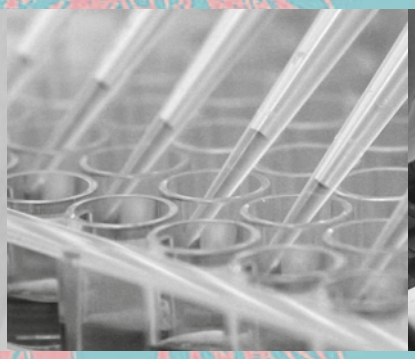
Division of Surgical Research

Annual Report 2003

Department of Surgery
University Hospital Zurich
Switzerland




Division of Surgical Research
Department of Surgery
University Hospital
Rämistrasse 100
CH - 8091 Zurich

Photo & Graphic, Division of Surgical Research
Nico Wick and Carol De Simio

Content

Preface

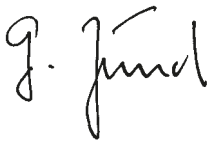
Dear Colleagues

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

I am delighted to send you the Annual Report 2003 of the Division of Surgical Research at the University Hospital Zurich.

2003 was a very eventful year for our division and staff. It was due to the successful collaboration between the University and the University Hospital that a re-organisation of human resources entailing the outsourcing of electron microscopy and the integration of surgery photo/graphics was completed. This enabled to create additional academic positions in the Division of Surgical Research.
The Division's quarterly internal interim reports detailing the respective on equipment and resources and the investments made enabled us to carry out quality control by means of project management on schedule and within the budget. The investments made in the past year relate primarily to restructuring within the IT sector, with the result that approximately 90% of all installations are now up-to-date.
In scientific terms, the introduction of weekly on-the-job training courses conducted by staff from the individual competence groups furthered net-working by the exchange of specific know-how. The sawing course for beginners which was offered to the students at the University Hospital got an excellent feedback and will be reorganized next year.
I would like to express my sincere thanks to every member of staff and the research partners of the University Hospital, the University and the ETH Zurich for the excellent collaboration in the past year.

Yours sincerely,



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

1. Organisation

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

Prof. Dr. med. Marko Turina, Director of Cardiac Surgery

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

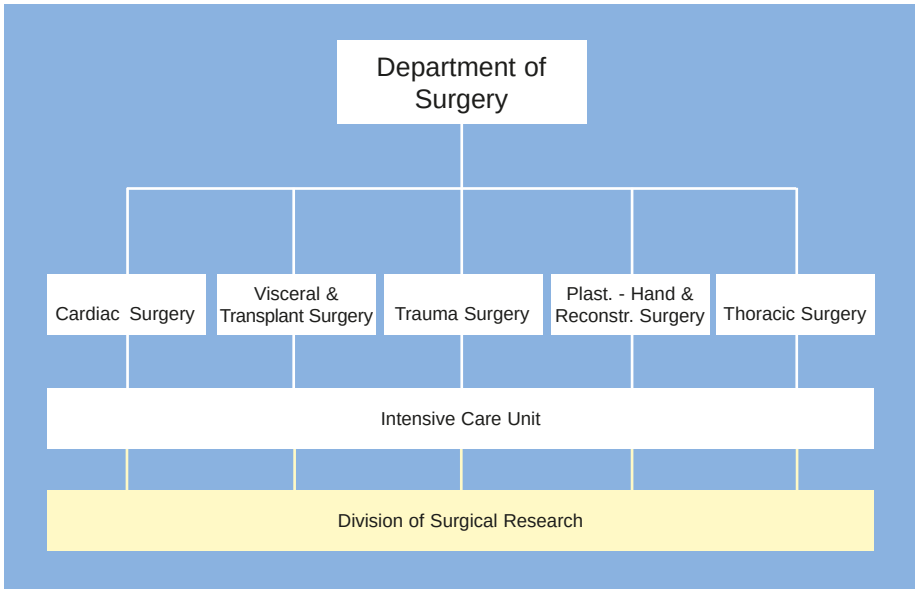
Prof. Dr. med. Otmar Trentz, Director of Trauma Surgery

Prof. Dr. med. Viktor Meyer, Director of Plast. - Hand & Reconstr. Surgery

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

Prof. Dr. med. Reto Stocker, Head of Intensive Care Unit

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

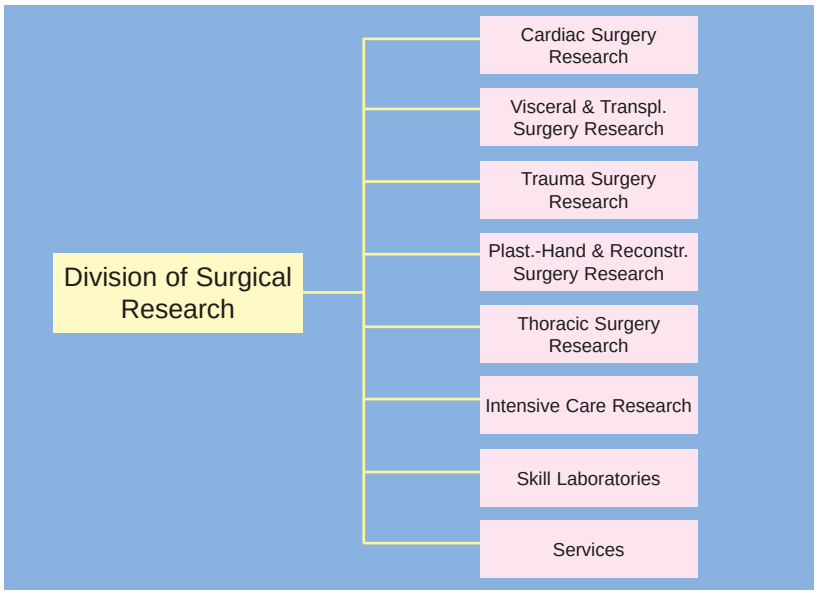


1.2 Structural Organisation of the Division of Surgical Research

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

PD Dr. phil. II
Rolf Graf,
Co-Head Division of
Surgical Research

Gabriella Muolo-
Giaquinta,
Administration
Division of Surgical
Research



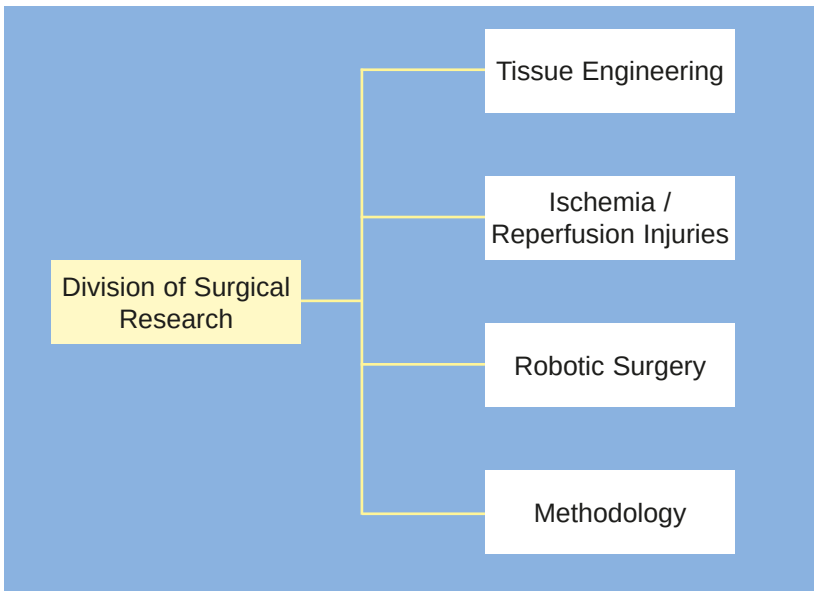
1.3 Scientific Sections within the Division of Surgical Research

PD. Dr. med.
Simon Philipp
Hoerstrup
Tissue
Engineering

Dr. phil II
Wolfgang Moritz
Ischemia /
Reperfusion
Injuries

PD Dr. med.
Guido Wanner,
Robotic Surgery

PD Dr. phil II
Rolf Graf
Methodology

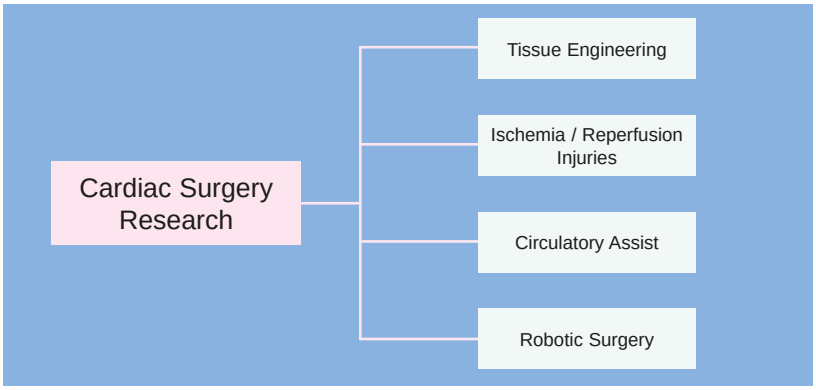


2. Research and Development

2.1 Cardiac Surgery Research

Prof. Dr. med.
Gregor Zünd

Prof. Dr. med.
Marko Turina



PD Dr. med.
Simon Philipp
Hoerstrup

PD Dr. sc. nat.
Stefan
Neuenschwander

Dr. med.
Christina
Günter

Anita Mol
PhD Student

Dr. med.
Ian Cummings

Dr. med.
Dörthe Schmidt

Sirpa Price

Dr. med.
Alberto
Weber

cand. med.
Sidika
Yakarasik

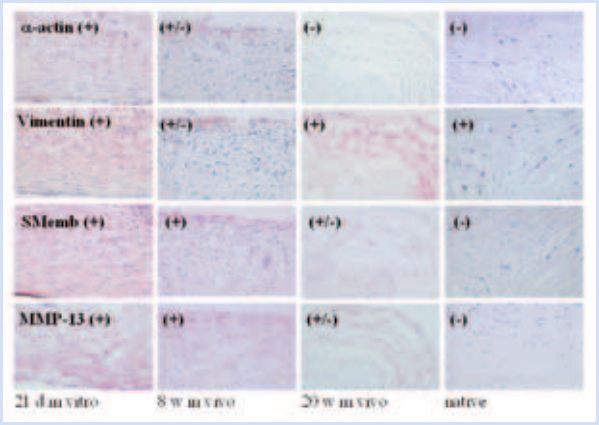
2.1.1 Tissue Engineering and Cell Transplantation - Regenerative Medicine

PD Dr. med. Simon Philipp Hoerstrup (Head Tissue Engineering)

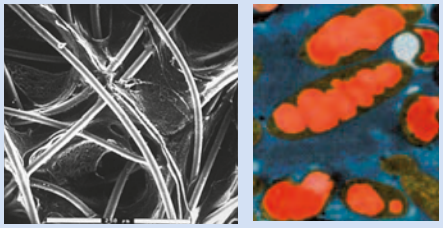
The Laboratory for Tissue Engineering and Cell Transplantation is focused on the development and in vitro generation of novel, cell based implants for cardiovascular applications, such as blood vessels, heart valves and myocardium. Presently utilized replacements carry disadvantages for the patients mainly because non-living, artificial devices are inserted into the human organism. The technology of tissue engineering enables the in vitro production of autologous, living and functional replacements as an alternative to state of the art artificial replacements. A specific focus is the development of living devices with the capacity of growth for congenital applications.

Research projects:

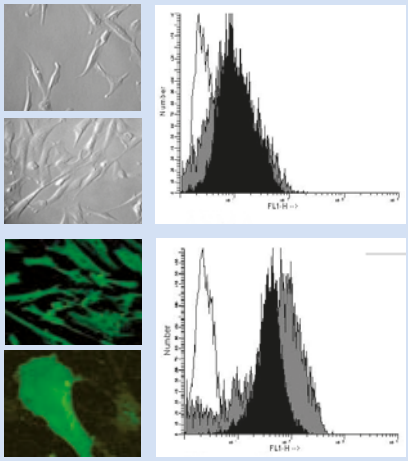
- Human Cell Systems (progenitor, foetal, adult)
- Extracellular Matrix (proteins, tensegrity)
- Biomaterials (biodegradable, bioactive)
- Bioreactor Systems (tension, flow)
- Biomechanics, Computational Models (2-D, 3-D)
- Animal Models (small and large)
- Tissue Engineered Cardiovascular Structures (Heart Valves, Vascular Grafts, Myocardium)

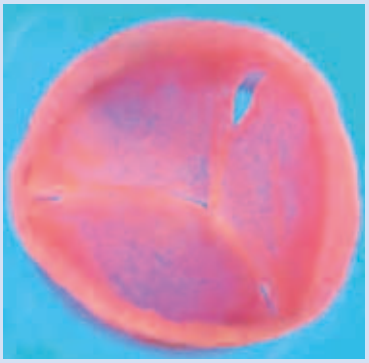


Evolution of cell phenotype of tissue engineered heart valves during in vivo growth in animal model
(Rabkin, Hoerstrup et al. J. Heart Valve Dis. 2002)

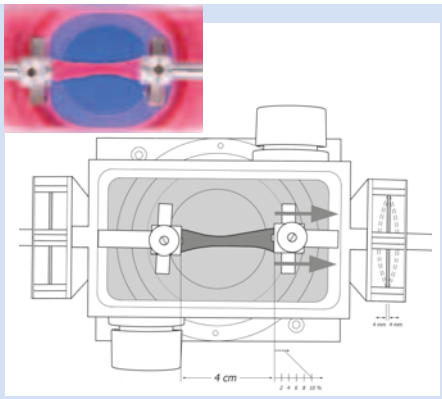


Novel biogradable polymers, transgenic bacterial fermentation.
(Hoerstrup et al. Circulation 2000)





Heart valve tissue engineered from human marrow stromal cells
(Hoerstrup et al. Circulation 2002)



Novel bioreactor for strain conditioning of cardiovascular structures
(Mol et al. Thorac. Cardiovasc. Surg. 2003)

Achievements 2003

- Cardiovascular Biology Award by the Swiss Society of Cardiology and Pfizer (awarded to S.P.Hoerstrup)
- Prix Roberval, Paris, France, Reportage Télévision Suisse Romande
- Swiss National Foundation Grant (Principle Investigator S.P. Hoerstrup)
- Guest-Professorship, Department of Biomedical Engineering, Technical University Eindhoven, The Netherlands (to S.P. Hoerstrup),
- Semester Award 2003, University Zurich (awarded to the MD-Thesis of Sidika Yakarasik, Principle Investigator S.P. Hoerstrup)

Collaborations

- Department of Materials, Federal Institute of Technology, Zürich,Switzerland
- Department of Biochemistry, University Zürich, Switzerland
- Department of Mathematics, Federal Institute of Technology, Zürich, Switzerland
- Department of Computational Science, Federal Institute of Technology, Zürich, Switzerland
- Department of Veterinary Surgery, MSRU Vetclinics, University Zürich, Switzerland
- Department of Cardiology, University Hospital Zürich, Switzerland
- Department of Cardiac Surgery, Children's Hospital, Harvard Medical School, Boston, MA, USA
- Department of Biomedical Engineering, Technical University Eindhoven, The Netherlands
- Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
- Massachusetts Institute of Technology (MIT), Cambridge, MA, USA
- Laboratory for Tissue Engineering, German Heart Centre, Berlin, Germany
- Laboratory for Transplantation Immunology, University Hospital Zürich, Switzerland
- Institute of Biotechnology, Federal Institute of Technology, Zürich, Switzerland
- Feto-maternal Hematology Research, Department of Obstetrics, University Hospital Zürich, Switzerland

