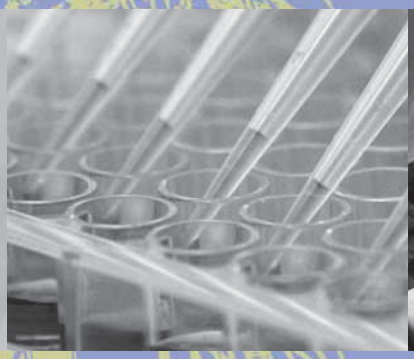
Division of Surgical Research

Annual Report 2002

Departement of Surgery
University Hospital Zurich
Switzerland




Division of Surgical Research
Departement of Surgery
University Hospital
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CH - 8091 Zurich

Realisation:
Photo & Graphics / Section Surgery
Nico Wick, Annia Hofmann

Content

Preface

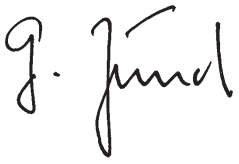
Dear Colleagues

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

I am delighted to be able to send you the annual report of the Division of Surgical Research at the University Hospital Zurich for 2002.

2002 was a very eventful year for our division. We were able to bring the arrangements for the new organisation structure to a successful conclusion in both an administrative and a scientific sense. It was possible to guarantee project management in line with both time and financial constraints thanks to the introduction of quarterly interim reports giving details of expenditure on materials and investment effected. Investment over the course of the past year has predominantly been concerned with restructuring within the information technology sector, with the result that approx. 60% of all installations have now been brought up-to-date. From a scientific point of view, four new competence groups ("Tissue Engineering", "Ischemia Reperfusion Injuries", "Navigation and Robotic Surgery" and "Methodology") have been established within the division thanks to cross-linking and these guarantee an exchange of know-how within the Research Division and promote progress in common interests. The newly introduced monthly research reports are eagerly awaited by all staff members and help to encourage the flow of information within the division.
I would like to take this opportunity to thank all staff members and research partners of the University Hospital, the University of Zurich and the Federal Institute of Technology Zurich for their efforts over the course of the past year.

Sincerely yours



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

1. Organisation

1.1 Position Division of the 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

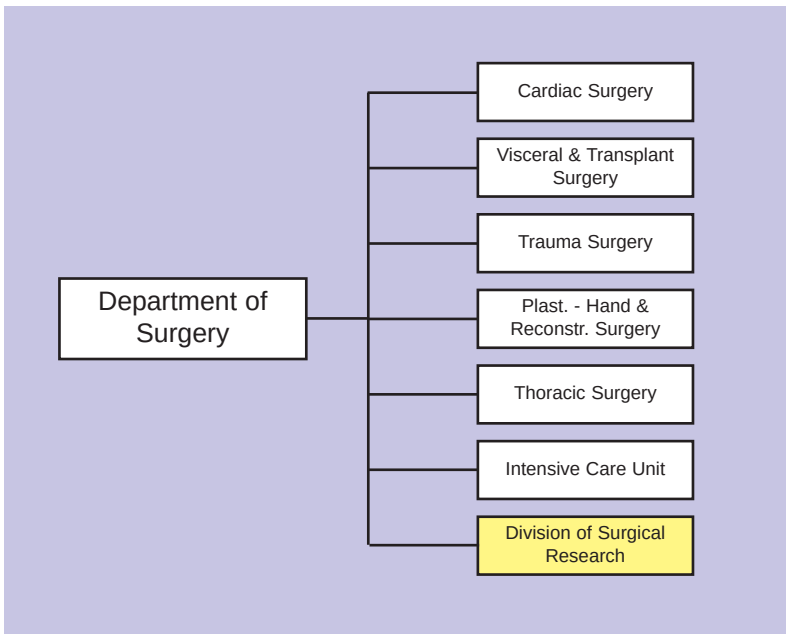
Prof. Dr. med. Otmar Trentz, Director of Trauma Surgery

