Covid-19 ARDS.

Intensive Care medicine &COVID Research
Our ICU departments treated over-proportionally many critically ill COVID Patients since 2020 and thus took a leading role, together with our department of infectious diseases, in defining and improving treatment procedures. This gave us the opportunity to set up key structures for important research projects and collaborations.

Clinical Covid Research

RISC ICU
Mathias Hilty and Pedro David Wendel Garcia, founded with the support of SGI (Swiss Society for Intensive Care Medicine) an international registry with the aim to gather data from critically ill covid-19 patients around the world. Currently 69 intensive care units from 14 different countries are participating and already collected data from more than

Fig 3

3000 patients. The collection of identical parameters allows in depth comparisons and helped us for example in publishing an early evaluation in spring 2020 about risk factors for a severe outcome.

Microbiota
The impact of secondary bacterial infections (superinfections) in coronavirus disease 2019 (COVID-19) is not well understood. Philipp Bühler und Silvio Brugger, together with the biobank of the Zinkernagel research team, created the microbiota cohort study, where a wide range of samples from patients in the beginning of acute severe infection is taken.
In this prospective, monocentric cohort study, we can show that patients with pulmonary superinfections have a higher incidence of bacteremia, virus reactivations, yeast colonization, and required intensive care treatment for a longer time. Superinfections are frequent and associated with reduced ventilator free days at 28 days despite a high rate of empirical antibiotic therapy. *(Cell reports Medicine 2021; 2: 100229) (medRxiv 2021.03.10.21253079;)*
Likewise, important insights into inflammation, immunomodulation, risk factors and SARS-CoV-2 transmission have already been obtained. *(Clin Infect Dis. 2020); (medRxiv 2021.02.02.21250940;) (Antimicrob Resist Infect Control. 2021 Jan 12;10(1):11.9); (Liver Int. 2021 May 21:10.1111/liv.1497)*
Futher aims of the present research are to improve therapeutic strategies in critically ill patients with ARDS due to SARS-CoV-2 infection by advancing the pathophysiological understanding of this novel disease. This research thus focuses on inflammation, microcirculatory dysfunction and superinfection, aiming to elucidate risk factors (RF) for the development of severe ARDS in SARS-CoV-2 infected patients and contribute to the rationale for therapeutic strategies.
For this purpose, a large interdisciplinary research group

consisting of infectiologists, dermatologists, immunologists, virologists and intensive care physicians could be formed to work on multiple questions within the framework of this project.

Clinical studies:

Philippe Bühler and Pedro Wendel in cooperation to other multicenter ICU, was able to show that Non Invasive Ventilations should be avoided whenever possible, due to the elevated ICU mortality risk. In analyzing a cohort of 1421 critically ill patients with COVID-19, High Flow therapy is the initial optimal therapeutic approach for recompensating patients in acute respiratory failure and reduces the rate of invasive ventilation. *(Crit Care 2021 May 25;25(1):175.doi: 10.1186/s13054-021-03580-y.)*

Lung-protective ventilation is key in bridging patients suffering from COVID-19 acute respiratory distress syndrome (ARDS) to recovery. Resource and personnel limitations during pandemics complicate the implementation of lung-protective protocols. Pedro Wendel with Daniel Hofmaenner and Philipp Bühler were able to show that automated ventilation modes were able to decrease the workload and who a higher degree of lung-protective ventilation. *(J Intensive Care Med. 2021 Jun 8;8850666211024139)*

Assessment of pulmonary mechanics and cardiopulmonary interactions represent a potential key role in the ventilation of COVID 19 patients. To better understanding and evaluate key parts of respiratory mechanics and cardiopulmonary interactions, a project is currently performed to analyze the qualitative nature and description of respiratory mechanics and pulmonary-cardiac interactions in COVID-19 ARDS patients. *(NCT04597853)*

Translational Covid Research

A key piece of the Covid-19 pathophysiology puzzle came from the discovery of direct viral infection by SARS-CoV-2 *(Lancet. 2020 May 2;395(10234):1417-1418.)* in May 2020 from a group of USZ researchers. This leading to profound endothelialitis in remote organs. This finding has raised researchers' attention around the globe and build the basis for a deeper understanding of its unique features of multiple organ failure. In this context, the group of S. David has found that in patients with severe Covid-19 the endothelial glycocalyx (a sugar-like structure on the endothelial surface that modulates a variety of functional processes along the vasculature - including barrier function and molecular signalling) is dramatically degraded, thereby increasing the endothelium`s susceptibility to permeability *(Am J Respir Crit Care Med. 2020 Oct 15;202(8):1178-1181)*. They found that Covid-19 patients suffer from an acquired deficiency of heparanase-2 - the enzyme that protects degradation of the glycocalyx under healthy conditions. They are currently investigating in a single center RCT if therapeutic plasma exchange can restore this lack of protective heparanase-2 and modulate the coagulopathy *(NCT04613986)*.

In another project they found that several biomarkers and mediators of endothelial dysfunction are strongly induced not only in the circulation of Covid-19 patients but also on the organ levels from autopsies. In a series of analysis we could show that endothelial dysfunction and pulmonary microvascular coagulopathy are closely linked (Eur Respir J. 2021 May 13;2100377.). That being said, the whole story appears to be much more complex as their data in circulating cardiovascular microRNAs underline *(Eur J Heart Fail. 2021 Mar;23(3):468-475.)*.

E.Keller, in collaboration with researchers from the Depts. of Neurology and Neuroradiology, performed a detailed workup in critically ill patients with COVID-19 and central nervous system involvement. Patients underwent computed tomography, magnetic resonance imaging, electroencephalography, cerebrospinal fluid analysis, and autopsy in case of death. The researchers found cerebral microinfarctions and microbleeds, indicating small and large cerebral vessels involvement in severely ill COVID-19 patients *(Stroke, 2020. 2020 Oct 15, 51(12):3719-3722)*.