Selected references:

- Hoerstrup SP, Kadner A, Melnitchouk S, Trojan A, Eid K, Tracy J, Sodian R, Visjager J, Kolb S, Grunenfelder J, Zund G, Turina M (2002) Tissue enge neering of functional trileaflet heart valves from human marrow stromal cells. Circulation 106: I-143-150
- Hoerstrup SP, Kadner A, Breymann C, Maurus CF, Guenter CI, Sodian R, Visjager JF, Zund G, Turina M (2002) Living, autologous pulmonary artery conduits tissue engineered from human umbilical cord cells. Ann Thorac Surg,74; 46-52
- Rabkin E, Hoerstrup SP, Aikawa M, Mayer JE, Schoen FJ (2002) Evolution of cell phenotype and extracellular matrix in tissue-engineered heart valves during in vitro maturation and in vivo remodelling. J Heart Valve Dis,11(3); 308-314
- Hoerstrup SP, Zund G, Sodian R, Schnell AM, Grunenfelder J, Turina M (2001) Tissue engineering of small caliber vascular grafts. Eur J Cardiothorac Surg 20(1); 164-169
- Hoerstrup SP, Sodian R, Daebritz S, Wang J, Bacha E A, Martin D P, Moran A M, Guleserian K J, Sperling J S, Hatsuoka S, Kaushal S, Vacanti J P, Schoen F J, Mayer J E (2000) Functional living trileaflet heart valves grown in vitro. Circulation 102(III): 44-49

2.1.2 Ischemia / Reperfusion Injury

PD Dr. med.
Reza Tavakoli

Dr. rer. nat.
Anna Bogdanova

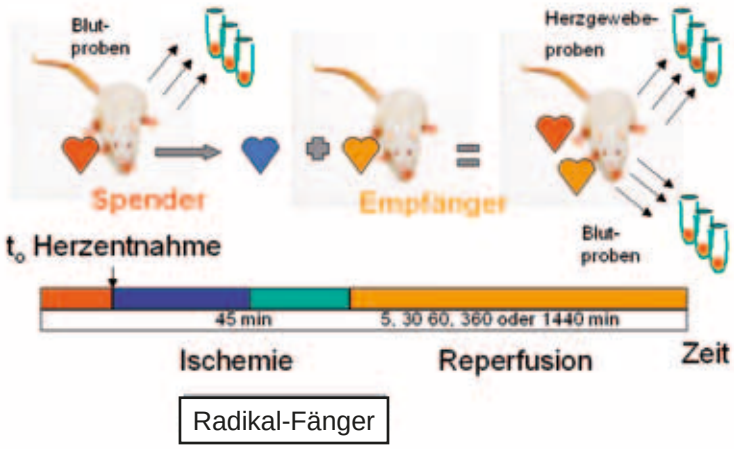
Involvement of oxygen-derived free radicals in myocardial ischemia-reperfusion injury in a rat heart transplant model
PD Dr. med. R. Tavakoli, Dr. rer.nat. A. Bogdanova

Oxygen-derived free radicals (ROS) are thought to be involved in the pathogenesis of tissue damage during ischemia-reperfusion injury encountered after open-heart surgery with ischemic cardiac arrest. In this study we investigate the effect of radical scavenging on myocardial reperfusion injury.

Isogenic heterotopic heart transplantation is carried out in Lewis rats. All grafts are subjected to 45 min of ischemia and studied at 5 min, 30 min, 1, 6 or 24 hours after reperfusion. Three groups are investigated: group 1: control group without treatment, group 2 receiving dismutase+castalase 20 min. prior to reperfusion, group 3 receiving mercaptopropionyl glycine (MPG) 20 min. prior to reperfusion. The oxidative stress is measured by reduced to oxidized glutathione ratio (GSH:GSSG) and sarcolemmal integrity by Na+, K+ and Ca2+ levels in tissue and blood.

Both post-ischemic oxidative stress and heart tissue damage are substantially reduced in treated grafts with either SOD+CAT or MPG 20 min prior to reperfusion. Oxidation of GSH is significantly reduced and Ca2+ release compensated already within the first 5-30 min of reperfusion.

Operationsschema



Achievements 2002

- Oxygen-derived free radicals are involved early after reperfusion of the ischemic myocardium in development of tissue injury. Using ROS scavengers significantly improves post-ischemic recovery and reduces reperfusion injury.

Collaborations:

- Professor Max Gassmann, [2]Institute of Veterinary Physiology, University of Zurich
- Dr. Peter Ossent, Institute of Pathology Vetsuisse Faculty of the University of Zurich
- Dr. med. Lukas Bestmann, Institute of clinical chemistry, University Hospital Zurich

Selected references:

- Boyle, JrEM, Pohlman TH, Johnson MC, Verrier ED. The systemic inflammatory response. Ann Thorac Surg 1997; 64: S31-7.
- Otani H, Engelman RM, Rousou JA, Breyer RH, Lemeshow S, Das KD. Cardiac performance during reperfusion improved by pretreatment with oxygen free-radical scavengers. J Thorac Cardiovasc Surg 1986; 91: 290-5.
- Stewart JR, Gerhardt EB, Wehr CR, Shuman T, Merrill WH, Hammon JW, Bender HW. Free radical scavengers and myocardial preservation during transplantation. Ann Thorac Surg 1986; 42: 390-3.

2.1.3 Circulatory Assist


PD Dr. med.
Mario Lachat


Dr. med.
Andreas Künzli


Dr. med.
Jürg Müller


Dr. med.
Thomas Syburra


Dr. med.
Denis
Berdajs


Boris
Leskosek


Alush Avdyli

Research, development, preclinical studies in the field of cardiovascular perfusion and ventricular support systems
PD Dr. Mario Lachat, Dr. Andreas Künzli, Dr. Jürg Müller, Dr. Syburra Thomas

- Hemodynamics, biocompatibility, clinical studies of new centrifugal and micro axial blood pumps
- Minimally invasive perfusion techniques

Blood pump studies

Biocompatibility, especially long-term biocompatibility of the new bearing less centrifugal blood pump (CentriMag®, Levitronix®, see Fig. 1) and the safety of its drive unit has been extensively studied and demonstrated in our lab. That promising results could be confirmed in a prospective clinical trial performed at the clinic for cardiovascular surgery of the University Hospital of Zurich. Consecutively, the pump got approval for a duration- time of up to two weeks in the European community and is under investigation for FDA approval.

A newer and smaller type of the bearing less centrifugal blood pump (UltraMag®, Levitronix®, see Fig. 2), with a titanium housing, and intended for a long-term support (>2 weeks of duration) is now under investigation in our lab. We could show a very low-grade hemolysis in a preliminary in vitro study.

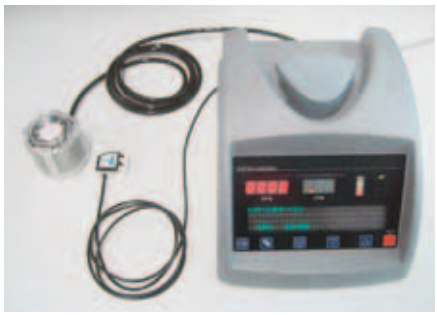
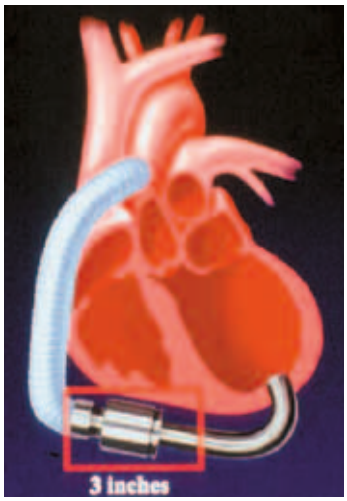


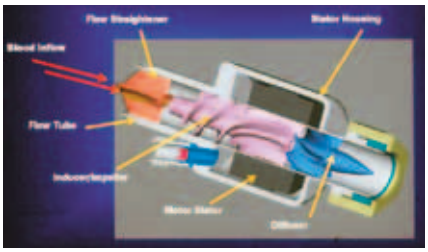
Fig. 1: the CentriMag® blood pump

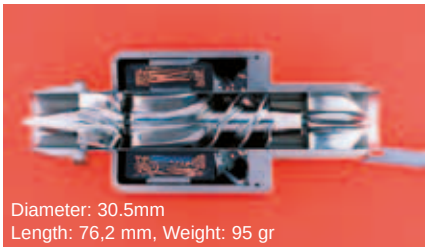
A cooperation with the Helmholtz-Institut (RWTH) in Aachen, Germany, where a new very small micro axial blood pump (see Fig. 3), intended as a long term left ventricle has been started.


Fig. 2: the UltraMag® blood pump


Fig. 3: the micro axial pump: a cooperation with the Helmholtz-Institut in Aachen, Germany







After extensive in vitro performance testing, DeBakey LVAD could be sucessfully introduced into the treatment of terminal heart failure at University Hospital Zurich. Since 2000, 15 patients have been supported by DeBakey LVAD implantation at our institution.

Achievements 2003

- Presentations on national and international meetings (i.e. Day of clinical research, USZ; Congress of the Swiss society of Surgery, Interlaken and CTS congress, San Diego, CA)

Collaborations:

- Levitronix® Inc. (Zürich, Boston, MA)
- Prof. Dr. Ing. H. Reul and Prof. Dr. G. Rau, Helmholtz-Institut RWTH Aachen, Germany

Selected references:

- Jaggy C, Lachat M, Inderbitzin D, Leskosek B, Candinas D, Burkhard T, Turina M. Optimized veno-venous bypass with the affinity pump. ASAIO J. 2001 Jan-Feb; 47(1):56-9. PMID: 11199316
- Jaggy C, Lachat M, Leskosek B, Zund G, Turina M.Affinity pump system: a new peristaltic blood pump for cardiopulmonary bypass. Perfusion. 2000 Jan;15(1):77-83. PMID: 10676871
- Jaggy C, Lachat M, Leskosek B, Kunz M, Zund G, Turina M. Flow measurements through aortocoronary and intraluminal coronary shunts. Swiss Surg. 1999;5(5):228-32. PMID: 10546522
- Lachat M, Jaggy C, Leskosek B, von Segesser L, Zund G, Vogt P, Turina M.Hemodynamic properies of the hemopump HP14. Int J Artif Organs. 1999 Mar;22(3):155-9. PMID: 10357244

2.1.4 Robotic Surgery and Innovative Technologies

Dr. med.
Jürg
Grünenfelder

Dr. med.
Oliver
Reuthebuch

Dr. med.
Alexander
Kadner

Dr. med.
Hitendu
Dave

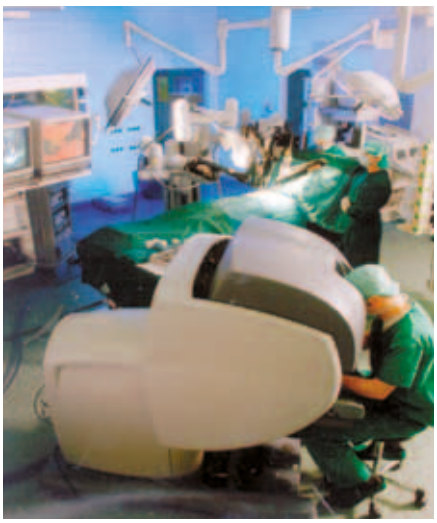
Dr. med.
Achim Häussler

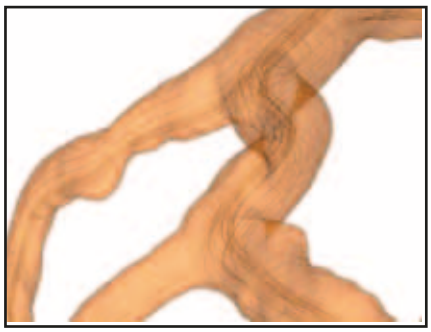
Dr. med.
André Plass

Robotics and Innovative Technologies in Cardiovascular Surgery
Dr. med. Jürg Grünenfelder; Dr. med. Oliver Reuthebuch;
Dr. med. Alexander Kadner; Prof. Gregor Zünd

- Automated coronary artery bypass operation in the beating heart
- Visualization and computational flow simulation in coronary arteries
- Device development for beating heart coronary artery bypass operations
- Development of a microstructured drug delivery system

Minimally invasive surgery (MIS) approaches have revolutionized surgery in the past decade, dramatically reducing morbidity and time required for healing and rehabilitation. Of the numerous barriers to more widespread implementation of MIS, probably the most significant is the problem of visualization. This general need to visualize the surgical site then relates to the needs for modeling patients, planning procedures, registering these plans to the patient, and guiding the surgeon in real time. Surmounting these barriers will open the way to MIS in a wide variety of new procedures.
The focus of this laboratory is the development of precise, adaptable, and widely deployable computer-integrated systems and devices that make a wide variety of surgical interventions newly amenable to minimally invasive cardiac surgical approaches by presenting minimally invasive tools as well as information about preoperative plans through simulation, anatomy, tool position and surgical progress to the surgeon in an ergonomic fashion.





Achievements 2003

- Swiss National scientific foundation grant for computer aided and image guided medical intervention
- 1st Poster prize at the Swiss Society of Surgery meeting in Interlaken 2003
- Clinical application of the surgical robotic system (da Vinci)

Collaborations:

- Department of Radiology, University Hospital Zürich (Simon Wildermuth, MD)
- Laboratory for Thermodynamics in Emerging Technologies, ETH Zürich (Prof. Dimos Poulikakos)
- Institute of Mechatronic Systems, ZHW (Prof. Charles Brom)
- Physical Electronics Laboratory, ETH Zürich (Tobias Vancura, PhD)
- Computer Vision Laboratory, ETH Zürich (Prof. Gabor Szekely)

Selected references:

- Grünenfelder J, Haussler A, Plass A, Reuthebuch O, Dave H, Leskosek B, Turina M, Zund G. A single bicaval venous cannula used for optimization of endoscopic robotically assisted procedures of the heart. Heart Surg Forum. 2003;6(5):393-5.

- Reuthebuch O, Comber M, Grunenfelder J, Zund G, Turina M. Experiences in robotically enhanced IMA-preparation as initial step towards totally endoscopic coronary artery bypass grafting. Cardiovasc Surg. 2003;11(6):483-7.