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

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

PD Dr. med. Reto Stocker, Head of Intensiv Care Unit

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

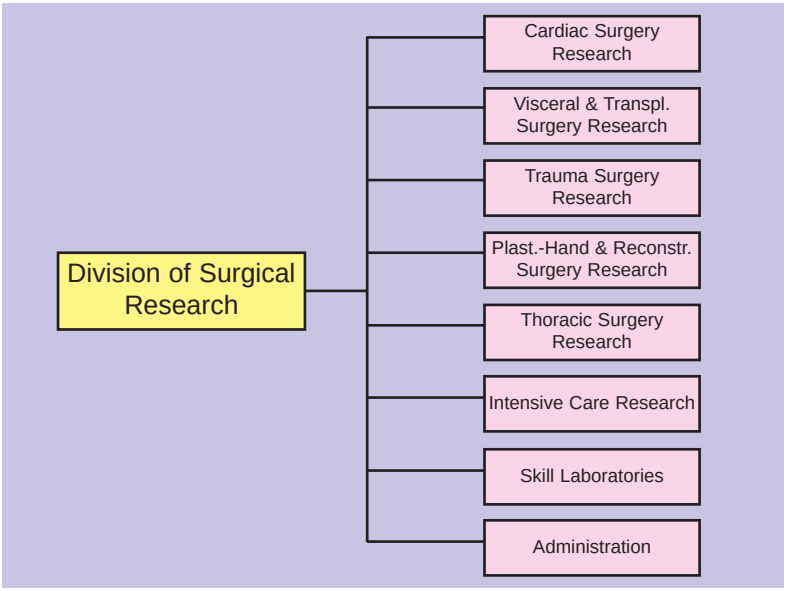


1.2 Structural Organisation of the Division of Surgical Research

PD 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



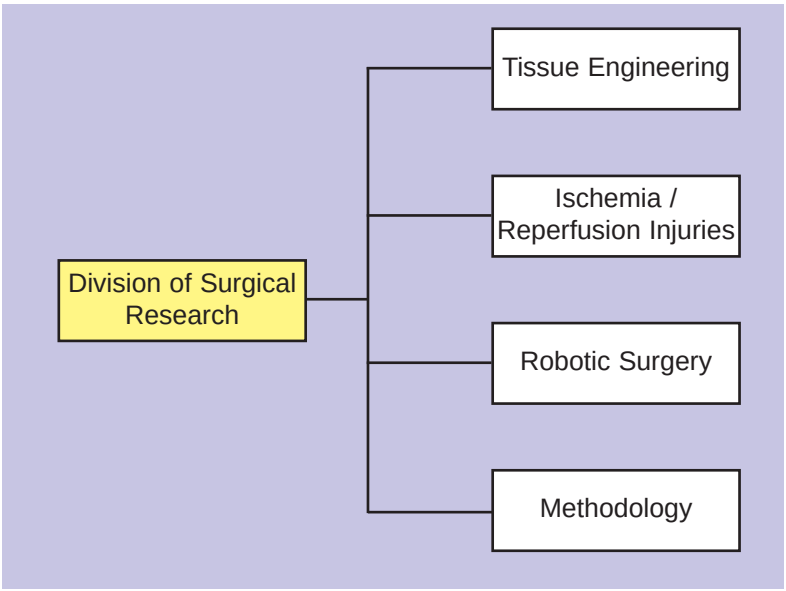
1.3 Scientific Sections within the Division of Surgical Research