Along the same lines, D. Kirschenbaum, D. Frontzek, together with researchers from the IFI found evidence for intracerebral endotheliitis and (asymptomatic) microbleeds in autopsies from deceased Covid-19 patients *(Neuropathol Appl Neurobiol. 2021 Apr;47(3):454-459.)*. A key symptoms that distinguishes SARS-CoV-2 from other viral respiratory infection is the inodorous-/ and tastelessness. Several researchers from the IFI were involved in the discovery of the underlying pathophysiological correlate, i.e. an inflammatory olfactory neuropathy *(Lancet. 2020 Jul 18;396(10245):166.)*.

Collaborations:

- Dr. Andrew Aswani, Guy's and St. Thomas' NCS Foundation Trust, London, UK, Critical Care Medicine and Anasthesia
- Dr. Nadine Bienefeld, ETH, Department für Management, Technologie und Ökonomie
- PD Dr. Christian Bode, University Hospital Bonn, Germany, Operative Intensive Care Medicine
- Prof. Dr Dominique Brodbeck, Fachhochschule Nordwestschweiz, Institut für Medizintechnik und Medizininformatik
- PD Dr. Silvio Brugger, Universität Zürich, Infektionskrankheiten und Spitalhygiene
- Prof. Dr. Ulrich Budde, University Hospital Hamburg, Germany,
- Prof. Dr. Lukas Flatz, Universitäts-Hautklinik, Tübingen, Germany, Dermaoncology
- Dr. Marian Galovic, University Hospital Zürich, , Department of Neurology
- Prof. Dr. Catherine Gebhard, Universität Zürich,
- Dr. Eva Caroline Gebhard, Universitätsspital Basel, Intensivmedizin

→

Collaborations (Continuation)

- Prof. Dr. Hermann Haller, Mount Desert Island Biological Laboratory, Bar Harbour, Maine, USA,
- Prof. Dr. Marius Hoeper, Hannover Medical School, Germany, Respiratory and Critical Care Medicine
- PD Dr. Christoph Jüngst, Universität Zürich, Gastroenterologie und Hepatologie
- Prof. Dr. Jan Kielstein, Academic Teaching Hospital Brunswick, UK, Nephrology
- Prof. Dr Thomas Krämer, Universität Zürich, Forensische Pharmakologie und Toxikologie
- Prof. Dr. Michael Krauthammer, Universität Zürich, Mediziniformatik
- PD Dr. Bernhard Morell, Universität Zürich, Gastroenterologie und Hepatologie
- Prof. Dr. Beat Müllhaupt, Universität Zürich, Gastroenterologie und Hepatologie
- Prof. Dr. Alberto Pagnamenta, Ente Ospedaliero Cantonale (EOC), Department of Intensive Care Medicine
- Prof. Dr. Samir Parikh, Harvard Medical School, Boston, MA, USA,
- Prof. Christian Putensen, University Hospital Bonn, Germany, Operative Intensive Care Medicine
- Prof. Dr. Vera Regitz-Zagrosek, Universität Zürich, Sex Gender specific medicine
- Dr. Benjamin Seeliger, Hannover Medical School, Translational Intensive Care Research Group
- Prof. Dr. Mervin Singer, University College London, London, UK, Intensive Care Medicine
- PD Dr. Klaus Stahl, Hannover Medical School, Translational Intensive Care Research Group
- Dr. Paul van Slyke, Pharmadruc Inc, Toronto, Canada, Vasomune Therapeutics
- Prof. Dr. Tobias Welte, Hannover Medical School, Germany, Respiratory and Critical Care Medicine
- Dr. Stefan Wolf, Charité Universitätsmedizin Berlin, Klinik für Neurochirurgie
- Prof. Dr. Malgorzata Wygrecka, University Gießen, Germany, Biochemistry
- Prof. Dr. Reinhard Zbinden, Universität Zürich, Mikrobiologie
- Prof. Dr. Annelies Zinkernagel, Universität Zürich, Infektionskrankheiten und Spitalhygiene

Prof. Dr. med.
Reto Schüpbach,
MSc

KD Dr. med.
Peter Steiger

Prof. Dr. med.
Dominique Bettex

Prof. Dr. med.
Sascha David

Prof. Dr. med.
Emanuela Kelleri

Dr. med.
Karl Philipp Bühler

Dr. med.
Matthias Hilty

Dr. med.
Stephanie Klinzing

Dr. med.
Giovanna Brandi

Dr. sc. ETH
Jan Bartussek,
Coordinator
Data management
and analysis

Dorothea
Heuberger,
PhD Student

Pedro Garcia
Wendel,
Wissenschaftlicher
Mitarbeiter

Dr. med. Daniel
Hofmänner,
Wissenschaftlicher
Mitarbeiter

Dr. sc. Stefanie
Keiser
Wissenschaftliche
Mitarbeiterin

Dr. sc. Martina
Maibach
Study Nurse

Catharina
Wolfensberger,
Head Development
and Administration

Prof. Sascha David, MD

Animal Welfare in Biomedical Research

Prof.
Margarete Arras,
DVM

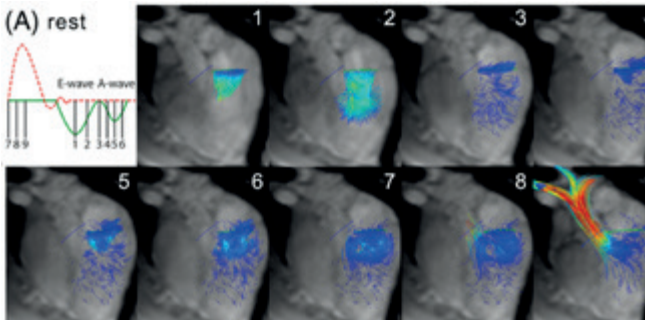
Miriam Weisskopf,
DVM

Large Animal Models in Basic- and Translational Research

From an in depth understanding of disease mechanism to the discovery, and development of a new treatment method, a research continuum starting at basic research leading over pre-clinical studies into clinical practice, is required. In particularly, in basic research and pre-clinical studies, animal models, in addition to *in-vitro* and *in-silico* methods, play an important role. Rodent models thereby do not always reflect the clinical situation, thus, large animal models mimicking human anatomy and physiology more closely are used.