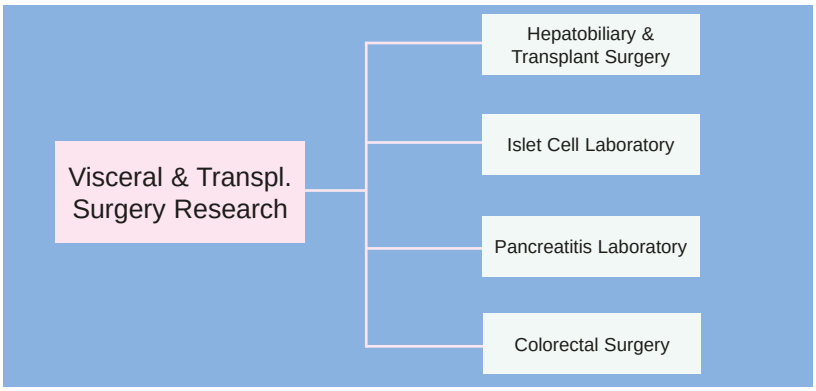
- Cattin P, Dave H, Grunenfelder J, Szekely G, Turina M, Zund G. Trajectory of coronary motion and its significance in robotic motion cancellation. Eur J Cardio-thorac Surg 2004 (in press)

- Boutsianis E, Dave H, Grunenfelder J, Frauenfelder T, Ventikos Y, Wildermuth S, Turina M, Zund G. Computational simulation of intracoronary flow based on real coronary geometry. Eur J Cardio-thorac Surg 2004 (in press)

2.2 Visceral & Transplant Surgery Research

PD Dr. phil II
Rolf Graf

Prof. Dr. med.
Alain Clavien



2.2.1 Hepatobiliary & Transplant Surgery

Clin. Ass. Prof.
Dr. med.
Markus Selzner

Dr. med.
Yinghua Tian

Dr. med.
Harm Hoekstra

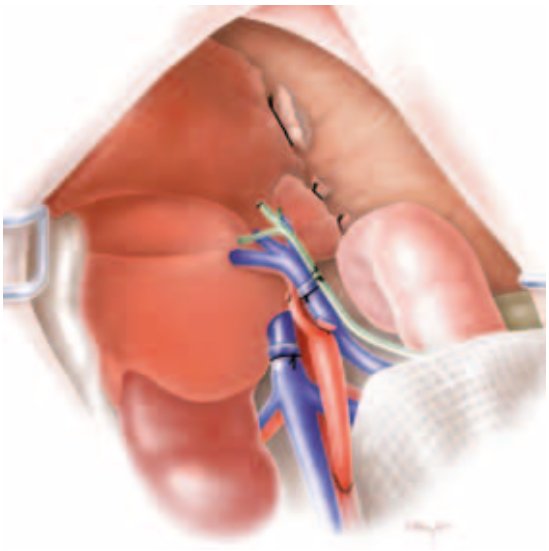
Dr. med.
Panco Georgiev

Astrid Morger

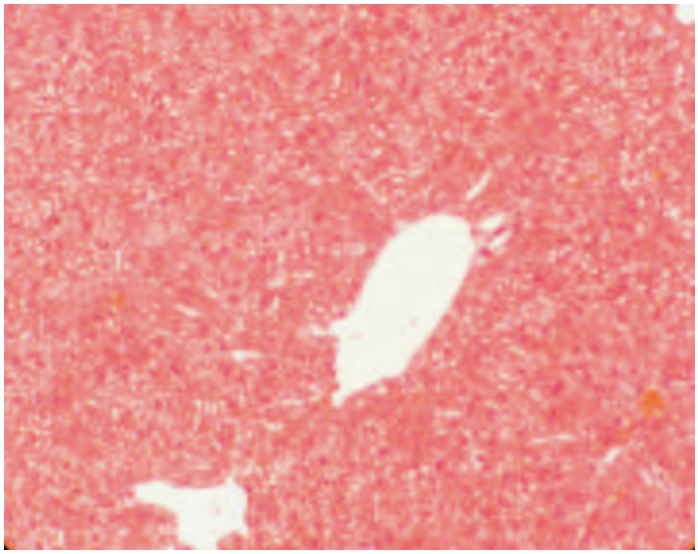
Ischemia / Reperfusion Injury and Liver Transplantation
Dr. med. Markus Selzner; Dr. med. Yinghua Tian; Dr. med. Harm Hoekstra
Dr. med. Panco Georgiev

Ischemia/reperfusion injury of the liver represents an important problem in major hepatic surgery, liver transplantation, shock and trauma. Two types of injury have to be differentiated: (1) warm ischemic injury, occurring during liver resection, trauma and shock and (2) cold ischemic injury, occurring during organ preservation. Our group has a longstanding interest in the cellular processes leading to these two types of injuries. Recently, we and others have identified apoptosis as a critical mechanism of injury. Using various models of warm hepatic ischemia in mice, we could identify extracellular cytokines inducing programmed cell death in hepatocytes. Inhibiting this pathway was not only protecting from parenchymal injury in the liver but also prevented animal death after prolonged ischemic periods.
Using sophisticated models of liver transplantation in mice and rats, we investigated mechanisms of injury induced by cold ischemia. Our studies indicated that cellular blood elements (i.e. leukocytes, platelets) are critical in inducing apoptosis in sinusoidal endothelial cells.

Currently, our efforts shifted towards the development of protective strategies against ischemic injury. For example, we and others demonstrated that ischemic preconditioning (i.e. a short cycle of ischemia and reperfusion prior to the prolonged ischemic insult) confers strong protection against ischemic injury in mice models as well as in the clinical setting.



Schematic representation of the anastomoses after an orthotopic liver transplantation in the mouse



Histological section of a small-for-size liver two days after transplantation.

Collaborations:

- PD Dr. W. Jochum, Institut für Klinische Pathologie, UniversitätsSpital Zürich
- PD Dr. B. Ludwig , Forschungsabteilung, Kantonsspital St.Gallen

Selected references:

- Selzner N, Selzner M, Jochum W, Clavien PA. Ischemic preconditioning protects the steatotic mouse liver against reperfusion injury: an ATP dependent mechanism. J Hepatol 2003;39:55-61.
- Rudiger HA, Graf R, Clavien PA. Sub-lethal oxidative stress triggers the protective effects of ischemic preconditioning in the mouse liver. J Hepatol 2003;39:972-7.
- Rudiger HA, Graf R, Clavien PA. Liver ischemia: apoptosis as a central mechanism of injury. J Invest Surg 2003;16:149-59.
- N Selzner, HA Rüdiger, R Graf, PA Clavien. Protective strategies against ischemic injury of the liver. Gastroenterology 2003;125:917-936.
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Dr. med.
Nazia Malekkiani
Selzner

Dr. med.
Mickael Lesurtel

Dr. med.
Stefan Heinrich

Liver regeneration

Dr. med. Nazia Selzner, Dr. med. Mickael Lesurtel, Dr. med. Stefan Heinrich

The liver is the only solid organ with the ability to regenerate to its initial size, which is a critical process after major liver resections. While several intracellular mediators of regeneration have been discovered during the past decade, the extracellular mediators of hepatocyte regeneration are still unknown. In rodent models using partial hepatectomy or partial liver transplantation, we were able to further dissect the complex extracellular mechanisms including the involvement of cytokines and the interaction of various cell types in the sinusoids.

Animal studies in the steatotic liver indicated that the process of liver regeneration is significantly impaired at several levels of the pathway.

Also, we were able to show in a mouse model, that the aging liver has a decreased capacity to regenerate. These findings may open novel avenues for treatment of patients with hepatic steatosis and elderly patients.

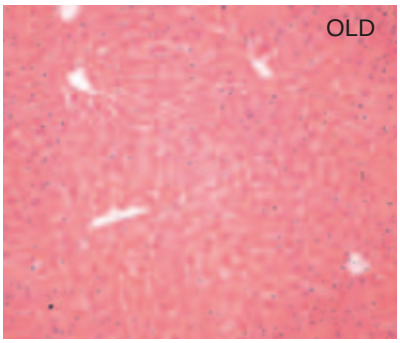


Fig. 1a

OLD + PC

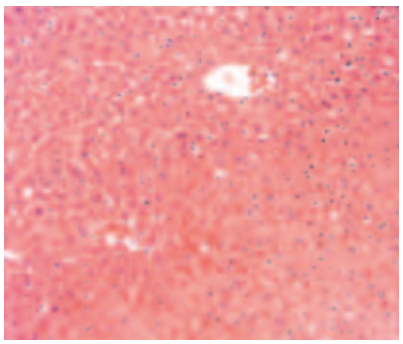


Fig. 1b

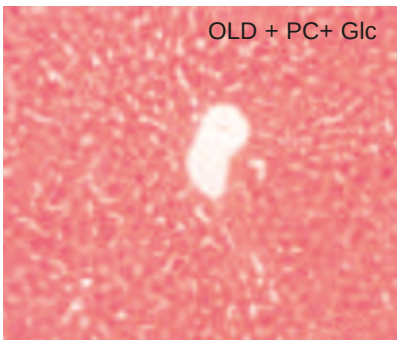


Fig. 1c

Old mice have a decreased tolerance to ischemic injury of the liver with presence of necrosis after 60 minutes of ischemia and 4hr of reperfusion. (Fig. 1a). Ischemic preconditioning is not protective in old mice and increase the necrosis of the liver (Fig. 1b). Pretreatment of old mice with intravenous glucose significantly improve the injury of the liver with almost complete regression of necrosis (Fig. 1c).

Collaborations:

- PD Dr. B. Odermatt, Labor für Molekulare Diagnostik, Institut für klinische Pathologie
- Prof. Chr. Gachet, INSERM 311 EFS Alsace 67065 Strasbourg

Selected references:

- Tian Y, Graf R, Jochum W, Clavien PA. Arterialized partial orthotopic liver transplantation in the mouse: a new model and evaluation of the critical liver mass. Liver Transpl 2003, 9:789-95.
- Selzner N, Selzner M, Odermatt B, Tian Y, Van Rooijen N, Clavien PA. ICAM-1 triggers liver regeneration through leukocyte recruitment and Kupffer cell-dependent release of TNF-alpha/IL-6 in mice. Gastroenterology 2003, 124:692-700.
- Selzner N. Selzner M. Tian Y. Kadry Z. Clavien PA. Cold ischemia decreases liver regeneration after partial liver transplantation in the rat: A TNF-alpha/IL-6-dependent mechanism. Hepatology 2002, 36: 812-8.

Clin. Ass. Prof.
Dr. med.
Markus Selzner

Dr. med.
Daniel Dindo

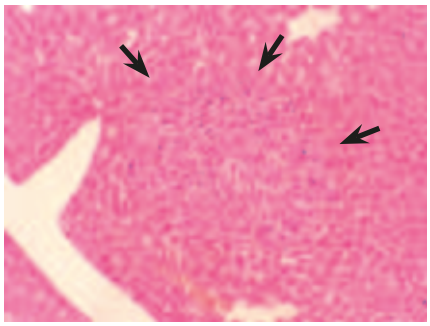
Dr. med.
Stefan Heinrich

Oncology

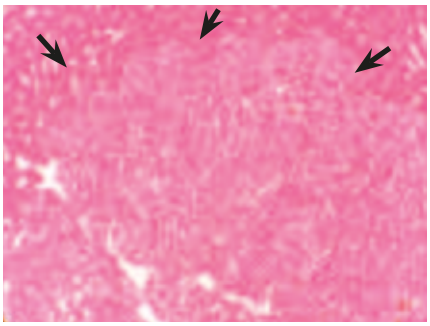
Dr. med. Markus Selzner; Dr. med. Daniel Dindo, Dr. med. Stefan Heinrich

The development of cancer is the result of uncontrolled proliferation and the inability of the host to remove the unwanted cells. Usually, these cells die due to apoptosis, the programmed cell death. If these cells lose the ability to undergo apoptosis, a tumor develops. We are currently investigating several approaches to induce apoptosis in tumor cells in order to promote cell death. One approach using human colon cancer cells has opened promising insights.
Application of a synthetic form of the sphingolipid ceramide induced apoptosis. In addition, the inhibition of ceramide metabolism prevented liver metastases in a mouse model.
To increase the understanding of tumor cell death we are currently investigating the mechanisms by which apoptosis is induced in this model. Finally, we hope to establish new therapeutic approaches.

In order to further test these promising results from our cell culture experiments in-vivo, we evaluated murine tumor models for colorectal cancer. Using BALB/c mice and an established syngeneic cell line (CT-26), we were able to establish a reliable model for liver metastases by intrasplenic cell inoculation. In addition, we established a model for lung metastases by intravenous injection of the cells into the penile vein.



H&E sections of the liver two weeks after injection of CT-26 cells into the spleen



H&E sections of the liver three weeks after injection of CT-26 cells into the spleen.

Achievements 2003

Scientific

- Our research focuses on the elucidation of mechanisms of cellular injury in the liver following ischemia and reperfusion. We had previously shown that apoptosis is the prevalent mechanism of endothelial cell injury. Furthermore, understanding the mechanisms of regeneration after the injury is a major focus of our research.
- Following our demonstration that TNFa, and not Fas, induces apoptosis after normothermic ischemia and reperfusion, the mechanisms of regeneration were studied. The presence of ICAM-1, an intercelleular adhesion molecule, turned out to be crucial for the recruitment of leukocytes and the Kupffer cell dependent release of TNFa/IL-6 which induce hepatic regeneration (Gastroenterology).
- We continued to develop a unique model of arterialized partial liver trans plantation in mice. We could show that small-for size livers (30%) do not survive while transplantation of 50% of the liver resulted in 100% organ survival. The pathology of the small-for size liver is currently under investigation. The model will be used to devlop new strategies for therapeutic apporaches (Liver Transplantation).
- The role of ATP and energy levels during organ preservation and transplantation is still controversial. We investigated the presence of ATP in the steatotic mouse liver. We could show that ischemic preconditioning, a surgical procedure is protec tive increasing ATP levels. (J. Hepatology).
- Further investigations in the protective mechanism of ischemic preconditioning demonstrated that this strategy induces a transient sub-lethal oxidative stress which renders the organ more viable during the actual operation (J. Hepatology).
- We were invited to write a comprehensive review on 'Protective strategies against ischemic injury of the liver' (Gastroeneterlogy) and another review 'Liver ischemia: apoptosis as a central mechanism of injury' was published in J. Invest. Surgery.

Personnel

- Dr. M. Selzner received a prize from the Swiss Society of Surgery
- Dr. Tian was awarded a poster prize at the Second Day of Clinical Research, USZ

Intra- and extramural activities

- As part of our training program for the fellows in the laboratory, international scientists (visiting professors) were invited for discussion of projects and to give a seminar in the weekly Surgical and Gastroenterological Grand Round.
- We organized the second Hepatobiliary and Gastrointestinal Research Retreat in Vulpera, in which several groups (Prof. M. Fried, Gastroenterology, Prof. P. Meier-Abt, Clinical Pharmacology and Toxicolgy, Prof. W. Schaffner, Institute of Molecular Biology and Prof. P.-A. Clavien, Visceral and Transplant Surgery) from Zürich participated. In addition, internationally recognized scientist were invited to give lectures summarizing research from their own laboratory.

Collaborations:

- Prof Dr. Y. Hannun, Dept. of Biochemistry and Molecular Biology, University of South Carolina, Charleston, USA

Selected references:

- Selzner M. Bielawska A. Morse MA. Rudiger HA. Sindram D. Hannun YA. Clavien PA. (2001). Induction of apoptotic cell death and prevention of tumor growth by ceramide analogues in metastatic human colon cancer. Cancer Research 2001, 61:1233-40.