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

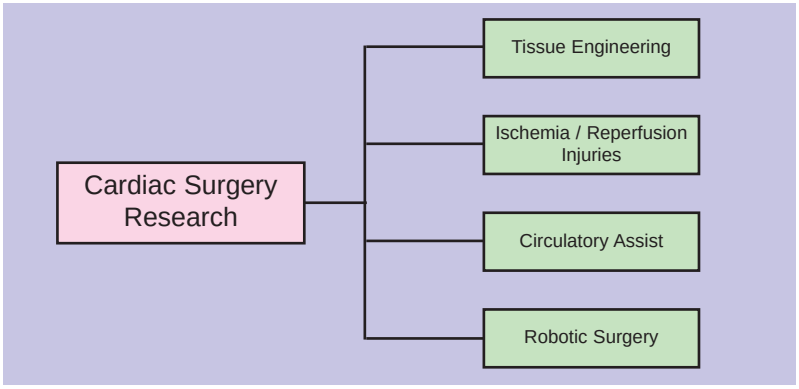


2. Research and Development

2.1 Cardiac Surgery Research

PD Dr. med.
Gregor Zünd

Prof. Dr. med.
Marko Turina



2.1.1 Tissue Engineering

PD Dr. med.
Simon Philipp
Hoerstrup

PD Dr. sc. nat.
Stefan
Neuenschwander

Dr. med.
Christina
Günter

Dr. med.
Alexander
Kadner

Sirpa Price

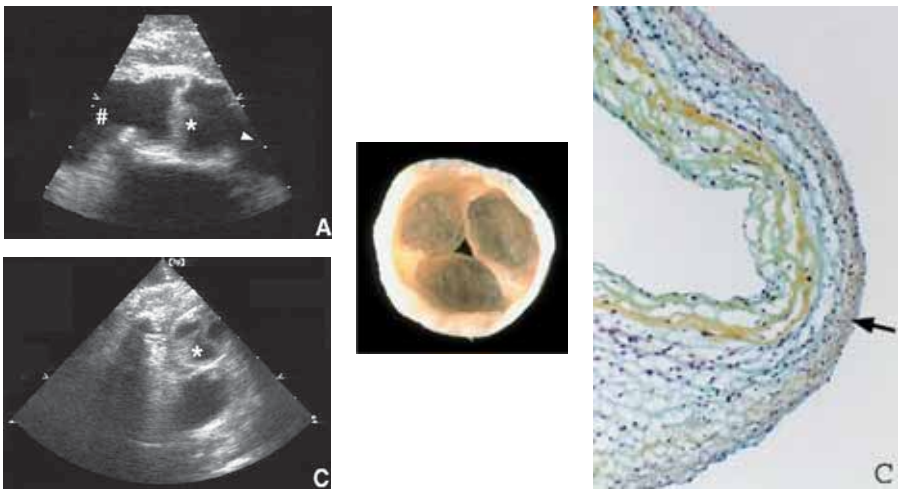
Klaus Marquardt,
Electron Microscopy

Laboratory for Cardiovascular 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 surgery, 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.

Research projects:

- Expansion, differentiation and characterization of human cells for tissue engineering
- In vitro cell systems
- Development of biodegradable scaffold materials
- Development of in vitro bioreactor systems
- Animal models
- Tissue engineering of cardiovascular structures:
  - Tissue engineered heart valves
  - Tissue engineered vascular grafts
  - Tissue engineered myocardium



Tissue engineered heart valve after 14 days in vitro (middle); Echocardiography after 8 weeks in animal model (left, short + long axis view) Histology after 5 months in vivo function (right) (Hoerstrup et al, Circulation 2000)

Achievements 2002

- C. Walton Lillehei Award, European Association of Cardiothoracic Surgery
- Ethicon-Prize, German Society of Thoracic and Cardiovascular Surgery
- 1st Clinical Day of Research Price, University Hospital Zurich
- "Image of the month", Press release, Swiss National Scientific Foundation
- Swiss National Scientific Foundation Grant (Principle Investigator S.P. Hoerstrup)

Collaborations:

- Department of Materials, Federal Institute of Technology, Zürich, Switzerland
- Department of Cardiac Surgery, Children's Hospital, Harvard Medical School, Boston, MA, USA
- Department of Pathology , Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
- Massachussetts Institute of Technology, Cambridge, MA, USA
- Laboratory for Tissue Engineering, German Heart Centre, Berlin, Germany
- Dutch Institute of Technology, Eindhoven, Netherlands

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 engineering 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