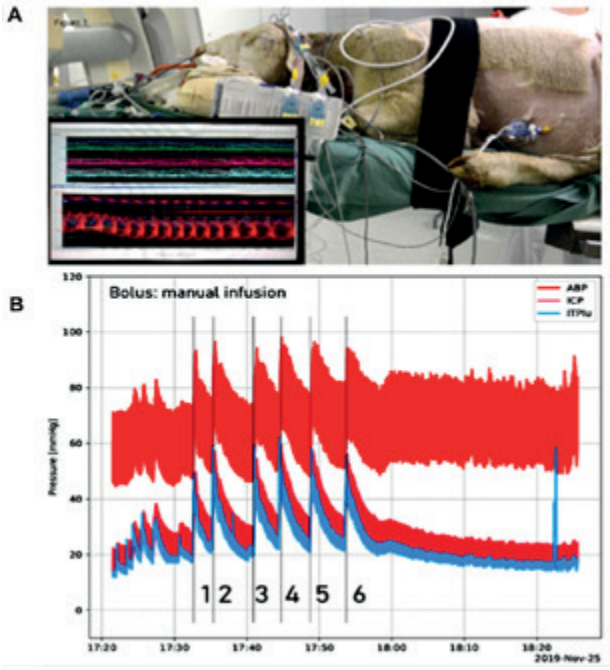
One of the focuses of our work at the Center for Surgical Research is the development of large animal models in research and the professional support of researchers in finding the most accurate model for their respective scientific question. Over the last decade, we have established a great number of collaborations with various clinics within the USZ, departments of the ETH and with partners from the private industries.

These collaborations have allowed us to gain extensive expertise in the establishment of novel acute and chronic large animal models (pigs and sheep) used in various fields of basic and pre-clinical research.



Cesarovic N, Weisskopf M, Kron M, et al. Septaly Oriented Mild Aortic Regurgitant Jets Negatively Influence Left Ventricular Blood Flow-Insights From 4D Flow MRI Animal Study. Front Cardiovasc Med. 2021;8:711099. Published 2021 Aug 9. doi:10.3389/fcvm.2021.711099

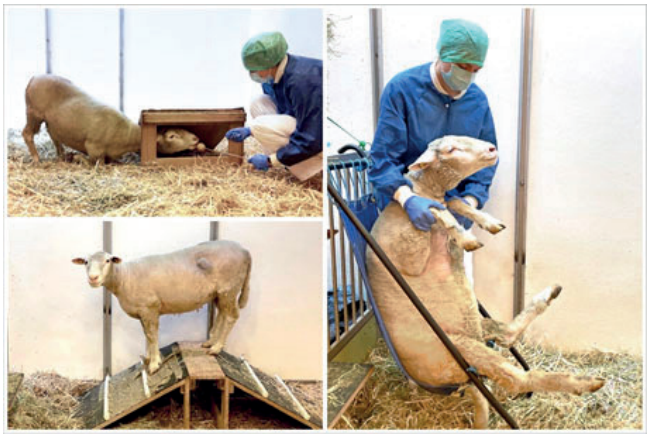
The focus of one major collaboration lies on intra-cardiac blood flow and cardiac work. Medical and technological advances assisting insufficiently working hearts to pump blood have led to improvement in both life expectancy and quality. However, the design and optimization of such devices is complicated and often lead to mechanical factors altering intra-cardiac fluid dynamics and causing turbulence in the blood flow thereby creating excessive dissipation of energy.



Set-up of an acute trial; sheep are equipped with multiple pressure sensors in the cerebral ventricle, the lumbar intra-thecal space, at four different positions in the abdominal cavity and intravascular (carotid artery and jugular vein). The table is tilted anti-Trendelenburg to assess posture-dependent pressure changes in all compartments. In the processed data pressure changes due to bolus injections are visible.

Paravalvular leakage p.ex. significantly affects the short- and long-term prognosis for patients undergoing transcatheter aortic valve implantation (TAVI). In this context, we established a translational large animal model to create paravalvular leakages with a transcatheter technique and

assessed their impact on left ventricular fluid dynamics by 4D flow MRI, together with the ETH Zürich and the German Heart Center in Berlin.

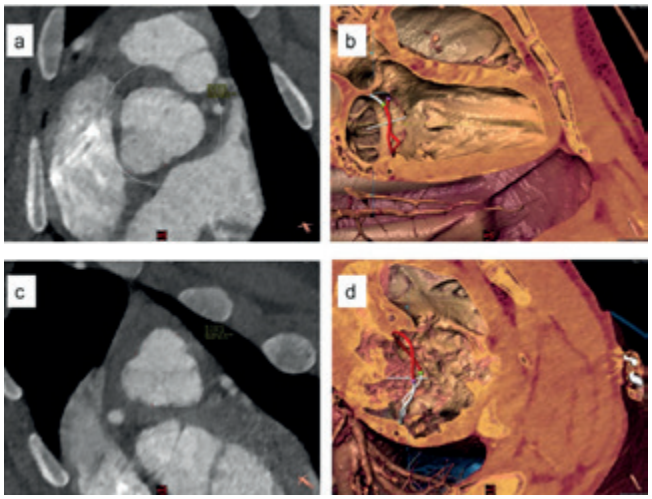


By positive reinforcement training (clicker training) the animals are trained to take different positions and walk over a bridge. They are also placed in a sheep chair to mimic a human-like sitting posture