2.2.2 Islet Cell Laboratory

PD Dr. med.
Markus Weber

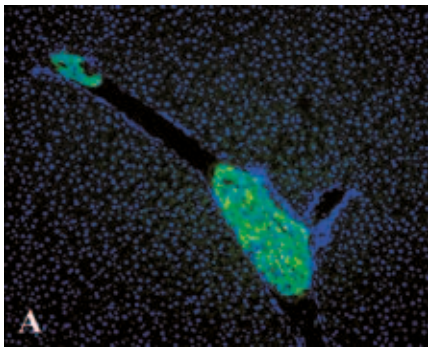
Dr.phil. II
Wolfgang Moritz

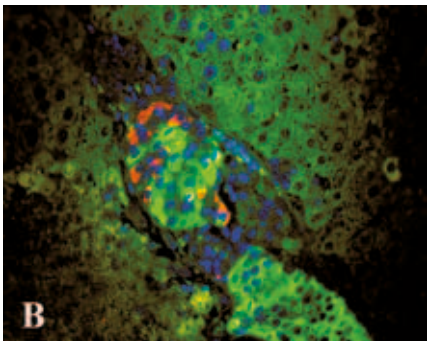
Urs Büchler

Improvement of cell survival in the immediate posttransplantation period

PD Dr. med. Markus Weber, Dr. Wolfgang Moritz

Our main research interest is focused on islet cell transplantation in particular to develop strategies to improve its efficacy and is performed in close collaboration with the Endocrinolology and Diabeteolgy Unit of the University Hospital. For the last three years, islet transplantation has become a widely used therapy for patients with type 1 diabetes mellitus. Islets are isolated from pancreata of heart-beating donors and transplanted into the liver of diabetic recipients by transhepatic portal catherization. Unfortunately, the requirement of donor tissue is quite high (2-3 pancreata) in order for a diabetic patient to become insulin independent. The reasons for such a high demand are manifold; insufficient isolation efficiency and graft rejection are certainly to mention. But equally important, we have shown, that due to their devascularized state, isolated islets undergo massive cell death which is pronounced in the central areas and probably a consequence of diffusion-limited oxygen and nutrient supply. We therefore are investigating strategies to interfere successfully with the deleterious effects of hypoxia and nutrient deprivation for the immediate posttransplantation period until complete revascularization of the transplant has taken place.





Rat islets after intrahepatic transplantation into syngenic rat: staining for insulin (green), activated caspase-3 (red) and nuclei (DAPI, blue). Magnification 100x (A) and 400x (B)

Achievements 2003

Since we have been able to demonstrate by in vitro studies that hypoxia is detrimental to islet cell viability and survival, we now plan to validate these observations in vivo. The main focus of our research in the recent year was to develop an in vivo model of islet transplantation in order to study the engraftment process within the immediate phase after transplantation. Our primary interest is to evaluate the processes involved in the course of the engraftment, such as graft survival, function and revascularization, which are independent of a diabetic state and immnological constraints but might be related to long term ischemia. Isolated islets are administrated by portal injection in syngenic, diabetic rats and graft survival is assessed by histological examination at various time points after transplantation.

Our first observations indicate occasional focal necrosis in the liver parenchyma, which is most likely a consequence of portal embolization by administrated islets. In some cases islet transplantation led to a regeneration process of the liver tissue as indicated by positive PCNA staining. We are also able to detect macrovesicular steatosis as an expression of the lipogenic effect of insulin secreted by the islet graft. However, after evaluation of the entity of insulin-positive cells, it is evident that total graft mass declines or becomes non-functional within the first few days after transplantation, despite no obvious inflammatory event. We are currently performing detailed analysis of the processes that lead to graft loss in this syngenic islet transplantation model.

This project is part of the Swiss National Science Foundation research grant that has been approved in 2002. Additional funding has been receved by the Olga-Mayenfisch, Hartmann-Müller and the Hermann-Klaus Stiftung.

Collaborations:

The research project is also part of a close collaboration with PD Dr. Lehmann and Dr. Züllig of the Unit of Endocrinology and Diabetology in Internal Medicine of the University Hospital Zürich and Prof. Max Gassmann of Veterinary Physiology of University of Zürich.

Selected references:

Moritz W., Meier F., Sroka D. M., Giuliani M., Kugelmeier P., Nett P.C., Lehmann R., Candinas D., Gassmann M., Weber M. (2002)
Apoptosis in hypoxic human islets correlates with HIF-1 alpha expression.
FASEB J. 2002 May; 16:745-7

2.2.3 Pancreatitis Research Laboratory

PD Dr. phil. II
Rolf Graf

PD Dr. med.
Daniel
Bimmler

Dipl. phil. II
Theresia
Reding Graf

Dr. med.
Marc
Schiesser

Martha Bain

Philippe
Appenzeller
cand.med.

Analysis of secretory stress proteins during pancreatitis
PD Dr. Rolf Graf, PD Dr. med. Daniel Bimmler

Pancreatic stone protein (PSP/reg) and pancreatitis-associated protein (PAP) belong to a family of conserved proteins predominantly expressed in the pancreas. Synthesis and secretion during stress and disease are highly increased and suggest that they belong to the acute phase reaction. Our laboratory developed isoform-specific ELISAs against rat PSP/reg and PAP I, II & III. These diagnostic tools are used to understand the regulation of PSP/reg and PAP in animal models of chronic pancreatitis (WBN/Kob rat) and experimental acute pancreatitis (cerulein pancreatitis).

The correlation of inflammatory processes in the exocrine pancreas with the highly increased levels of secretory stress proteins implies complex regulatory mechanisms: they are, in part, stimulated by normal hormonal action (CCK, secretin) as well as by cytokines. It is the goal of our laboratory to understand the regulation and functional properties of these proteins. Implications for the understanding of the pathology of pancreatitis, particularly chronic pancreatitis, may be used to develop better diagnostic tools.

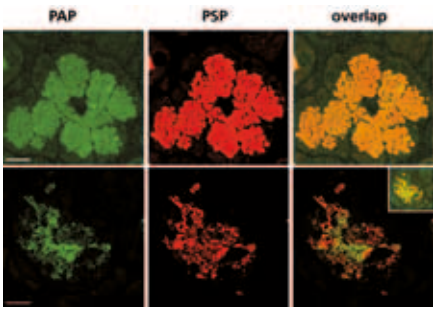


Fig. 1
Confocal immunohistochemistry of PAP (green) and PSP/reg (red) to demonstrate collocalization (overlay, yellow) of pancreatic secretory stress proteins in acinar cells. Bottom row shows acinar cells from a pancreas with chronic pancreatitis. Note disturbed cellular architecture and separation of pancreatic stress proteins (PAP: green; PSP/reg: red).

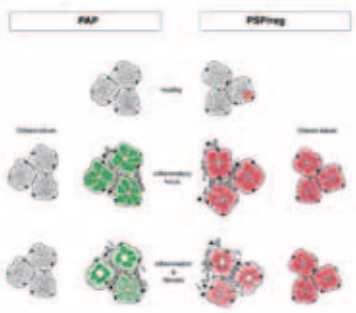


Fig. 2
Schematic overview of acinar changes during inflammation and fibrosis. Left: expression of PAP (green), predominantly in acinar cells in the process of destruction. Right: expression of PSP/reg (red), this protein is indicative of pancreatic stress and is present even in areas distal from an inflammatory focus.

Achievements 2003

- Scientific

1) We have been able to establish specific antibodies and design ELISAs for the detection and determination of human and mouse pancreatic secretory stress proteins. These diagnostic tools will be used in conjunction with clinical assessment of stress and disease relating to pancreatic inflammation.
2) The demonstration of changes in the cellular architecture of acinar cells during inflammation and fibrosis has been documented using light- and electronmicroscopy. Immunohistochemistry localizing the pancreatic stress proteins to various compartments indicated a premature activation of pancreatic enzymes, a process normally inhibited in the healthy pancreas (Cell and Tissue Research).
3) Demonstration of the ability of pancreatic juice to efficiently suppress activation of pancreatic zymogens based on the secretion of pancreatic secretory trypsin inhibitors (Pancreatology). The presence of these inhibitors suggests that premature activation may be restricted and may result in a focally contained inflammation.

- Personnel

Severin Meili won the 'Forschungs-Förderungspreis' of the Swiss Society of Gastroenterology and Hepatology.

Collaborations:

- Dr. Aurel Perren, Institut für klinische Pathologie, Universitätsspital Zürich
- Dr. Pia März & Prof. U. Otten, Physiologisches Institut, Universität Basel
- PD Dr. Marius Keel & Dr. Luc Härter, Klinik für Unfallchirurgie, Universitätsspital Zürich
- Dr. Martin Hersberger, Institut für Klinische Chemie, Universitätsspital Zürich
- Dr. George Scheele, Institute of Genomic Medicine, LaJolla, Ca. USA

Selected references:

- Meili, S., Graf, R., Perren, A., Schiesser, M. and Bimmler, D. (2003). The secretory apparatus assessed by pancreatic secretory stress protein expression in a rat model of chronic pancreatitis. Cell and Tissue Research 312: 291-299
- Graf, R., Klauser, S., Fukuoka, S.-I. ,Schiesser, M. , Bimmler, D. (2003). The bifunctional rat pancreatic secretory trypsin inhibitor / monitor peptide provides protection against premature activation of pancreatic juice. Pancreatology 3: 195-206

2.2.4 Colorectal Surgery

Dr. Franc Hetzer MD, Dr. Dieter Hahnloser MD

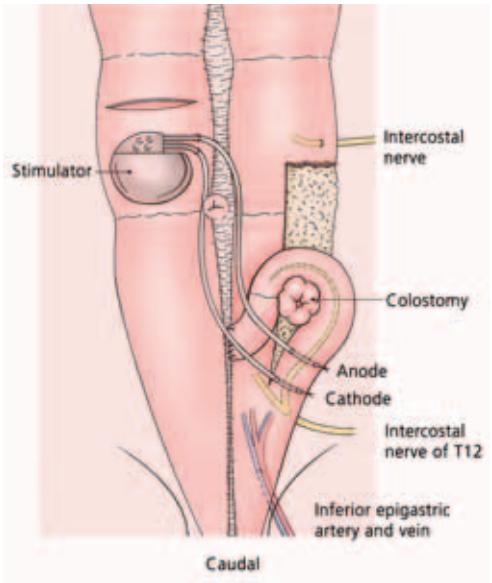
Dr. med.
Franc Hetzer

Clin. Ass. Prof.
Dr. med.
Dieter
Hahnloser

Every year, around 600 patients receive new permanent colostomies in Switzerland. The figures for the United States are 100 000. At least 50% of these patients have a life expectancy of more than five years at the time of the procedure. Stoma patients experience a clear decrease in quality of life with several limitations of their private and professional activities, e.g. continuous involuntary bowel movement or fear of bad smells or leakage from the stoma bag. Various techniques such as irrigation or colostomy plug are available but are only regularly used by one-third of patients.

At present, there is no surgery that would significantly improve the quality of life of stoma patients. Following the success of the dynamic graciloplasty the creation of a neosphincter around a stoma using similar principles merits investigations.

In a pilot study we demonstrated the feasibility of a continent stoma in an animal model with a dynamic rectus neosphincter. A distal based rectus muscle sling surrounding the stoma 270 degrees and a low frequency conditioning schema achieved a continent colostomy for more than 12 hours during 5 days. The neosphincter profile revealed a 40 mm segment of high pressure, with mean of 74 mmHg (range 67-82 mmHg). Type I muscle fibres increased from 38% (32-42%) to 74% (66-78%) after 12 weeks conditioning. Long-term results remain to be confirmed in a larger series be fore use in humans can be considered.



Schematic illustration of dynamic graciloplasty

Achievements 2003

- Poster award: Development of a Dynamic Rectus Abdominis Sphincteroplasty for Colostomy: an Animal Model. 65th Annual Congress of the Swiss Society of Gastroenterology and Hepatology. Luzern 5. - 7.10.00

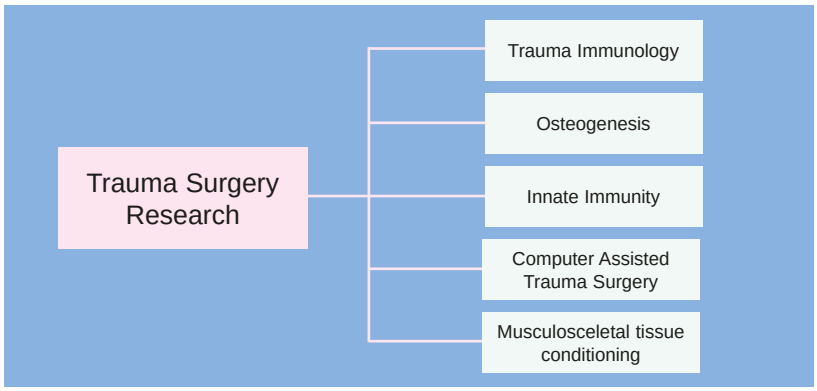
Selected references:

- Hetzer FH, Künzi W, Schwizer W, Demartines N. Continent colostomy with rectus abdominis neosphincteroplasty: development of an animal model. Br J Surg, 2003;90:1273-9

2.3 Trauma Surgery Research

PD Dr. med.
Marius Keel

Prof. Dr. med.
Otmar Trentz



2.3.1 Trauma Immunology

PD Dr. med.
Marius Keel

Dr. rer. nat.
Luc Härter

Dr. med.
Ludwig Labler

Dr. med.
Ladislav Mica

Ursula
Steckholzer

Immunomodulation in polytrauma patients
PD Dr. med. Marius Keel MD, Dr. rer. nat. Luc Härter

- Regulatory mechanisms of neutrophil apoptosis
- Regulation of Toll-like receptors in phagocytes from patients with sepsis

Reduction of neutrophil (PMN) apoptosis during sepsis contributes to the pathogenesis of multiple organ failure (MOF). The expression of the Bcl-2 proteins, Mcl-1, Bid, Bcl-2 and Bax was investigated in septic neutrophils. Mcl-1-protein levels decreased in patients, but remained stable in controls. Mcl-1-mRNA was found in freshly isolated PMN from controls and patients, but remained elevated only in patients. Bid protein level decreased significantly in control PMN undergoing apoptosis, but less prominent in septic patients. Bid mRNA was detected only in freshly isolated PMN. No Bcl-2 mRNA or protein was detected in neutrophils from patients or controls, whereas detectable Bax protein and mRNA levels remained unchanged in all samples. This indicates that upregulation of Mcl-1 in patients with sepsis participates in regulation of apoptosis during sepsis and alterations of Bid protein in neutrophils may reflect the level of apoptosis.
The reduced responsiveness of monocytes or granulocytes towards endotoxins ("endotoxin tolerance") during sepsis may depend on the expression of endotoxin receptors, the Toll-like receptors (TLR). Measurement of TLR-2 and TLR-4 expression on freshly isolated PMN from patients with sepsis revealed a significantly ($P<0.05$) higher mean fluorescence for TLR-2 (78.0 ± 18.6) and TLR-4 (11.4 ± 2.3) than controls (12.8 ± 2.2 and 2.3 ± 0.4). Similarly, monocytes from patients exhibited higher TLR-2 and TLR-4 expression (300.8 ± 40.6 and 92.7 ± 12.1) than cells from controls (149.5 ± 27.1 and 52.2 ± 7.6) (Fig. 1).
Interestingly, incubation with LPS or MALP-2 had no effect on TLR-4 or TLR-2 expression in cells from either controls or patients. Despite increased TLR expression in cells from patients with sepsis the endotoxin-induced release of TNF-a and IL-8 was indistinguishable from controls.