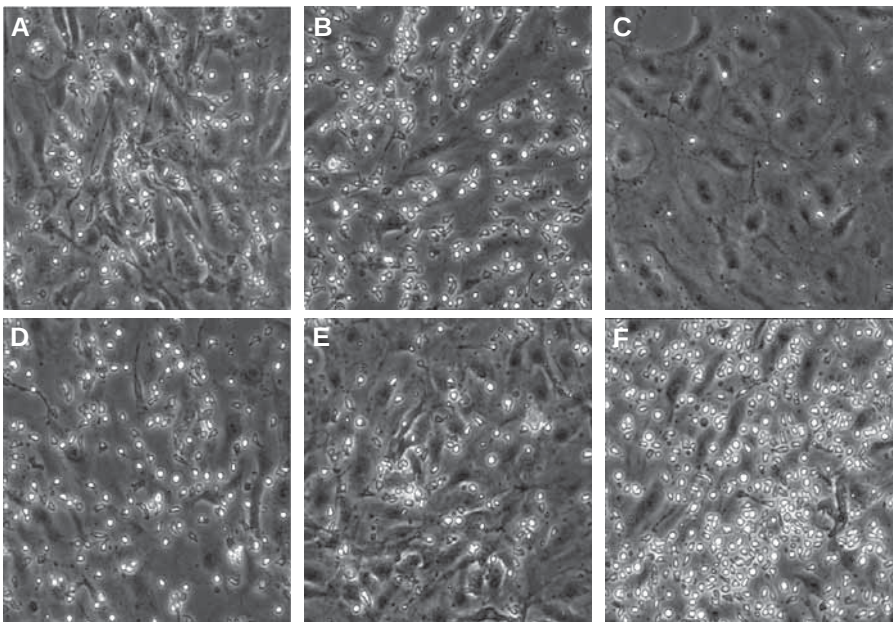
Dr. med.
Christine
Maurus

Dr. med.
Dörthe
Schmidt

Dr. med.
Reza Tavakoli

Ischemia / Reperfusion Injury
Dr. med. Christine Maurus

The contribution of neutrophiles and T-cells in ischemia/reperfusion injury and rejection of vascularized transplants has been widely studied. The role of another leukocyte subset, natural killer cells (NK cells), has been established in the setting of xenotransplantation, but little is known so far in the context of alloreactivity against endothelial cells (EC).
Therefore, we developed an *in vitro* cell culture model to study interactions between human NK cells and human endothelium and to evaluate the impact of hypoxia, reoxygenation and inflammation on chemotaxis, adhesion, migration and direct and ADCC (antibody-dependent cell-mediated cytotoxicity)-driven target lysis. Functional differences between micro- and macrovascular EC were assessed. Methods used include cell isolation and culture techniques, flow cytometry, immunohistochemistry, apoptosis assays, adhesion assays under both static and rolling conditions and standard ^{51}Cr-release assays. Furthermore, we evaluated a broad spectrum of different HLA-allocombinations. In addition, the system allows to test potential endothelial-protective effects of different substances, such as dextrane sulfate.
The overall aim is to further define the role of NK cells in solid organ rejection and ischemia/reperfusion injury.



Monolayers of microvascular endothelial cells were subject to A) no treatment, B) TNF-a, C) Hypoxia, D) TNF-a and Hypoxia, E) Hypoxia and Reoxygenation, and F) TNF-a, Hypoxia and Reoxygenation. NK cells (white) adhered differentially to pre-stimulated EC.

Achievements 2002

- University of Zürich Research grant 2002-2004
- 3 oral presentations: Annual Assembly of the European Association for Cardio-Thoracic Surgery (EACTS), Monte Carlo/Monaco, Day of Clinical Research, USZ and Transplantation Club, USZ
- 3 poster presentations: Annual Assembly of the Swiss Society for Allergology and Immunology (SGAI), Lugano/CH, Day of Clinical Research, USZ and Cardiovascular Research and Clinical Implications Meeting, Villars/CH

Collaborations:

- PD Dr. med. Jörg D. Seebach, Laboratory for Transplantation Immunology, Department of Internal Medicine, USZ
- Prof. Dr. med. Peter Groscurth, Division of Cell Biology, Institute of Anatomy, University Zürich
- PD Dr. Robert Rieben, Cardiovascular Research Laboratory, Inselspital Bern

Selected references:

- Schneider MK, Strasser M, Gilli UO, Kocher M, Moser R, Seebach JD. Rolling adhesion of human NK cells to porcine endothelial cells mainly relies on CD49d-CD106 interactions. Transplantation. 2002 Mar 15;73(5):789-96.
- Choo JK, Seebach JD, Nickeleit V, Shimizu A, Lei H, Sachs DH, Madsen JC. Species differences in the expression of major histocompatibility complex class II antigens on coronary artery endothelium: implications for cell-mediated xenoreactivity. Transplantation. 1997 Nov 15;64(9):1315-22.
- Maurus CF and Seebach JD. Seilschaften am immunologischen Checkpoint. Swiss Med. Forum. 2002 Oct 9;41:976-977