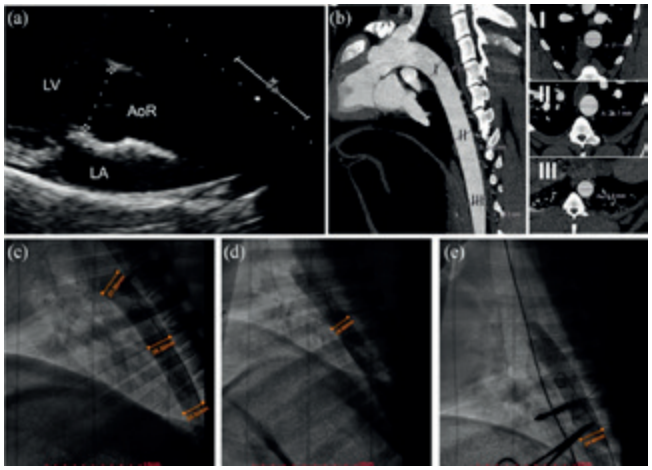
In April 2019, together with the Product Development Group Zurich of the Department of Mechanical and Process Engineering, ETH Zurich, we received a grant from the Swiss National Science Foundation (SNSF) with the goal to develop a sheep model to examine the pathophysiology of cerebrospinal fluid (CSF) pathways. The 4-year internal project, for which we are working closely together with the Department of Neurosurgery of the University Hospital Zurich, focuses on the basic understanding of physiological dynamic pressure and volume variations in the individual compartments adjacent to the intracranial and spinal CSF spaces (e.g. blood vessels, abdominal cavity, respiratory system), as well as on the pathophysiology associated with normal pressure hydrocephalus (NPH), an idiopathic pathologic condition affecting CSF physiology. In the acute study, infusion tests and tilt tests are used to obtain physiologic data on pressure dynamics, comparable to human tap and tilts tests. During the chronic phase the sheep will be trained via positive reinforcement training, to engage in different exercises which require body posture changes and therefore induce cerebrospinal fluid flow and pressure changes.

In addition, it is always our moral and ethical obligation to maximize knowledge output and to further use the gained experience and the overall collected study data to continuously improve applied animal models and to share these findings publicly in observance of the obligation to the 3R principles. Analyzing computed tomography images from innumerable pigs from a variety of different projects over the past years, for instance, now allows us for an optimized study animal selection prior to, for example, testing a particular cardiac implant. Together with a partner from the industry, we recently successfully developed and refined a sheep model for percutaneous circulatory device testing.

Following this collaboration, we have concluded, that the preselection of sheep by trans-thoracic aortic annulus diameter assessment allows for a sufficient conclusion regarding the mid-thoracic descending aortic diameter, allowing again to optimize pre-study animal selection.



Lipiski M, Eberhard M, Fleischmann T, et al. Computed Tomography-based evaluation of porcine cardiac dimensions to assist in pre-study planning and optimized model selection for pre-clinical research. Sci Rep. 2020;10(1):6020. Published 2020 Apr 7. doi:10.1038/s41598-020-63044-1



Weisskopf M, Kron M, Giering T, Walker T, Cesarovic N. The sheep as a pre-clinical model for testing intra-aortic percutaneous mechanical circulatory support devices. Int J Artif Organs. 2021;3913988211025537. doi:10.1177/03913988211025537

Collaborations:

- Department of Health Sciences and Technology Translational Cardiovascular Technology, ETH Zürich, Berlin Heart Center, Charité Universitätsklinik Berlin, Prof. Dr. Volkmar Falk/ Dr. Nikola Cesarovic Dipl. ECLAM, Dipl.SVLAS
- Product Development Group Zürich, ETH Zürich, Dr. Marianne Schmid Daners
- University of Umea, Sweden, Dr. Anders Eklund
- Jörg Huwyler, Pharmazeutische Technologie, University of Basel
- Petra Seebeck, Zurich integrative Rodent Physiology, University of Zurich

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Miriam Weisskopf,
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Flora Nicholls,
Dipl. biol.

Nina Eva Trimmel,
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Ferran Riano-
Canalias,
DVM, PhD

Simone Jucker,
DVM

Thea Fleischmann,
DVM, Dipl.ECLAM

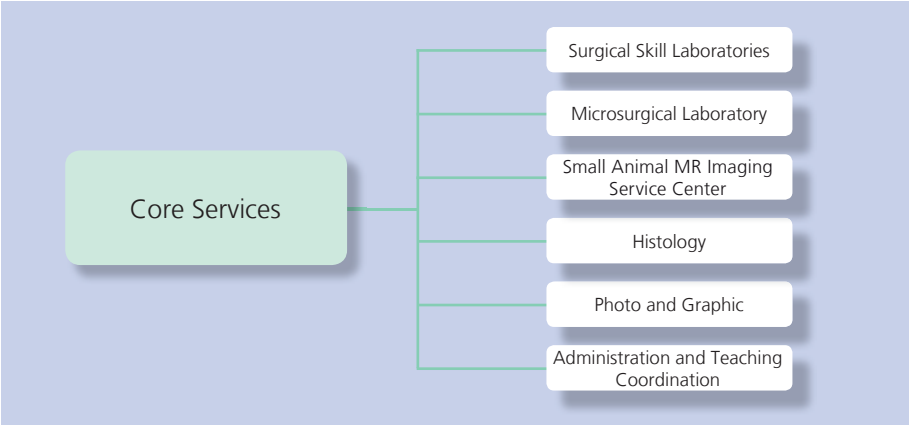
Mareike Sauer,
DVM, Dipl.ECLAM

Marko Canic,
DVM

Nina Trimmel, DVM

Ines Kleiber-Schaaf and Andrea Garcete-Bärtschi, Histology Lab

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.

Small Animal MR Imaging Service Center

The Small Animal MRI Service Center (SAMISC) is now administered as part of the Center of Surgical Research and Conny Waschkies, PhD, was recruited to oversee its activities. SAMISC is equipped with a Bruker 4.7T PharmaScan® MRI system designed for high throughput preclinical imaging. It features routine MRI sequences optimized for mice and rats, and is operated by ParaVision® 5 and 6 software packages for data acquisition, reconstruction, analysis and visualization. An EchoMRI system is available for body fat composition analysis in mice and tissue probes (down to 0.3g).