This indicates that the response to endotoxin in patients with sepsis does not solely depend on TLR-2 or TLR-4 expression. Endotoxins activate transcriptionfactors like NFkB and STAT-3. Inhibition of STAT-3 with the STAT-3 inhibitor Curcumin (20mM) abolished the IFN-g -induced upregulation of TLR-2 and TLR-4 in PMN and monocytes from healthy controls and patients with sepsis. This indicates that IFN-g must be involved in regulating leukocyte responsiveness towards endotoxins by TLR upregulation and that this upregulation is partly controlled by STAT-3. Also PMN apoptosis in patients with sepsis is regulated by the activity of STAT-3. Inhibition of STAT-3 abolished the LPS-induced survival in PMN from patients with sepsis (23.5 ± 2.6% to 47.7 ± 4.7%) and from healthy controls (22.7 ± 2.9% to 55.1 ± 1.0%). Expression of STAT-3 mRNA was found in control PMN, but not in patients with sepsis. STAT-3 protein was reduced in cells from patients compared to controls. Incubation with LPS reduced STAT-3 mRNA expression in control cells, but reduced apoptosis in cells from controls and patients with sepsis. This strongly indicates an involvement of STAT-3 in the regulation of neutrophil apoptosis through control of TLR expression.

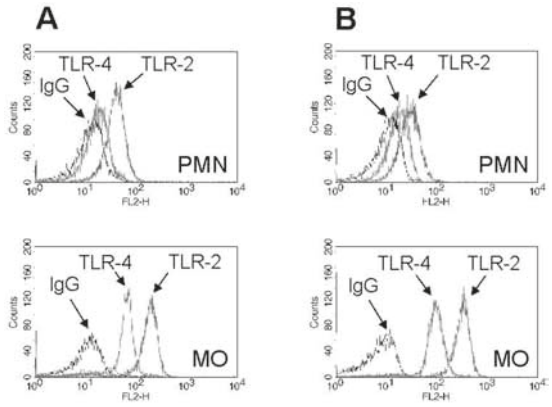


Figure 1. Expression of TLR-2 and TLR-4 receptors on PMN and monocytes Freshly isolated human neutrophil granulocytes (PMN) or monocytes (MO) from a healthy control (A) or a patient with sepsis (B) were incubated with PE-labeled anti-IgG (IgG), anti-TLR-2, or anti-TLR-4 antibodies. Specific fluorescence was measured in FACS. Depicted are one representative PE-fluorescence histogram for each group.

Achievements 2003

Talks: Marius Keel:

- 89th annual meeting of the American College of Surgeons, Oct. 19-23, Chicago, IL. USA: Endotoxin reduceds CD95-induced neutrophil apoptosis by cIAP-2-mediated caspase-3 degradation.

Talks Luc Härter:

- 120 Kongress der Deutschen Gesellschaft für Chirurgie, München 29.04.-02.05.2003: Beschleunigte Ubiquitinierung und Degradation der aktivierten Kaspase-3 in neutrophilen Granulozyten (Fritz-Linder-Preisträgersitzung).

Talks: Ladislav Mica:

- 67 Jahrestagung der Deutschen Gesellschaft für Unfallchirurgie, Berlin 11-14. Nov. 2003: Das Proteasom reguliert die LPS-vermittelte Reduktion der spontanen Apoptose neutrophiler Granulozyten unabhängig von NF-kB.
- Jahreskongress der Schweizerischen Gesellschaft für Chirurgie, Interlaken: Die Endotoxin-vermittelte Hemmung der Apoptose neutrophiler Granulozyten ist Proteasom, jedoch nicht NFkB-abhängig.

Talks: Ludwig Labler:

- KCI joint meeting on vacuum-assisted closure system, Salzburg 15-16.05.2003. Erste Erfahrungen mit dem neuen VAC Abdominal-Wundverband [VAC Abdominal Dressing] zur Behandlung von open abdomen Situationen.
- Day of clinical research 2003, USZ 9.-10.05.2003: 3 Posters (Keel, Härter, Mica)

Supported by grants from UBS, Heuberg Stiftung and from Rentenanstalt Swiss Life.

Collaborations:

- Dr. H. Hentze, Dr. M. Latta, Biochemische Pharmakologie, Universität Konstanz, Deutschland
- PD Dr. M. Leist, Fa. Lundbeck, Kopenhagen, Dänemark
- Hr. R. Dahlmann, VAC-Therapy, Fa. KCI Schweiz

Selected references:

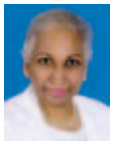
- Nolan B, Collette H, Baker S, Duffy A, De M, Miller C, Bankey P. Inhibition of neutrophil apoptosis after severe trauma is NFkappabeta dependent. J Trauma 2000; 48(4): 599-605.
- Suzuki Y, Nakabayashi Y, Takahashi R. Ubiquitin-protein ligase activity of X-linked inhibitor of apoptosis protein promotes proteasomal degradation of caspase-3 and enhances its anti-apoptotic effect in Fas-induced cell death. PNAS 2001; 98:8662.
- Sabroe I, Jones EC, Usher LR, Whyte MK, Dower SK. Toll-like receptor (TLR)2 and TLR4 in human peripheral blood granulocytes: a critical role for monocytes in leukocyte lipopolysaccharide responses. J Immunol 2002; 168(9):4701-4710

Own references:

- Härter L, Mica L, Stocker R, Trentz O, Keel M. Mcl-1 correlates with reduced apoptosis in neutrophils from patients with sepsis. J Am Coll Surg 2003 197(6):964-73.
- Mica L, Härter L, Trentz O, Keel M. Beschleunigte Ubiquitinierung und Degradation der aktivierten Caspase-3 in Neutrophilen Granulozyten von Patienten mit Sepsis. Chirurgisches Forum 2003 32:13-15.
- Mica L, Härter L, Trentz O, Keel M. Endotoxin-vermittelte Hemmung der Apoptose neutrophiler Granulozyten ist Proteasom, jedoch nicht NF-KB abhängig. Swiss Surgery Supplementum 2003 1: 5.
- Härter L, Mica L, Stocker R, Trentz O, Keel M. Increased expression of Toll-like receptor-2 and -4 on leukocytes from patients with sepsis. 2004 submitted.
- Mica L, Härter L, Trentz O, Keel M Endotoxin reduces CD95-induced neutrophil apoptosis by cIAP-2-mediated Caspase-3 degradation. 2004 submitted.

2.3.2 Osteogenesis Laboratory

Fr. Dr. med. O. A. Trentz, Dr. med. A. E. Handschin, Fr. S. Hemmi



Dr. med.
Omana A.
Trentz

Dr. med.
Alexander E.
Handschin

Dr. rer. nat.
Li K. Sun

Sonja Hemmi

Heterotopic Ossification

Heterotopic ossifiaction (HO) is defined as ectopic bone formation at sites that do not normally ossify. Mature HO shows cancellous bone with harversian canals, cortex, blood vessels and bone marrow with only a minor amount of hematopoesis. Paraarticular and intramuscular bone formations cause restricted range of motion, pain and ankylosis. Mature ossifications can be resected, but with a high recurrency rate. The onset of HO usually occurs after several months, but its induction probably starts immediately following the initial trauma. We have observed early changes of bone metabolism following trauma (see Fig. 1+2). Because osteocalcin is an important regulator of bone metabolism (see Fig. 3), we focused our study on osteocalcin and other phenotype marker expression in osteoblasts from both iliac crest and HO.

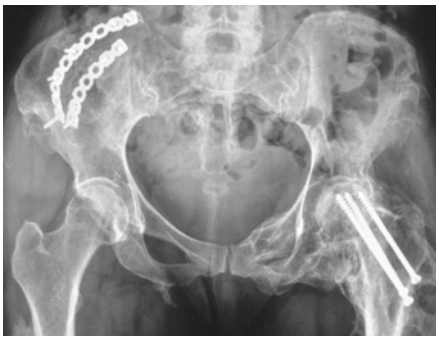


Fig. 1

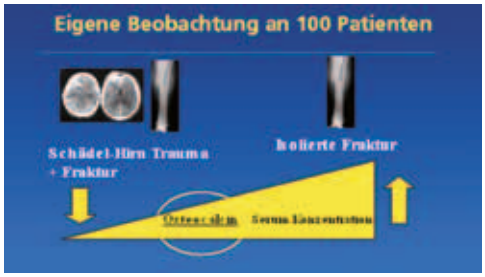


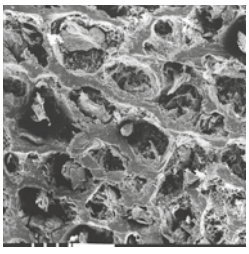
Fig. 2

Fig. 3

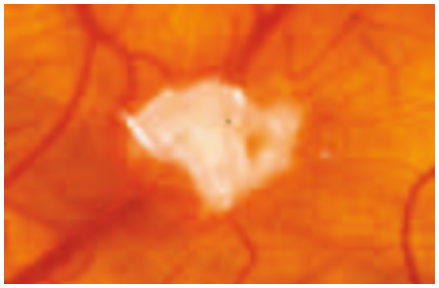
Tissue Engineering

The repair of large osseous defects remains still an unsolved problem in bone surgery. The use of autogenous bone grafts is widely accepted and considered to be the golden standard in the treatment of bony defects. However the disadvantage of autogenous bone grafts are limited availability, harvesting morbidity and insufficient biomechanical properties. The problems with autografts have initiated the development of several allogenic, xenogenic and synthetic bone graft alternatives. Their complication rate due to interaction between biomaterials and host tissues could be reduced, but still cell-mediated immune responses, and synthesis and resorption by osteoblasts resp. osteoclasts are not yet fully solved.

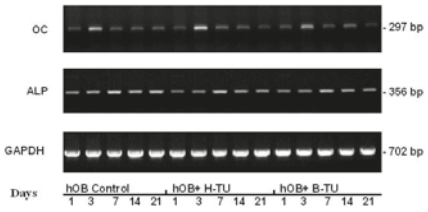
Tutoplast Disc



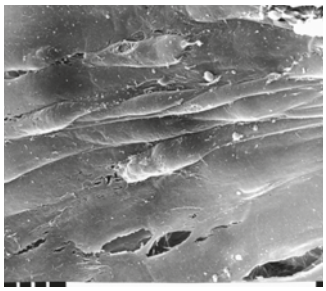
Tutoplast SEM (1000 µ) without cells



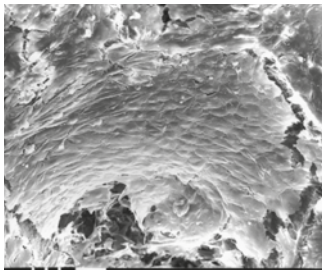
Angiogenesis in chicken embryo
(in Chorio-allantoin-membrane (CAM)



RT-PCR: Osteocalcin (OC) and ALP



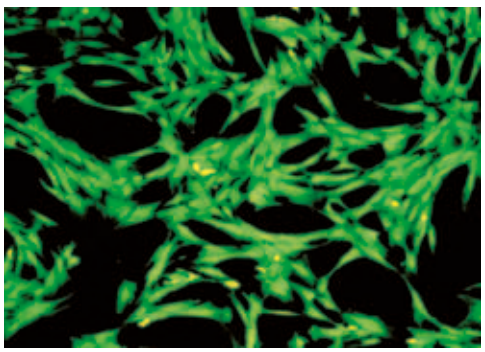
Day 7 on Tutoplast



Day 21 on Tutoplast

Fondaparinux Effect on Primary Human Osteoblasts *in vitro*

Prophylaxis and treatment of venous thromboembolism may require long-term heparin therapy. The prolonged administration of heparin has been associated with an increased risk of heparin-induced osteoporosis (1). This effect was also demonstrated in in-vitro studies on osteoblasts (2,3). Fondaparinux (Arixtra®) is a new antithrombotic drug, which, in contrast to heparin preparations, is a full synthetic, single chemical entity that has the ability to specifically inhibit factor Xa. Fondaparinux-sodium has been recently approved by the Food and Drug Administration (FDA) in the prevention of venous thromboembolism in orthopaedic surgery after proven efficient in four phase III trials and is increasingly used in many orthopaedic surgery centres (4). However, critics of the available trials point out, that more data and experience, including potential side-effects, are required before the role of fondaparinux in thromboprophylaxis after major orthopaedic surgery is established with confidence (5). Because of the known interactions of other antithrombotic and anticoagulatory agents on bone remodelling, we wanted to analyse the effect of fondaparinux on human osteoblasts in vitro and compare them to the effect of heparin.



Human osteoblasts under heparin incubation

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- 5. Lowe GDO, Sandercock PAG. Prevention of venous thrombo-embolism after major orthopaedic surgery: Is fondaparinux an advance? The Lancet 2003; 362: 503-504

Achievements 2003

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  Posttraumatic disturbances of humoral biochemical markers of bone metabolism
  IBMS-JSBMR, Osaka, Japan.
  Bone 2003; Vol.32: 565.
- 2. Trentz OA, Simon P. Hoerstrup, Li K. Sun, Lukas Bestmann, Andreas Platz, Otmar L.Trentz. Osteoblasts Response to Bone Substitutes *in vitro.*
  Swiss Society for Biomaterials. DSR-Cité Universitaire, Neuchâtel, Switzerland.
  SBB, Suppl 1, 2003, Vol.5: 55
- 3. Trentz OA, A.E. Handschin, A. Platz, O. Trentz, G. Zund, S. V. Hoerstrup
  Phenotypic Osteoblasts for in vitro Testing of Bone Implants and Substitutes
  4th European cells and material meeting in Davos 2003,
  ECM Suppl 2, 2003, Vol 5: 92
- 4. Trentz OA, Bestmann L, Handschin AE, Sun LK , Hemmi S, Platz A. , Trentz O.
  Vergleichsuntersuchungen phänotypischer Marker an Osteoblasten von Beckenkamm-Spongiosa und Heterotopen Ossifikationen
  Deutsche Gesellschaft für Unfallchirurgie, Berlin 2003.
- 5. Trentz OA, Handschin AE et al.
  Influence of Brain Injury on Posttraumatic Bone Metabolism. J Trauma, submitted 2003
- 6. Handschin AE, Trentz OA et al.
  Effect of Dalteparin and Fondaparinux (Arixtra®) on primary human Osteoblasts in vitro. Br J Surg, submitted 2003

Collaborations:

- Institute for Clinical Chemistry, University Hospital of Zürich, Switzerland. Prof. Dr. A. von Eckardstein, Lukas Bestmann
- University of Heidelberg, Germany. Trauma Division, PD Dr. H.J. Kock
- University Hospital Nijmegen, Netherlands. Prof. Dr. Jan Goris

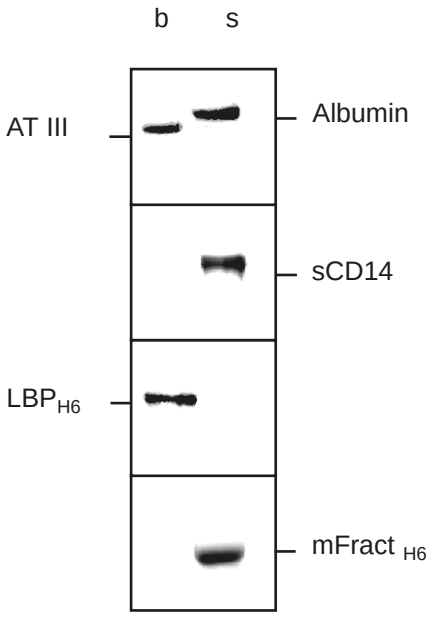
2.3.3 Innate Immunity Laboratory

PD Dr. med.
Michael
Heinzelmann

Dr. med.
Herbert Bosshart

Modulation of Host Responses to Bacterial Endotoxin
PD Dr. med. Michael Heinzelmann; Dr. med. Herbert Bosshart

Lipopolysaccharide (LPS) is unique to Gram-negative bacteria. Mammals are equipped with an LPS-sensing machinery consisting, primarily, of LPS-binding protein (LBP), CD14 and Toll-like receptor 4 (TLR4). Modest stimulation of TLR4 facilitates the elimination of invading microorganisms. Potent TLR4 stimulation, however, produces severe reactions in the host, often leading to multi-organ failure and death. Our research focuses on the identification of synthetic or naturally-occurring LPS-modifying substances. Specifically, we aim to elucidate the molecular mechanisms by which these substances interfere with LPS activation. These efforts are ultimately geared towards the development of novel anti-sepsis drugs.