2.1.3 Circulatory Assist

PD Dr. med.
Mario Lachat

Dr. med.
Jürg Müller

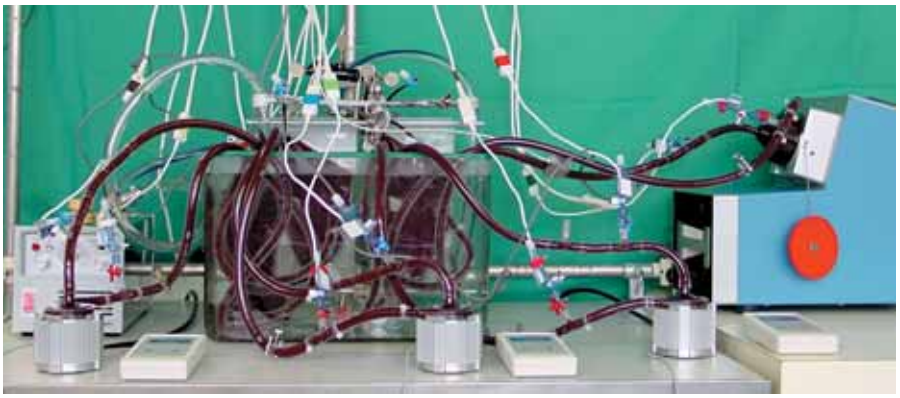
Boris
Leskosek

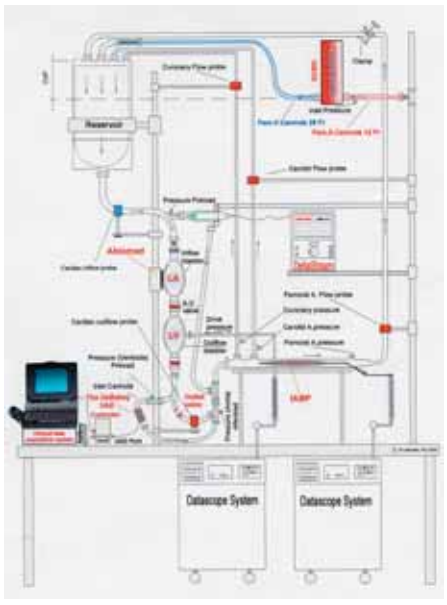
Alush Avdyli

Research, development and education in the field of cardiovascular perfusion and ventricular support systems
PD Dr. med. Mario Lachat, Dr. med. Jürg Müller

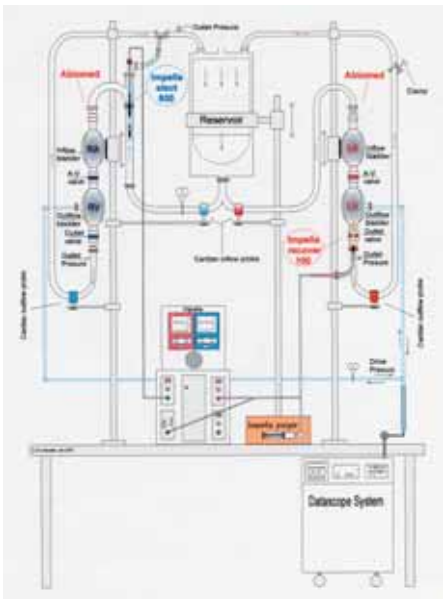
- Hemodynamics and biocompatibility of new blood pumps
- Minimally invasive perfusion techniques

An in vitro model was developed to mimic a pulsatile circulatory system. Flow condition of the failing heart can be reproduced and effects of mechanical support demonstrated. Moreover, with this model, all the elements of a perfusion system (cannulae, tubing, blood pumps, oxygenator) can be tested and demonstrated.
A new bearingless blood pump could be extensively tested in that in vitro circulatory model before it was successfully validated in the long-term application.