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.

Teaching Coordination and Administration

The Surgical Research Division is responsible for organization of the learning and teaching units in the Department of Surgery, including both lectures and clinical courses in coordination with the University of Zurich, as well as the coordination of the clinical rotations during the last years of study. Further tasks include financial management (accounting, controlling, reporting) and personnel administration of the Division, as well as organization and coordination of various events.

Prof. Margarete Arras, DVM

Nikola Cesarovic, DVM, PhD

Dr. sc. nat. Conny Waschkies, Scientific Administrator

Andrea Garcete-Bärtschi, Technician

Ines Kleiber-Schaaf, Technician

Carol De Simio, Scientific Illustrator

Nico Wick, Photographer

Christoph Stulz, Photographer

Tina Wentz Manager Division of Surgical Research

Donata Gröflin, Teaching Coordination Division of Surgical Research

Photo and Graphic Services

FAOL Stress test 2019; Emergency (o.), Security (u.)

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- layout of printing matters
- preparation of files for external printing
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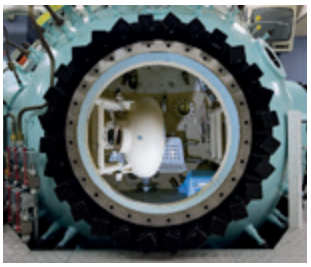
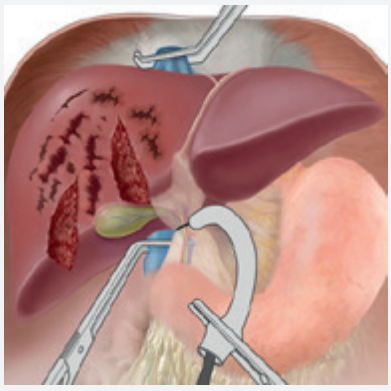
- cutting and converting of video-files for presentation and web
- construction and maintainance of websites
- maintainance of the digital image archives

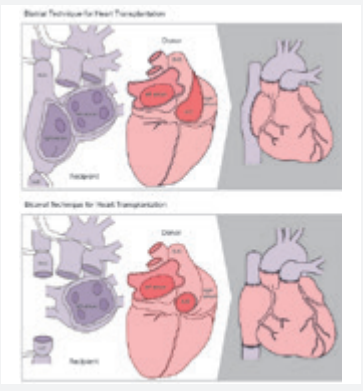
Catering

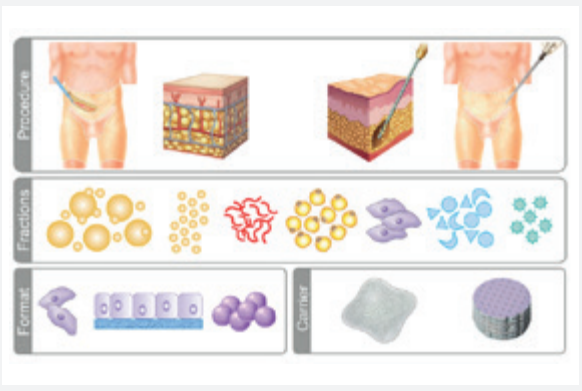


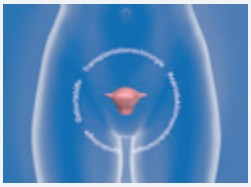
Pressure Chamber

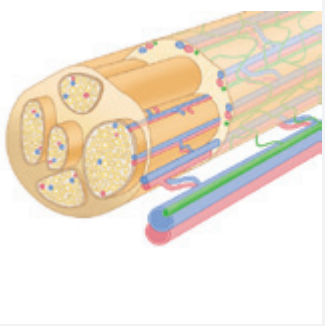
Lecture Hall NORD

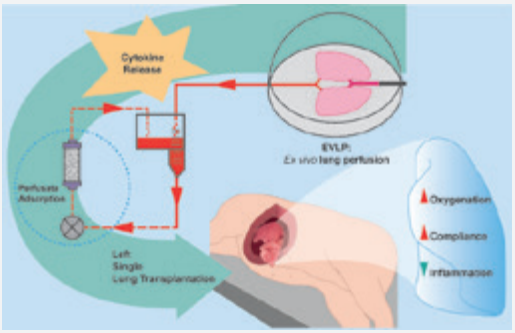






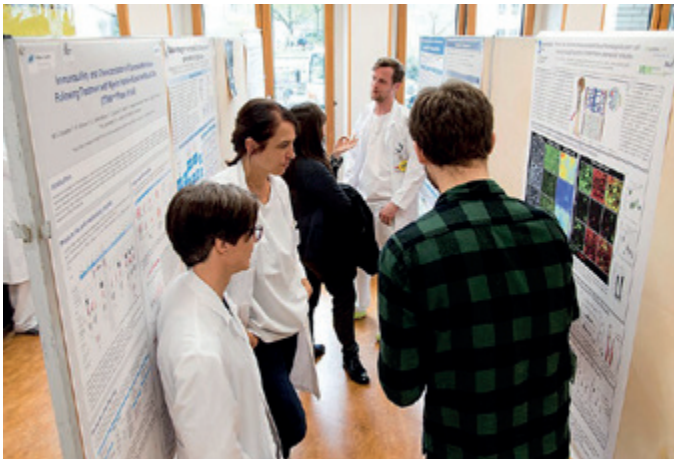






4. Events and Workshops at the Division of Surgical Research



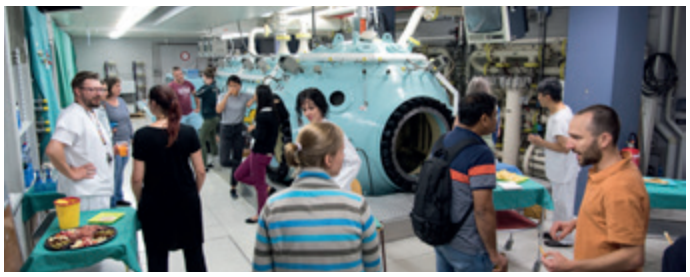




18th Day of Clinical Research, April 11, 2019

Lab Retreat, Les Diablerets, January 11 – 13, 2019

Surgical Suture Skills Course, Winterthur, May 30- 31, 2019; photos: Lorenzo Kaeser