Specific binding of heparin to lipopolysaccharide-binding protein (LBP). Heparin-agarose (50 μl) was incubated for 2 hr at room temperature with 5 μg of a mixture of human antithrombin III (AT III) and human serum albumin (Albumin), 2 μg of recombinant human soluble CD14 (sCD14), 2 μg of recombinant histidine-tagged human LBP (LBP_{H6}) or 2 μg of recombinant histidine-tagged murine fractalkine ($mFract_{H6}$). Agarose beads (b) and supernatants (s) were analysed separately by SDS-PAGE and protein bands visualized by Coomassie staining.

Achievements 2003

- We have identified plasma-derived LPS-binding protein (LBP) as a novel heparin-binding protein. Using a fluorescence-based assay, we found that clinically used heparin preparations significantly enhance the ability of LBP to catalytically disaggregate and transfer LPS to CD14, the LPS receptor. The presence of clinically relevant heparin concentrations in human whole blood increased LPS-induced production of proinflamm atory cytokines. Fondaparinux, which is identical to the antithrombin III-binding pentasac-charide in heparin, did not bind to LBP or alter LBP function. Thus, this novel anticoagulant drug is a potential candidate for safe administration to patients who have endotoxemia and require anti coagulation.
  LPS-enhancing effects are not unique to heparin or heparin-like structures. We found that arginine-rich cationic polypeptides, such as human CAP37 or the small structurally related salmon protamines, also enhance LPS-induced monocyte activation. The mechanism by which polycations (protamines) act synergistically with LPS differs in a funda mental way from the mechanism employed by polyanions (heparin). Polycations bind to both, LPS and cellular surfaces. Polycations are therefore LBPs which, like liver-derived endogenous LBP, mediate LPS activation of peripheral blood monocytes. These observations support the prediction that other strongly basic proteins could also act as amplifiers of LPS responses.
  Synthetic poly-L-histidines (Hn) have the capacity to neutralize LPS-induced cell activation. We observed that the Hn-mediated LPS-neutralizing effect is tightly coupled to a protonated state. This finding was unexpected because other polycations such as synthetic poly-L-arginines (Rn) or the above-mentioned salmon-derived protamines enhance LPS responses. Our results support a model in which Hn-bound LPS is neutralized, presumably because Hn fails to efficiently transfer LPS to cell surface-localized LPS receptors. We also discovered that a short synthetic histidine-rich peptide, derived from the human histidine- and proline-rich glycoprotein (HPRG), posseses potent LPS-neutralizing properties. Studies to define the role of HPRG in the context of LPS signalling are ongoing.

- Funding
  1. Novartis
  2. AO Research Commission
  3. Olga Mayenfisch Research Foundation
  4. Theodor and Ida Herzog-Egli Research Foundation
  5. Hartmann Muller Research Foundation
  6. Sanofi Synthelabo

Collaborations:

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- Jean-Marc Herbert, Cardio vascular and Thrombosis Research Department, Sanofi Synthelabo, 195 route d'Espagne, 31036 Toulouse CEDEX - France
- Hans-Peter Beck, SwissTropical Institute, Socinstrasse 57, CH 4002 Basel - Switzerland
- Jerome Pugin, Geneva University Hospital Department of Internal Medicine 24, rue Micheli-du-Crest, CH 1211 Geneva 14 - Switzerland

Selected references:

- Bosshart H, Heinzelmann M. Arginine-rich cationic polypepti des amplify lipopolysaccharide-induced monocyte activation. Infect Immun, 2002; 70: 6904-6910.
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- Heinzelmann M, Bosshart H. Fondaparinux sodium lacks immunomodulatory effects of heparin. Am J Surg, 2004; 187: 111-113.
- Heinzelmann M, Bosshart H. Heparin binds to lipopolysac charide (LPS)-binding protein, facilitates the transfer of LPS to CD14, and enhances LPS-induced activation of peripheral blood monocytes 2004, in press.

2.3.4 Computer Assisted Trauma Surgery

PD Dr. med.
Peter Messmer

PD Dr. med.
Guido Wanner

PD Dr. med.
Marius Keel

PD Dr. med. Peter Messmer; PD Dr. med. Guido A. Wanner; Dr. med. Marius Keel

Computer assisted surgery is a forthcoming technology in trauma departments being on the cutting edge from the experimental approach to a routine clinical application. While robotics play a minor role in trauma surgery, the field of passive navigation systems is continuously increasing. The fascination of these systems is the integration of digitalized medical imaging information and surgical action, i.e. the intraoperative position of instruments and implants. Herein, two basically different developments can be distinguished: first, navigation based on preoperative CT data sets, second, navigation in intraoperative C-arm images.
After preliminary precision studies on spinal instrumentation and virtual training of the surgeons the navigation system (MedivisionR) was introduced for clinical applications in the Division of Trauma Surgery in September 2002. Meanwhile, the C-arm based navigation assisted implantation of transpedicular screws for the stabilization of traumatic spine injuries of the thoracolumbar region is a routine procedure. Postoperative precision analysis of 12 cases of dorsal spinal instrumentation using CT-scans confirmed the high accuracy of this technology associated with a significant reduction of intraoperative radiation exposure. First encouraging experiences were made with the CT-based navigation assisted percutaneous transiliosacral screw osteosynthesis of posterior pelvic ring instabilities and C-arm based navigated screw placements in the proximal femur. Summarizing the pilot period, the computer assisted navigation system was successfully introduced in the clinical routine of our department. The expected advantages, i.e. the possibility of accurate preoperative planning, high precision of implant placement and low exposure to intraoperative radiation, were confirmed.
Next step is to further extend the scope of the navigation technology, e. g. for the operative treatment of cervical and thoracic spine injuries as well as minimal invasive pelvic surgery using intraoperative 3D imaging with a new mobile C-arm/CT combination equipment.

Collaborations:

- PD Dr. Simon Wildermuth, Institut für Diagnostische Radiologie, USZ Zürich
- Dr. Paul A. Grützner, Berufsgenossenschaftliche Unfallklinik Ludwigshafen, Unfallchirurgische Klinik der Universität Heidelberg
- PD Dr. Peter Messmer, Departement Chirurgie, Abteilung Traumatologie, Kantonsspital, Universitätskliniken Basel

Selected references:

- Grützner PA, Vock B, Schulte-Bockholt D, Wentzensen A: Computer assistierte Operationsverfahren in der Unfallchirurgie. Trauma Berufs krankh 4:S145-S152, 2002.
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2.3.5 Musculosceletal tissue conditioning

PD Dr. med.
Guido Wanner

Dr. med.
Claudio Contaldo

PD Dr. med. Guido A. Wanner; Dr. med. Claudio Contaldo

In peripheral occlusive disease as well as after trauma and tissue transfer, ischemia/reperfusion with its effects on the microcirculation and cellular metabolism is the critical determinant for the loss of tissue viability. The deterioration of the microcirculation of peripheral tissue remains a clinical challenge which requires advanced in vivo methods to study both the understanding of the mechanisms of injury and the developement of therapeutic strategies to counteract microvascular and metabolic dysfunction. Ischemia-reperfusion injury consists of hypoxic no-reflow and the inflammatory reflow paradox. We introduced a well established osteomyocutaneous flap model in the rat which allows for quantitative assessment of the microhemodynamics (intravital microscopy).
We will implement the microdialysis technique to collect interstitial markers reflecting the mitochondrial energy metabolism. One therapeutic approach to ameliorate capillary no-reflow consists in normovolemic hemodilution with cristalloid solutions. By adding artificial oxygen carriers to the colloids new formulations are created which exceed their role as a simple red blood cell substitute. We will delineate the function of artificial oxygen carriers as a potential oxygen therapeutic in a complex pathophysiological situation. On the other hand we will elucidate the potential role of heat shock protein induction, blockade of adhesion molecules and inactivation of oxygen radicals to reduce the post-ischemic inflammatory response.
Furthermore in the same model the orthogonal polarization spectral (OPS) imaging technique is validated against intravital microscopy for the study of soft tissue and periosteal microcirculation.

Achievements 2003

Experimental setup for preclinical microdialysis in peripheral tissues.

Establishement of orthogonal polarization spectral imaging technique (OPS) and intravital microscopy (IVM) setup.

Talks 2003

- Contaldo Claudio: IX International Symposium on Blood Substitutes (9-ISBS) March 3-5, Tokyo, Japan
  Influenc of hemodilution and oxygen affinity of Hbvs on oxygenation in ischemic hamster flap tissue.

- Contaldo Claudio: Jahreskongress der CH G. für Plastische-, Rekonstruktive und Aesthetische Chirurgie (SGPRAC) September 3-6, Lugano
  From microcirculation to metabolism: new methods to assess flap ischemia

- Claudio Contaldo: 7th Annual meeting of the European Congress of scientists and Plastic surgeons(ECSAPS)September 19-20, Geneva
  Normovolemic hemodilution with artificial oxygen carriers attenuates anaerobic metabolism in ischemic hamster flap tissue

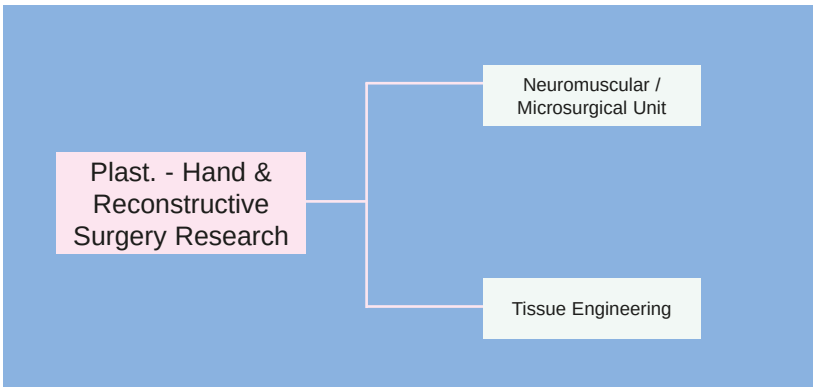
Selected references:

- Contaldo C, Tsuchida E, Erni D. Improved oxygenation in ischemic hamster flap tissue is correlated with increasing hemodilution with Hb vesicles and their O2 affinity.
  Am J Physiol Heart Circ Physiol 2003;285:H1140-H1147.
- Harder Y, Contaldo C, Erni D. Improved skin flap survival after local heat preconditioning in pigs. J Surg Res [in press]

2.4 Plast. - Hand & Reconstructive Surgery Research

PD Dr. med.
Gertrude Beer

Prof. Dr. med.
Viktor E. Meyer



Dr. med.
Doris Burg

PD Dr. med.
Gertrude Beer

2.4.1 Neuromuscular / Microsurgical Unit

Functional, electrophysiological and morphometric evaluation of nerve regeneration from coaptation on regenerated nerve fibres – experimental studies on the peroneal nerve in the rabbit
PD Dr. med.G.M. Beer, Dr. med. D. Burg

Despite continued research efforts, the results of nerve repair surgery are often discouraging. Among various efforts to improve clinical outcome, one thrust of research has been to identify the optimal site for coaptation in nerve repair. If the surgeon relies on visual observation alone, he or she can only judge the condition of the nerve sheaths but not the quantity or quality of nerve fibres. However, with the advent of intraoperative neurography and the nerve action potential recording, it is possible to judge the quality of the nerve parenchyma during operations. In order to successfully reinnervate a distal nerve stump or a nerve graft, it is commonly assumed that a sufficient number of "good" quality nerve fibres are required. Whereas the importance of the quantity of nerve fibres at a coaptation site is generally acknowledged, the prerequisite "quality" of these nerve fibres has yet to be defined. The question arose whether it is necessary to cut a damaged nerve back to healthy tissue or whether the resection can be restricted to the segment actually impeding regeneration and the coaptation carried out on freshly regenerated nerve fibres.
Further studies will deal with nerve regeneration under further suboptimal conditions such as interposition of nerve grafts or repeated nerve crushes before transection and coaptation.

Immunohistochemical (GCDFP (gross cystic disease fluid protein)) differentiation and analysis of localisation of eccrine and apocrine glands in the axilla of normhidrotic adults.

S. Baumüller, D. Mihic, N. Zech, G.M. Beer

The histological differentiation of the eccrine and apocrine glands in the axilla with routine stainings has been demanding and this might be one reason why the exact localisation of the glands has been discussed rather contradictorily. In case of hyperfunction of the eccrine glands (hyperhidrosis) or the apocrine glands (bromhidrosis) surgical excision may prove inevitable. The aim of this study is to exactly localise of the glands by use of immunohistological markers, such as the GCDFP or S 100 protein, for eccrine and apocrine differentiation.

After ethical approval, in 40 normhidrotic adults who will undergo axillary surgery a piece of 1 x 1 cm measuring skin is removed for histological evaluation morphometrically. Normhidrosis is evaluated by the "gravimetrical test" (< 50 mg/min).

If basic data of the number and distribution of the glands are available, the study is extended to patients with hyperhidrosis and / or bromhidrosis.

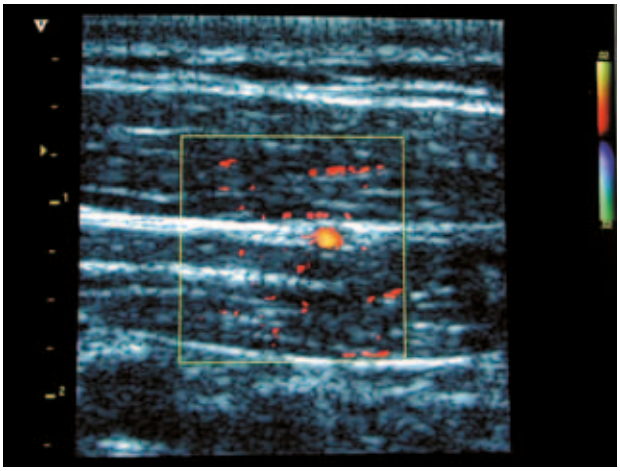
The thoracoacromial vessels as recipient vessels in microsurgery and supermicrosurgery: anatomic and sonographic studies.