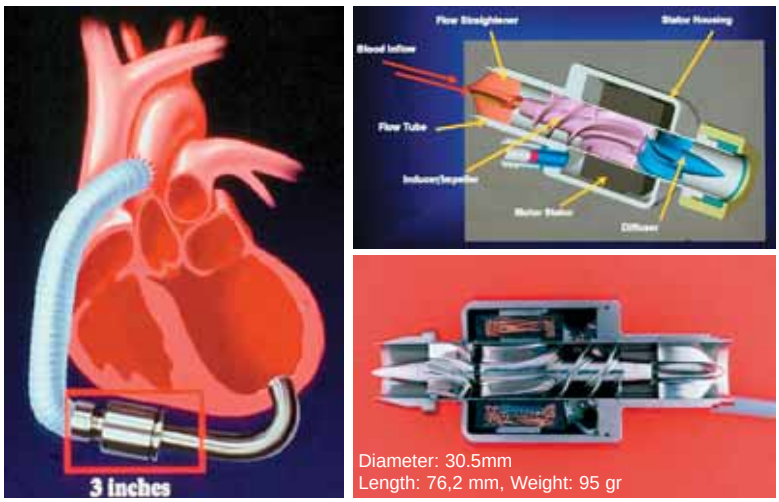




Temporary ventricular assistance and ECMO without pump



Impella - biventricular assistance



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 2002

- Education: Second Swiss Workshop on Temporary Ventricular Assistance 29th November 2002. Excellent speakers from Europe and Switzerland and the active participation of all the participants have greatly contributed to the success of The Second Swiss Workshop on Temporary Ventricular Assistance, which was very well attended.
- Research and development: hemodynamics and performance of a new bearingless blood pump for long-term cardiac support.

Collaborations:

- Levitronix, Inc.(Zürich, Boston, MA)
- MicroMed Technology, Inc. and Baylor College of Medicine (Houston, TX)

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 properties of the hemopump HP14. Int J Artif Organs. 1999 Mar;22(3):155-9. PMID: 10357244

2.1.4 Robotic Surgery

Dr. med. Jürg Grünenfelder

Dr. med. Oliver Reuthebuch

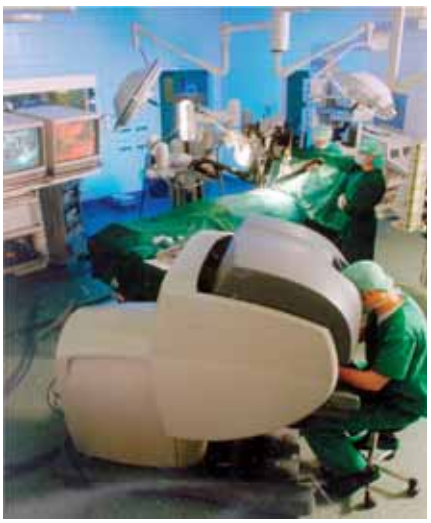
Dr. med. Hitendu Dave

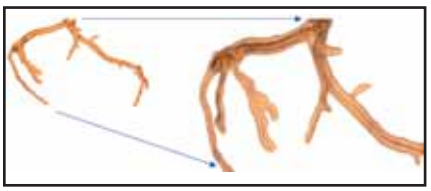
Robotics in Cardiovascular Surgery
Dr. med. Jürg Grünenfelder; Dr. med. Oliver Reuthebuch; PD Dr. med. Gregor Zünd

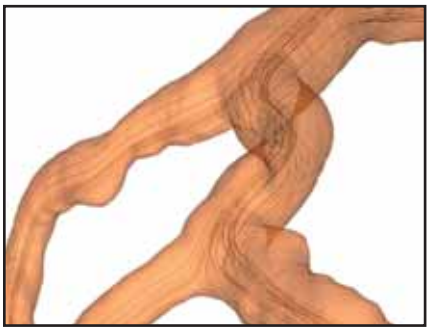
- Automated coronary artery bypass operation in the beating heart
- Visualization and computational flow simulation in coronary arteries
- Device development for beating heart coronary artery bypass operations

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 2002

- The group was able to prolong the financial committment of the CO-ME project for another 2 years. We fulfilled the milestones of the project and were able to develop several minimally invasive surgical prototypes which we presented in scientific surgical meetings. Furthermore the commercially available robotic system (da Vinci) was successfully introduced into the clinical routine.