Prof. Rolf Graf, resigning treasurer, receives the Lifetime Achievement Award from Prof. Anders Molven (Bergen), President of the EPC, June 28, 2019



Farewell Nikola Cesarovic, July 11, 2019

Farewell Prof. Walter Weder, Director of Thoracic Surgery, May 23, 2019

Winter Party, December 19, 2019

5. Grants

Surgery and Transplantation Research:		
Lungenliga	INSPIRA clinical trial	Horisberger K
SNF	HOPE clinical trial - finishing	Dutkowski P
SNF	Liver function assessment during HOPE prior to transplantation	Dutkowski P
SNF	Division of tasks in the regenerating liver	Clavien P.-A.
SNF	HIPEC-mediated tumor-specific immunity	Lehmann K.
SNF	The role of serotonylation in pancreatic cancer	Graf R
SNF	Uterus transplantation: the role of ischemia reperfusion injury	Clavien P, Dutkowski P
SNF	Behavioral changes in humans after Roux-en-Y Gastric Bypass	Büeter M
SNF	MD-PhD fellowship	Birrer D
FOUNDATIONS:		
Olga Mayenfisch Stiftung	Behavioral changes in humans after Roux-en-Y Gastric Bypass	Bueter M.
Edoardo R.-, Giovanni, Giuseppe und Chiarina Sassella-Stiftung	Dampening of tumor-specific immunity through peripheral serotonin	Gupta A
Edoardo R.-, Giovanni, Giuseppe und Chiarina Sassella-Stiftung	HIPEC-mediated tumot-specific immunity	Roth L, Gupta A
Virometix AG	Cancer treatment via synthetic viroids	Gupta A, Graf R, Clavien P.-A.
Kurt und Senta Herrmann Stiftung	Role of gastrokines in pancreatic cancer	Steiner S.
B. Braun Stiftung	Preemptive endoscopic vacuum therapy in esophagectomy	Gutschow CA
Wyss Translational Center Zurich	Liver4Life	Clavien P.-A., von Rohr P. (ETHZ)
Innovation grant USZ	Intraoperative fluorescence imaging in parathyroid surgery	Vetter D
LGID	HPB fellowship	Clavien P.-A.
LGID	ITPP clinical trial	Clavien P.-A., Graf R

Trauma Surgery Research:		
Theodor und Ida Herzog-Egli Stiftung	The switch between pluripotency to differentiation: The role of Pramel7 in embryonic 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	Real-time high-dimensional level analysis of stem cell heterogeneity at single cell resolution by mass cytometry	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
SNF	Tendon repair 310030_197578	J. Buschmann
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
Sassella Foundation	Lipedema Foundation, grant numbers LF14, 27 and 27A	E. Gousopoulos

Thoracic Surgery Research:

Schweizer Nationalfonds	Improving Mesothelioma Patients Outcomes by Early Non-Invasive Diagnosis	I. Opitz
Krebsliga Schweiz	Mesoscape 001 - pS6: construction of a multi-institutional European tissue bank	I. Opitz
Iten-Kohaut Stiftung (USZ Foundation)	Tracking down Non-Small Cell Lung Cancer: on the Road to Personalized Medicine for Lung Cancer - TrackTHORAX	I. Opitz
SUVA	Intracavitary Cisplatin-Fibrin Localized Chemotherapy After Pleurectomy/ Decortication or Extrapleural Pneumonectomy for the Treatment of Patients With Malignant Pleural Mesothelioma - INFLuenCe-Meso II Clinical Trial	I. Opitz
Baugarten Stiftung	SINCERE - SurgIcal compared to broNChoscopic lung volumE Reduction in patients with severe Emphysema: a multi-center randomized controlled trial	I. Opitz
Lunge Zürich	SurgIcal compared to broNChoscopic lung volumE Reduction in patients with severe Emphysema: a multi-center randomized controlled trial (SINCERE)	I. Opitz
Stiftung für Angewandte Krebsforschung	Immune cell profiling of oligo-metastatic non-small cell lung cancer patients: Comparison of primary tumor with different sites of metastasis for impact on prognosis and immunotherapy	I. Opitz
Stiftung für Angewandte Krebsforschung	Innovation in Management of Small Pulmonary Nodules	I. Opitz
Stiftung für Angewandte Krebsforschung	Establishment and long-term expansion of primary non-small cell lung cancer organoids: setting the foundation for an individualized precision medicine using ex-vivo cancer models	I. Opitz
Stiftung für Angewandte Krebsforschung	Multi-omics profiling for identification of novel circulating biomarkers for malignant pleural mesothelioma	I. Opitz
Stiftung für Angewandte Krebsforschung	Proteogenomic biomarker Analysis of malignant pleural mesothelioma	I. Opitz
Stiftung für Angewandte Krebsforschung – Polianthes Stiftung	Next Generation Sequencing of Malignant Pleural Mesothelioma for Therapy Response Prediction	I. Opitz
Schweizer Nationalfonds	RNA editing in mesothelioma: a new therapeutic target?	E. Felley-Bosco
Krebsliga Zürich	Sonic hedgehog signaling in malignant pleural mesothelioma	E. Felley-Bosco
Walter Bruckerhoff Stiftung	The Supraspliceosome, a multi-task RNA processing machine, as novel target for diagnosis and treatment of thoracic cancers	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
Stiftung für Angewandte Krebsforschung	RNA editing in mesothelioma: a new therapeutic target?	E. Felley-Bosco
Schweizer Nationalfonds	Reconditioning of marginal donor lung in ex vivo lung perfusion system using Perfluorocarbon based oxygen carrier	I. Inci
Theodor und Ida Herzog-Egli-Stiftung	Effekt von NAD+ (Nicotinaminadenindinukleotid) auf den Ischämie-Reperfusionschaden sowie die akute Organabstossung nach Lungentransplantation am Rattenmodell	I. Inci
Swiss Lung Foundation	Optimization of ex vivo lung perfusion system with negative pressure ventilation chamber: construction of a new chamber prototype	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
CytoSorbents Europe GmbH	Effect of continuous cytokine removal on graft function in lung transplantation	I. Inci
CytoSorbents Europe GmbH	The effect of cytokine removal during ex vivo lung perfusion on post-transplant graft function	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
Foundation A. P. Naef	Inhibition of ischemia-reperfusion injury using ATP sensitive potassium channel modulators in ex vivo lung perfusion system in lung transplantation	I. Inci
Stiftung für Angewandte Krebsforschung	Biomarkers with enzymatic activities for improved risk stratification of lung cancer patients	S. Hillinger
Stiftung für Angewandte Krebsforschung	Innovative Abklärungsmöglichkeiten des kleinen pulmonalen Rundherdes	S. Hillinger
Krebsliga Schweiz	A new therapeutic concept against lung cancer by inhibition of CD26/DPP4	W. Jungraithmayr
Stiftung für Angewandte Krebsforschung	Targeting human lung cancer by synergistic CD26- and checkpoint inhibitor	W. Jungraithmayr
Kantonalzürcherische Krebskommission	The role of microRNAs in malignant pleural mesothelioma progression and resistance to chemo- and immunotherapy	M. Kirschner
Stiftung für Angewandte Krebsforschung	The role of microRNAs in malignant pleural mesothelioma progression and therapy resistance	M. Kirschner
Krebsliga Zürich	Targeting lung cancer by CD26/DPP4 inhibition in combination with anti-PD-L1 antibody	J-H. Jang
Kurt und Senta Herrmann Stiftung	Tracking down Non-Small Cell Lung Cancer: on the Road to Personalized Medicine for Lung Cancer	R. Werner