G.M. Beer, P. Kompatscher, M. Manestar, A. Lang, V.E. Meyer

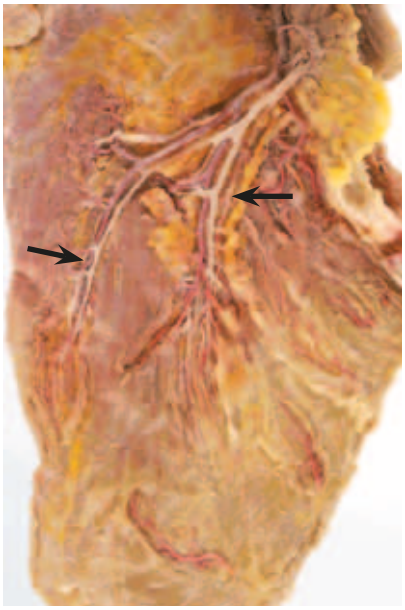
The currently most chosen recipient vessels for free flaps in breast reconstruction are the internal mammary vessels and the thoracodorsal vessels. Yet, each of these vessels has certain drawbacks.

The purpose of this study is to determine whether the pectoral branches of the thoracoacromial vessels are suitable as recipient vessels in microsurgery.

The presence and the precise course of the vessels is investigated by anatomical dissection and by colour Doppler ultrasound. In 18 cadavers the pectoral branch of the thoracoacromial vessels is followed caudally until the diameter of the artery diminishes to 1 mm. The same examination is carried out in 40 young female volunteers by tracing the vessel course with colour Doppler ultrasound. The 1 mm and the 2 mm cutoff point of the artery is measured with reference to the manubrium, the midsternal line, the clavicle and the upper border of the most closest rib. At both cutoff points, the diameter of the accompanying vein is measured and the relation to the pectoral nerve recorded.



Color Doppler ultrasound of the pectoral branch of the thoracoacromial vessels with cross-section of the pectoral artery on the point where the vessel diminished to 1 mm in diameter.



Pectoralis major muscle from an embalmed cadaver with the pectoral branch of the thoracoacromial vessels on the underside of the reflected muscle. The arteries are accompanied by one vein and by ➔branches of the lateral pectoral nerve underneath. At the medial border segmental perforating branches of the internal mammary vessels are seen.

Achievements 2003

- Habilitation Beer, Theme: Tierexperimentelle Untersuchungen am N. peroneus des Kaninchens zum Einsatz intraoperativer Funktionsdiagnostik bei der Nervenregeneration unter besonderer Beachtung der proxi malen Koaptationsstelle.

Collaborations:

- Prof. Dr. M. Müntener, Institute for Anatomy, University Zürich-Irchel
- Dr. H. Cristina-Schmitz, Institute for Laboratory Animal Science, Central Biological Laboratory, University of Zürich
- Prof. Dr. Th. Stallmach, Institute for Clinical Pathology, University Hospital Zürich
- Dr. M. Manestar, A. Lang, Institute for Anatomy, University Zürich-Irchel
- Devision of Plastic, Aesthetic and Reconstruktive Surgery, Landesklinikum Feldkirch, Austria
- Clinic of Dermatology, University Hospital Zürich

Selected references:

- Beer GM, Burg D, Zehnder A, Seifert B, Steurer M, Grimaldi H, Meyer VE. (2003) Functional, electrophysiological and morphometric evaluation of nerve regeneration from coaptation on regenerated nerve fibres - an experimental study in the rabbit. J Reconstr Micro-surg, in press
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- Hafner J, Beer GM (2003) Axillary sweat gland excision. In: Hyperhidrosis and Botulinum Toxin in Dermatology. Kreyden OP, Böni R, Burg G (eds), pp 57 - 63, Curr Prob Dermatol, Karger: Basel
- Kompatscher P, Manestar M, Schuster A, Lang A, Seifert B, Beer GM, The thoracoacromial vessels as recipient vessels in microsurgery and super microsurgery: a sonographic and anatomic study. Plast Reconstr Surg, in press

2.4.2 Tissue Engineering

Dr. med.
Volker Wedler

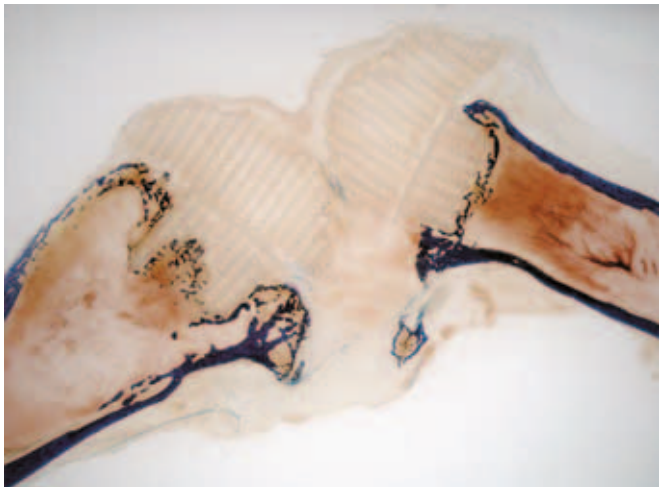
Dr. med.
Maria Schneller - Gustafsson

Engineering of articular cartilage using PEGT/PBT copolymer carriers and autologous grafting to repair full-thickness defects in small joints
V. Wedler, M. Schneller-Gustafsson, T. Woodfield, V.E. Meyer

We have replaced a complete articular defect in the distal knee joint of twenty White New Zealand Rabbits with autologous chondrocytes cultured on a synthetic biodegradable scaffold. The project is a co-operation with Isotis Tissue Engineering and extends for a time period of two years. The purpose of this animal study is to determine the amount and quality of the engineered cartilage, the incorporation of the implant, degradation/replacement of the scaffold and long term biomechanical properties after 6 weeks, 3 and 6 months respectively. The implants are evaluated with CT scans, histology, DMMB assay, MTT and biomechanical testing.

Sequential supplementation with TGF-ß1, IGF-1 and BMP-2 in human articular chondrocyte
M. Schneller-Gustafsson, P. Herzog, V.E. Meyer, V. Wedler

Tissue engineering of cartilage consists of two steps. First, autologous cells have to be multiplied. During this process the cells loose their cartilage phenotype. Secondly, these cells have to be stimulated to redifferentiate and produce cartilage matrix. Different growth factors can be used to increase cell proliferation, redifferentiation, extracellular matrix production and maturation. Additionally, it is believed that in order to obtain a qualitatively superior extracellular matrix, not only must the correct growth factors be given, they must also be administered in an optimal sequence. We are examining the response of human articular chondrocytes cultured on a biodegradable scaffold to sequential supplemented TGF-ß1, IGF-1 and BMP-2. The constructs will be assessed by DMMB assay, PCR for collagen type 2, aggrecans and Sox-9, DNA analysis for cell number and by histology.



Achievements 2003

- Establishment of a tissue engineering laboratory

Collaborations:

- IsoTis Tissue Engineering, Bilthoven, Netherlands
- PD Brigitte von Rechenberg, Veterinary Hospital, Irchel
- Institute for Laboratory Animal Science, Central Biological Laboratory, University of Zürich
- Institute of Pharmaceutical Sciences Drug Formulation and Delivery, ETH Zürich
- Department of Materials Polymer Technology, ETH Zürich

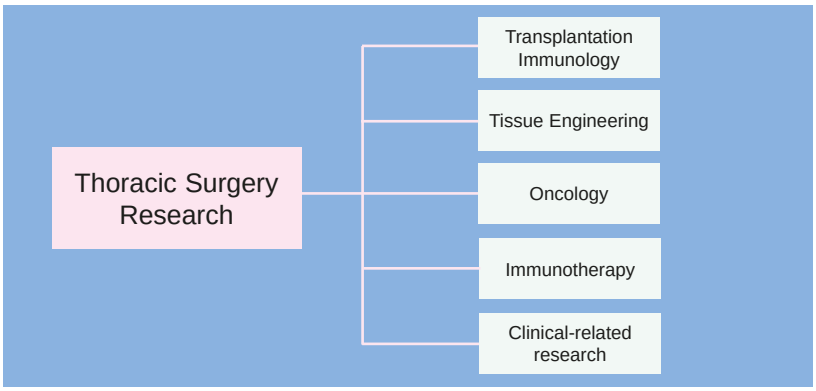
Selected references:

- Ochi M, Uchio Y, Kawasaki K, Wakitani S, Iwasa J. Transplantatio of cartilage-like tissue made by tissue engineering in the treatment of cartilage defects of the knee. J Bone Joint Surg. 2002;84-B(4):571-578.
- Perka C, Spitzer R-S, Lindenhayn K, Sittinger M, Schultz O. Matrix-mixed culture: New methodology for chondrocyte culture and preparation of cartilage transplants. J Biomed Mater Res. 2000;49:305-311.
- van Susante JLC, Buma P, van Beuningen HM, van den Berg WB, Veth RPH. Responsiveness of bovine chondrocytes to growth factors in medium with different serum concentrations. J Orthop Res 2000;18(1):68-78

2.5 Thoracic Surgery Research

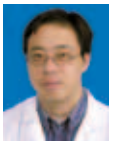
PD Dr. med. Stephan Korom

Prof. Dr. med. Walter Weder



2.5.1 Transplantation Immunology

PD Dr. med. Stephan Korom



Dr. med. Lin Yang

Dr. med. Florian Jung

Vlasta Strohmeier

Melatonin in Experimental Perfused Organ Transplantation
Dr. med. F. Jung; Dr. med. L. Yang; PD Dr. med. S. Korom

Melatonin, secreted by the pineal gland, is a multifunctional agent which (a) protects tissues from damage through free radical scavaging and attenuates ischemia/reperfusion injury in organ grafts; (b) acts synergistically with cellular antioxidants; (c) displays complex, dose-dependent immunoenhancing and -suppressing effects in vitro and in vivo. We analyzed the immuno-modulatory effect of melatonin on acute allograft rejection. Cardiac grafts were transplanted from LBNF1 to LEW rats and anastomosed to the abdominal great vessels. The effect of low dose (LD; 20 mg/kg/d) and high dose (HD; 200 mg/kg/d) melatonin treatment in recipients compared to untreated controls was investigated. HD melatonin therapy abrogated acute rejection, significantly prolonging allograft survival (mean survival: 12.3d ± 1d SD; n = 8; $P < 0.0001$) compared to untreated controls which rapidly reject the transplant (6.3d ± 1d n = 12). LD therapy did not extend survival significantly (7.3d ± 1.1d; n = 12). Allospecific IgM showed a significant decrease in animals receiving HD therapy vs. untreated recipients at days 10 and 14 post transplantation ($P < 0.01$), whereas in the LD group at day 10, a significant increase in allospecific IgM ($P < 0.01$) over the HD cohort was demonstrated. HD treatment markedly reduced lymphocyte proliferative capacity compared to controls and the LD group. HD melatonin treatment abrogated acute allograft rejection and significantly prolonged graft survival. Our results suggest an involvement of melatonin in humoral and cellular immune pathways following perfused organ transplantation. These findings may indicate a novel therapeutic approach, based on modulation of the neuroendocrine/immune axis through melatonin as a possible future immunosuppressant in organ transplantation.

The T Cell Costimulatory Antigen CD26/Dipeptidyl Peptidase IV (DPP IV) in Acute Rejection of Lung Allografts

Dr. med. Florian Jung; Dr. med. Lin Yang; PD Dr. med. Stephan Korom

The lymphocyte surface glycoprotein CD26 is a heterogenous molecule, characterized by an array of diverse functional properties. It belongs to an unique class of membrane-associated proteases, possessing dipeptidyl peptidase IV (DPP IV) enzymatic activity. Accumulating evidence indicates a central role for CD26 in allogeneic antigen-mediated immune pathways and during the memory T cell response. Based on our previous observations during acute and accelerated cardiac allograft rejection, we want to investigate the role of CD26/DPP IV in a different model of perfused allograft rejection.

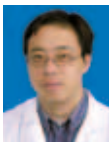
Collaborations:

- Dr. I. De Meester & Prof. Dr. S. Scharpé from the Dept. of Pharmaceutical Sciences, University of Antwerp, Antwerp, Belgium
- PD Dr. M. Keel and Dr. L. Härter, Dept. of Traumatology, USZ, Zurich

Selected references:

- Korom S, De Meester I, Stadlbauer THW, et al. 1997. Inhibition of CD26/dipeptidyl peptidase IV activity in vivo prolongs cardiac allograft survival in rat recipients. Transplantation 63:1495-1500.
- De Meester I, Korom S, Van Damme J, and Scharpé S. 1999. CD26, let it cut or cut it down. Immunology Today 20: 367-375.
- Florian Johannes Jung , Lin Yang , Luc Härter, Ilhan Inci, Didier Schneiter, Didier Lardinois, Marius Keel, Walter Weder and Stephan Korom. Melatonin in vivo prolongs cardiac allograft survival in rats. Journal of Pineal Research. 2004, in press.

2.5.2 Tissue Engineering



Dr. med.
Lin Yang

Dr. med.
Florian Jung

Manfred Welti

Trachea Reconstruction: A Bioreactor-aided Approach
Dr. med. L. Yang, Dr. med. F. Jung, PD Dr. med. S. Korom

In previous experiments, we have successfully generated chonrocyte-seeded neo-tracheal constructs using static culture conditions. Yet, although histomorphological appearance of these construct resembled tracheal tissue, biomechanical properties did not match the natural parameters. To induce a more favorable construct in terms of bio-mechanical benchmarks, our contemporary experiments focus on dynamic, bioreactor-aided in vitro cultivation systems.

Achievements 2003

- Construction of a bioreactor prototype for fabrication of neo tracheal constructs.

Collaborations:

- Dr. P. Neuenschwander, Institute of Polymer Research, ETH, Zurich, Switzerland.

Selected references:

- Yang L, Korom S, Welti M, Hoerstrup SP, Zund G, Jung FJ, Neuenschwander P, Weder W.
  Tissue engineered cartilage generated from human trachea using DegraPol scaffold.
  Eur J Cardiothorac Surg. 2003 Aug; 24(2): 201-7.

2.5.3 Oncology

Dr. med.
Didier Lardinois

Pharmacokinetic Study After Intrapleural Topical Application Of Chemotherapeutic Agents For Malignant Pleuromesothelioma In Immune Competent Rat Model

Dr. med. Didier Lardinois

Aim of the experiment: To investigate if local intrapleural application of cisplatin with the aid of surgical sealant has a prolonged local pharmacological tissue level in comparison to local administration without sealant while reducing systemic drug exposure. Furthermore, the effect on tumor activity will be investigated in vitro.