Urological Research :		
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
Baugarten Stiftung, Zürich	Neuro-elektromagnetische Stimulation und menschliche Muskelstammzellen zur Behandlung von Urininkontinenz	D. Eberli
Edoardo R. Giovanni, Giuseppe und Chiarina Sassella-Stiftung	Upregulation of prostate-specific membrane antigen (PSMA) expression by approved pharmacological compounds for improved prostate cancer imaging and therapy	B. Kranzbühler
Max und Hedwig Niedermaier Stiftung	Authophagy inhibition and second-line Hormone Therapy as a combined Therapy for Prostate Cancer	Souzan Salemi
Julius Müller Stiftung	Assay development for EV biomarker validation	Christopher Millan
Angela Reiffer Stifung	Development of a liquid biopsy diagnostic test for prostate cancer base on novel extracellular viscle-based biomarkers	Christopher Millan
Krebsforschung Schweiz	miRNAs in testicular cancer patient surveillance	Thomas Hermanns, Christian Fankhauser, Jörg Beyer
Gebert Rüf Sitfung	PROBAN: Urine assay for the screening of prostate cancer	Irina Banzola
Edoardo R. Giovanni, Giuseppe und Chiarina Sassella-Stiftung	Exosomal biomarkers for liquid biopsies to detect and monitor prostate cancer	Christopher Millan
Stiftung Krebsbekämpfung	ARN-509 (Apalutamide) and autophagy inhibitors: A promising double therapy for advanced prostate cancer	Souzan Salemi
Siemens- UZH Entrepreneur Fellowship	Multisystem Cell Therapy for Improvement of Urinary Continence — MUS.I.C.: reaching the people	Deana Mohr
SNF Spark Grant	Improvement of mitochondria in muscle precursor cells derived from old donor	Souzan Salemi

Cranio-Maxillofacial Surgery Research:		
SNF Grant	Osteoconduction and Exosomes in scaffold-based bone tissue engineering	F. E. Weber
Innosuisse grant	Least material at maximum strength in medical devices.	F. E. Weber
Bundesstipendium	Pulp Regeneration	F. E. Weber
Swiss Society for Endodontology	Regenerative Endodontics	F. E. Weber

Surgical Intensive Care Medicine:		
Vontobel-Stiftung	Biased PAR-2 Signaling by Thrombomodulin Bound Thrombin	R. Schüpbach
SPHN	Swiss Personalised Sepsis Study	R. Schüpbach
Béatrice Ederer-Weber Foundation	The bacterial microbiota in burn patiends – understanding microbial evolution under antibiotic selection pressure for future therapeutic and preventive approaches	P.Bühler

Animal Welfare in Biomedical Research:		
SNF	Quantitative study on the pathophysiology of hydrocephalus	M. Arras & M. Schmid Daners
Olga Mayenfisch Foundation 2019	Quantitative study on the pathophysiology of Hydrocephalus	M. Weisskopf
Hartmann-Müller Foundation 2019	Quantitative study on the pathophysiology of Hydrocephalus	M. Arras

6. Publications

1. Wagner, M. et al. Die CAD/CAM-Revolution in der kraniofazialen Rekonstruktion. Praxis 108, 321-328 (2019).
2. Valdec, S. et al. Vestibular bone thickness of the mandible in relation to the mandibular canal-a retrospective CBCT-based study. International Journal of Implant Dentistry 5, 37 (2019).
3. Bhattacharya, I., Ghayor, C., Pérez Dominguez, A. & Weber, F.E. N,N-Dimethlyacetamide Prevents the High-Fat Diet-Induced Increase in Body Weight. Frontiers in Pharmacology 10, 1274 (2019).
4. Chen, T.-H., Weber, F.E., Malina-Altzinger, J. & Ghayor, C. Epigenetic drugs as new therapy for tumor necrosis factor-α-compromised bone healing. Bone 127, 49-58 (2019).
5. Weber, F.E. Reconsidering Osteoconduction in the Era of Additive Manufacturing. Tissue engineering. Part B, Reviews 25, 375-386 (2019).
6. Valdec, S., Schiefersteiner, M., Rücker, M. & Stadlinger, B. Guided biopsy of osseous pathologies in the jaw bone using a 3D-printed, tooth-supported drilling template. International Journal of Oral and Maxillofacial Surgery 48, 1028-1031 (2019).
7. Ebner, J.J. et al. Novel application of the Clavien-Dindo classification system and the comprehensive complications index® in microvascular free tissue transfer to the head and neck. Oral Oncology 94, 21-25 (2019).
8. Schiefersteiner, M., Bichsel, D., Rücker, M. & Valdec, S. Antimykotika im zahnärztlichen Alltag. Swiss Dental Journal 129, 403-405 (2019).
9. Hingsammer, L. et al. Sentinel lymph node biopsy for early stage tongue cancer-a 14-year single-centre experience. International Journal of Oral and Maxillofacial Surgery 48, 437-442 (2019).
10. Liu, D. et al. IMB0901 inhibits muscle atrophy induced by cancer cachexia through MSTN signaling pathway. Skeletal Muscle 9, 8 (2019).
11. De Wild, M. et al. Osteoconductive Lattice Microarchitecture for Optimized Bone Regeneration. 3D Printing and Additive Manufacturing 6, 40-49 (2019).
12. Hungerbühler, A., Rostetter, C., Lübbers, H.-T., Rücker, M. & Stadlinger, B. Anatomical characteristics of maxillary sinus septa visualized by cone beam computed tomography. International Journal of Oral and Maxillofacial Surgery 48, 382-387 (2019).
13. Blumer, M. et al. Outcome of surgically treated fractures of the condylar process by an endoscopic assisted transoral approach. Journal of Oral and Maxillofacial Surgery 77, 133.e131-133.e139 (2019).
14. Schelbert, T. et al. Accuracy of Computer-Guided Template-Based Implant Surgery: A Computed Tomography-Based Clinical Follow-Up Study. Implant Dentistry 28, 556-563 (2019).
15. Sutter, E. et al. Guided apicoectomy using a CAD/CAM drilling template. International Journal of Computerized Dentistry 22, 363-369 (2019).
16. Ghayor, C., Chen, T.-H., Bhattacharya, I., Özcan, M. & Weber, F.E. Microporosities in 3D-Printed Tricalcium-Phosphate-Based Bone Substitutes Enhance Osteoconduction and Affect Osteoclastic Resorption. International Journal of Molecular Sciences 21, 9270 (2020).
17. Koch, F., Meyer, N., Valdec, S., Jung, R.E. & Mathes, S.H. Development and application of a 3D periodontal in vitro model for the evaluation of fibrillar biomaterials. BMC Oral Health 20, 148 (2020).
18. Terheyden, H., Stadlinger, B. & Gruber, R. Osteoklasten als Zellen des Immunsystems. Die Quintessenz 71, 1430-1435 (2020).
19. Thiel, Y. et al. Antimicrobial peptide gene expression in medication-related osteonecrosis of the jaw. Pathology, Research and Practice 216, 153245 (2020).
20. Khera, N. et al. Reversible Contraceptive Potential of FDA Approved Excipient N, N-Dimethylacetamide in Male Rats. Frontiers in Physiology 11, 601084 (2020).
21. Bornstein, M. et al. Leitlinie Antibiotika in der Oralchirurgie: Eine Stellungnahme der Schweizerischen Gesellschaft für Oralchirurgie (SSOS). Swiss Dental Journal 130, 916-917 (2020).
22. Kuster, I. et al. Autogenous bone augmentation from the zygomatic alveolar crest: a volumetric retrospective analysis in the maxilla. International Journal of Implant Dentistry 6, 59 (2020).
23. Berlowitz, I. et al. “Tobacco Is the Chief Medicinal Plant in My Work”: Therapeutic Uses of Tobacco in Peruvian Amazonian Medicine Exemplified by the Work of a Maestro Tabaquero. Frontiers in Pharmacology 11, 594591 (2020).
24. Bhattacharya, I., Ghayor, C., Pérez Dominguez, A. & Weber, F.E. From Influenza Virus to Novel Corona Virus (SARS-CoV-2)–The Contribution of Obesity. Frontiers in Endocrinology 11, 556962 (2020).
25. F. Carls, P. et al. Implant loss and sinusitis after sinus lift - an underestimated complication. Clinical Oral Implants Research 31, 281-281 (2020).
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31. Blumer, M. et al. Radiologic Analysis of Surgically Treated Fractures of the Condylar Process by an Endoscopic-Assisted Transoral Approach. Journal of Oral and Maxillofacial Surgery 78, 1151-1155 (2020).

32. Hingsammer, L. et al. Does Zygomatic Complex Symmetry Differ Between Healthy Individuals and Surgically Treated Patients Using Intraoperative 3-Dimensional Cone Beam Computed Tomographic Imaging? Journal of Oral and Maxillofacial Surgery 78, 798.e791-798.e797 (2020).

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35. Lienemann, P.S. et al. Smart Hydrogels for the Augmentation of Bone Regeneration by Endogenous Mesenchymal Progenitor Cell Recruitment. Advanced Science 7, 1903395 (2020).

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37. Huber, F.A. et al. Medication-Related Osteonecrosis of the Jaw-Comparison of Bone Imaging Using Ultrashort Echo-Time Magnetic Resonance Imaging and Cone-Beam Computed Tomography. Investigative Radiology 55, 160-167 (2020).

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39. Sutter, E. et al. Success rate 1 year after apical surgery: a retrospective analysis. Oral and Maxillofacial Surgery 24, 45-49 (2020).

40. de Matos, N.M.P. et al. Evaluating the Effects of Acupuncture Using a Dental Pain Model in Healthy Subjects – A Randomized, Cross-Over Trial. Journal of Pain 21, 440-454 (2020).

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