Achievements 2003

- D. Lardinois
  EACTS/ESTS meeting in Vienna. Best scientific contribution entitled:
  Non-steroidal anti-inflammatory drugs (NSAIDs) decrease the quality of pleurodesis after mechanical pleural abrasion
  Brompton Prize

Collaborations:

- Radio-Onkologie (V. Vuong, M. Pruschy, S. Bodis)
- Onkologie (R. Stahel)
- Pathologie (P. Vogt)
- Chemisches Institut (K. Rentsch)

Selected references:

- Ratto GB, Civalleri D, Esposito M, Vannozzi MO. Pleural space perfusion with cisplatin in the multimodality treatment of malignant mesothelioma: a feasibility and pharmacokinetic study.
  J Thorac Cardio-vasc Surg 1999; 117: 759-65.
- Prewitt et al. Orthotopic implantation of mesothelioma in the pneumonectomized immune-deficient rat: a model for innovative therapies.
  Int J Cancer 1993; 55: 877-80.
- Hanada K, Ninomiya K, Ogata H. Pharmacokinetics and toxicodynamics of cisplatin and its metabolites in rats: relationship between renal handling and nephrotoxicity of cisplatin. J Pharm Pharmacol 2000; 52: 1345-53

2.5.4 Immunotherapy for lung cancer

Dr. med.
Sven Hillinger

Epstein Barr virus-induced molecule 1 ligand chemokine (ELC/CCL19) in lung cancer therapy
Dr. med. Sven Hillinger

The overall goal of this project is to use murine lung cancer models to determine the efficacy and mechanisms of anti-tumor responses following intratumoral injection of recombinant Epstein Barr virus-induced molecule 1 ligand chemokine, (ELC/CCL19).
Due to dismal statistics in lung cancer survival new therapeutic strategies are clearly needed. Effective anti-tumor responses require both antigen presenting cells (APC) and lymphocyte effectors. Although lung cancers express tumor antigens, they are ineffective as antigen presenting cells. Our efforts to produce an effective cancer immune therapy are therefore focused on methods to restore tumor antigen presentation by utilizing chemokines that attract dendritic cells (DC) and lymphocyte effectors to the tumor site.
The following summarizes the proposed aims of our project:

- Evaluation of local and systemic anti-tumor efficacy and mechanisms of ELC/CCL19 responses in vivo;
- Determination and evaluation of the relative importance of the cellular and molecular phenotypes responsible for the anti-tumor effects by using selective blocking antibodies and specific knock-out mice;
- Studying the anti-tumor effect of ELC/CCL19 treatment by using a surgical model of 'residual' disease. Following surgical resection of the local tumor ELC/CCL19 will be administered to evaluate its effect on a secondary tumor challenge.

Future projects will address additional possibilities of this therapy in combination with other preventive or therapeutic options. With these experiments we will clarify the effectiveness and mechanisms of a novel immuno-therapeutic strategy, which would be highly feasible for clinical application in all lung cancer patients.

Achievements 2003

- SNF research fellowship grant: 'Tumor Cyclooxygenase-2-dependent Regulation of Dendritic Cell Function' at the University of California Los Angeles
- Zürich Cancer League and Sassella-Stiftung: 'Epstein Barr virus-induced molecule 1 ligand chemokine (ELC/CCL19) in lung cancer therapy'

Collaborations:

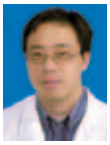
- Prof. S.M.Dubinett, Director of the UCLA Lung Cancer Program, Dr. S.Sharma, Associate Research Professor, University of California Los Angeles

Selected references:

- Hillinger S, Yang SC, Zhu L, Huang M, Duckett R, Atianzar K, Batra RK, Strieter RM, Dubinett SM, Sharma S. Epstein Barr Virus-Induced Molecule 1 Ligand Chemokine (ELC/CCL19) Promo-tes IFNg-dependent Antitumor Responses in a Lung Cancer Model. J Immunol. Dec 15;171 (12):6457-65 (2003)

2.5.5 Clinical-related Research

Dr. med.
Didier
Lardinois



Dr. med.
Lin Yang

Dr. med.
Didier
Schneiter

Non-steroidal anti-inflammatory drugs (NSAIDs) decrease the quality of pleurodesis after mechanical pleural abrasion
Dr. med. D. Lardinois, Dr. med. L. Yang

In this study, we investigated the effects of NSAIDs on adhesion formation after endoscopic mechanical pleural abrasion, which is a common procedure in thoracic surgery, being performed to prevent recurrence of a pneumothorax or a malignant effusion. Mechanical pleural abrasion was performed unilaterally by use of the video-assisted thoracic surgery (VATS) technique in an established pig model. Ten animals were divided into a treatment group and a control group. In the treatment group, animals received 100 mg diclofenac (2mg/kg body weight) orally daily for 3 weeks after surgery. At 3 weeks, all animals were sacrificed and efficacy of pleurodesis was macroscopically assessed by 3 independent reviewers blinded to the treatment of the animals using of a five-point severity pleurodesis score (from 0: no adhesions to 4: complete symphisis) and obliteration grade rating the distribution of adhesions (from 0: no adhesions to 4: adhesions in the whole chest). Microscopic evaluation was performed by 2 pathologists blinded to the study groups as well. A four-point score assessed the amount of collagen deposition (from 1: a few collagen fibers to 4: scar). Gross observation showed more dense adhesions in control animals with a median pleurodesis score of 3.67±1.0 in comparison to 2±2.2 in the treatment group (p=0.01*, Mann-Whitney nonparametric test). Distribution of adhesions were comparable in both groups with a median obliteration score of 3.67±1.3. Histopathologic examination showed a higher amount of collagen deposition in the control group, suggesting more dense adhesions, whereas in the treatment group there was loose granulation tissue (score of 4.0±0.8 vs. 2.3±1.0 in the treatment group, p=0.06). The degree of inflammatory reaction was comparable in the two groups.
Our results demonstrated that perioperative use of NSAI-drugs highly affects the quality of pleural adhesions obtained after mechanical abrasion in this pig model, which further suggests that these drugs should be avoided for pain management when a pleurodesis is performed.

Selected references:

- D. Lardinois, P. Vogt, L. Yang, I. Hegyi, M. Baslam, W. Weder. Non-steroidal anti-inflammatory drugs (NSAIDs) decrease the quality of pleurodesis after mechanical pleural abrasion.
  European Journal of Cardiothoracic Surgery, 2004.

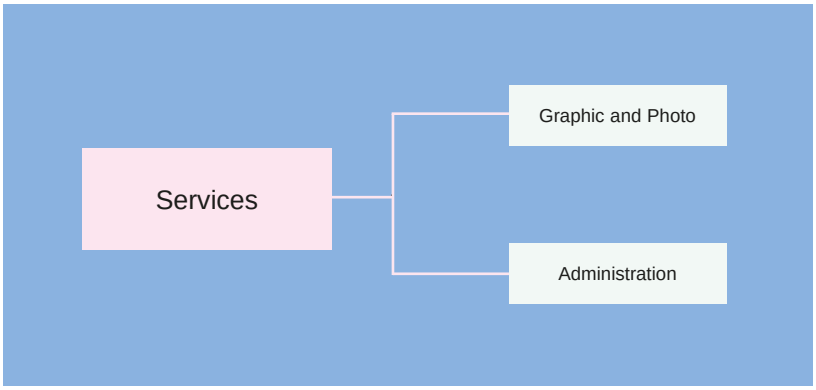
Robotic-aided thoracic surgery - feasibility assessment
Dr. med. D. Schneiter

In order to assess the advantages of robotic-aided thoracoscopic surgery, we investigated this novelty in a study with 6 sheep.
Installation of the apparatus and the handling of the extensive hardware went smoothly. Our first objective, the surgical-anatomical approach of the hilar region, was achieved without problems. Especially the crucial steps for lobectomy - preparation of the hilar vessels and the bronchus - were accomplished within a short training period. This was greatly enhanced by the superb visual display and the magnifying factor of the system made operating on a small surgical field easy. We were able to standardize the positioning of the trocars, the selection of instruments and the default settings for the operative console. For the future, we are ready to test the robotic surgery unit in selected thoracic surgery cases.

Achievements 2003

- D. Lardinois
  EACTS/ESTS meeting in Vienna. Best scientific contribution entitled:
  Non-steroidal anti-inflammatory drugs (NSAIDs) decrease the quality of pleurodesis after mechanical pleural abrasion
  Brompton Prize

3. Services



3.1 Graphic and photographic services

Nico Wick,
Photographer

Lea Schütz-Cohen,
Photographer

Stefan Schwyter,
Scientific
Illustrator

Carol De Simio,
Scientific
Illustrator

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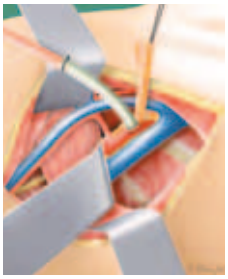
- layout of printing matters
- graphic and design of illustrations for papers and books
- construction and maintainance of websites
- maintainance of the digital image archives



3. 2 Administration

Gabriella Muolo-
Giaquinta,
Administration
Division of
Surgical Research

- Administrative office management
- Financial accounting of the Research Divison
- Organisation, planning and coordination of Workshop and vocational training
- Workshop, tutorials and seminars
- Quarterly reports preparation
- Meeting coordination for the head of the Research Divison
- Personnel administration of the employees of the University Hospital Zurich and the University Zurich

4. Events and Workshops at the Surgical Research Division in 2003

ATLS - Course, 30 january 2003

Installation of a new x-ray equipment for animal research

Zurich Cardiac Technical Course, 14 November 2003

Farewell of Annia Hofmann, Head of photographic section of the surgery department from 1996 to 2003

5. Publications 2003

- Dutly AE, Inci I, Hillinger S, Zalunardo M, Gaspert A, Rousson V, Seifert B, Weder W. Normal gas exchange after 30-h ischemia and treatment with phosphodiesterase inhibitor PDI747.
  European Journal of Cardio- Thoracic Surgery 2003; 24:594-600.
- Graf R, Klauser S, Fukuoka SI, Schiesser M, Bimmler D. The bifunctional rat pancreatic secretory trypsin inhibitor/monitor peptide provides protection against premature activation of pancreatic juice.
  Pancreatology 2003; 3:195-206.
- Grünenfelder J, Haussler A, Plass A, Reuthebuch O, Dave H, Leskosek B, Turina M, Zund G. A single bicaval venous cannula used for optimization of endoscopic robotically assisted procedures of the heart.
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- Hafner J, Beer GM (2003) Axillary sweat gland excision.
  In: Hyperhidrosis and Botulinum Toxin in Dermatology. Kreyden OP, Böni R, Burg G (eds), pp 57 - 63, Curr Prob Dermatol, Karger: Basel
- Hahnloser D, Petersen GM, Rabe K, Snow K, Lindor NM, Boardman L, Koch B, Doescher D, Wang L, Steenblock K, Thibodeau SN. The APC E1317Q variant in adenomatous polyps and colorectal cancers.
  Cancer Epidemiol Biomarkers Prev 2003; 12:1023-8.
- Härter L, Mica L, Stocker R, Trentz O, Keel M. Mcl-1 correlates with reduced apoptosis in neutrophils from patients with sepsis.
  Journal of the American College of Surgeons 2003; 197:964-73.
- Härter L, Mica L, Trentz O, Keel M. Beschleunigte Ubiquitinierung und Degradation der aktivierten Caspase-3 in Neutrophilen Granulozyten von Patienten mit Sepsis.
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- Hetzer FH, Schwizer W, Kuenzi W, Demartines N. Experimental model of continent colostomy using rectus abdominis neosphincteroplasty.
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- Maurus CF, Schmidt D, Schneider MK, Turina MI, Seebach JD, Zund G. Hypoxia and reoxygenation do not upregulate adhesion molecules and natural killer cell adhesion on human endothelial cells in vitro.
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- Meili S, Graf R, Perren A, Schiesser M, Bimmler D. The secretory apparatus assessed by pancreatic secretory stress protein expression in a rat model of chronic pancreatitis.
  Cell and Tissue Research 2003; 312:291-299.
- Meyer VE, Kilgus M, Stallmach Th, Beer GM, Burg D, (2003) Progress in nerve surgery by intraoperative application of electrodiagnostic methods. Proceedings of the II Congress of The World Society for Reconstructive Microsurgery, Monduzzi Editore, pp 73 - 79
- Mol A, Bouten CV, Zund G, Gunter CI, Visjager JF, Turina MI, Baaijens FP, Hoerstrup SP. The relevance of large strains in functional tissue engineering of heart valves.
  Thorac Cardiovasc Surg 2003; 51:78-83.
- Rudiger HA, Graf R, Clavien PA. Sub-lethal oxidative stress triggers the protective effects of ischemic preconditioning in the mouse liver.
  J Hepatol 2003; 39:972-7.
- Rudiger HA, Graf R, Clavien PA. Liver ischemia: apoptosis as a central mechanism of injury.
  J Invest Surg 2003; 16:149-59.

- Selzner M, Graf R, Clavien PA. IL-6: a magic potion for liver transplantation? Gastroenterology 2003; 125:256-9.
- Selzner N, Rudiger H, Graf R, Clavien PA. Protective strategies against ischemic injury of the liver. Gastroenterology 2003; 125:917-36.
- Selzner N, Selzner M, Jochum W, Clavien PA. Ischemic preconditioning protects the steatotic mouse liver against reperfusion injury: an ATP dependent mechanism. J Hepatol 2003; 39:55-61.
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- Tian Y, Graf R, Jochum W, Clavien PA. Arterialized partial orthotopic liver transplantation in the mouse: a new model and evaluation of the critical liver mass. Liver Transpl 2003; 9:789-95.
- Trentz OA , Simon P. Hoerstrup, Li K. Sun, Andreas Platz, Otmar L.Trentz. Osteoblasts Response to Allogenic and Xenogenic Solvent Dehydrated Cancellous Bone in vitro. Biomaterials 2003: 24;3417-3426.
- Trentz OA, L Bestmann, R Zellweger, G Zund, O Trentz, A Platz. Post-traumatic disturbances of humoral biochemical markers of bone metabolism. Bone 2003; Vol.32: 565.
- Trentz OA, Handschin AE et al. Influence of Brain Injury on Posttraumatic Bone Metabolism. J Trauma, submitted 2003
- Yang L, Korom S, Welti M, Hoerstrup SP, Zund G, Jung FJ, Neuenschwander P, Weder W. Tissue engineered cartilage generated from human trachea using DegraPol scaffold. European Journal of Cardio-Thoracic Surgery 2003; 24:201-7.

6. Awards 2003

- Dr. M. Selzner received a prize from the Swiss Society of Surgery
- Dr. N. Selzner: Preis der Schweizer Gesellschaft für Transplantation für die Arbeit *„ICAM-1 triggers liver regeneration through leukocyte recruitment and Kupffer cell-dependent release of TNF-alpha/IL-6 in mice“.*
- Dr. Tian was awarded a poster prize at the Second Day of Clinical Research, USZ
- Severin Meili received the 'Forschungsförderungspreis' of the Swiss Society of Gastroenterology and Hepatology.
- Semester Award 2003, University Zurich (awarded to the MD-Thesis of S. Yakarisik), Principle Investigator S. P. Hoerstrup.
- Cardiovascular Biology Award by the Swiss Society of Cardiology and Pfizer AG (awarded to S. P. Hoerstrup)
- Prix Roberval, Paris, France, Reportage Télévision Suisse Romande (awarded to S. P. Hoerstrup)
- Dr. Grünenfelder was awarded a poster prize from the Swiss Society of Surgery 2003
- D. Lardinois
  EACTS/ESTS meeting in Vienna. Best scientific contribution entitled:
  Non-steroidal anti-inflammatory drugs (NSAIDs) decrease the quality of pleurodesis after mechanical pleural abrasion
  Brompton Prize

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