Collaborations:

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

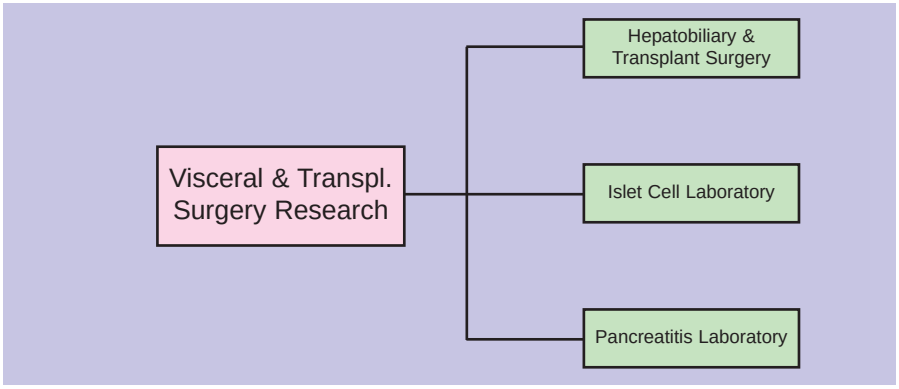
Selected references:

- Jürg Grünenfelder, Oliver Reuthebuch, Hitendu Dave, Boris Leskosek, Mario Lachat, Marko Turina, Gregor Zünd. Single bicaval venous cannula and atrial spreader faciliate totally endoscopic robotically-assisted atrial septal defect closure.CTT Meeting 2003, Miami Beach, USA, March 19-22, 2003 (Abstract)
- Evangelos Boutsianis, Hitendu Dave, Jürg Grünenfelder, Yiannis Ventikos, Vincent Butty, Thomas Frauenfelder, Simon Wildermuth, Dimos Poulikakos, Marko Turina, Gregor Zünd. Computational Coronary Flow Dynamics. CTT Meeting 2003, Miami Beach, USA, March 19-22, 2003 (Abstract).

2.2 Visceral & Transplant Surgery Research

PD Dr. phil II
Rolf Graf

Prof. Dr. med.
Alain Clavien



2.2.1 Hepatobiliary & Transplant Surgery

Dr. med.
Markus Selzner

Dr. med.
Yinghua Tian

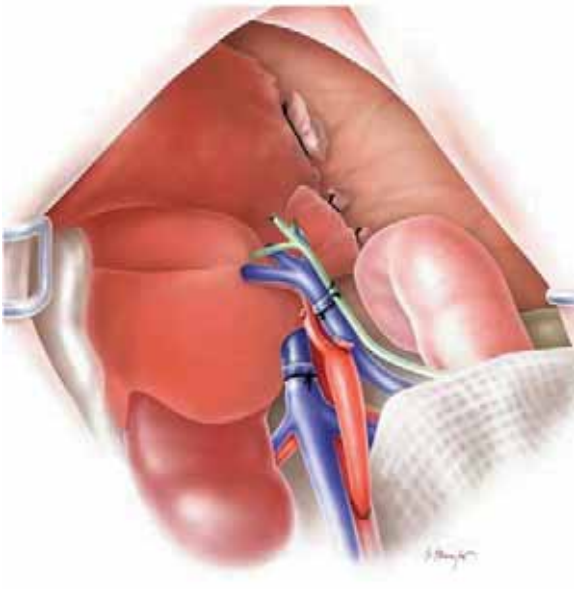
Dr. med.
Hannes Rüdiger

Astrid Morger

Ischemia / Reperfusion Injury and Liver Transplantation
Dr. med. Markus Selzner; Dr. med. Yinghua Tian;
Dr. med. Hannes Rüdiger

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 ischemia, occurring during organ preservation. Our group has a long-standing 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 heaptocytes. Inhibiting this pathway was not only protecting from parenchymal injury in the liver but was also preventing 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

Collaborations:

- Dr. W. Jochum, Insititute for Clinical Pathology, University Hospital of Zurich
- Dr. H.-M. Riehle, Insititute for Clinical Pathology, University Hospital of Zurich
- Dr. B. Ludwig , Research Department, Kantonsspital St. Gallen

Selected references:

- Selzner M, Rudiger HA, Selzner N, Thomas DW, Sindram D, Clavien PA. Transgenic mice overexpressing human Bcl-2 are resistant to hepatic ischemia and reperfusion. J Hepatol 2002: 36(2): 218-225.
- Rudiger HA, Kang KJ, Sindram D, Riehle HM, Clavien PA. Comparison of ischemic preconditioning and intermittent and continuous inflow occlusion in the murine liver. Ann Surg 2002; 235(3): 400-407.
- Tian Y, Rudiger HA, Jochum W, Clavien PA. Comparison of arterialized and non-arterialized orthotopic liver transplantation in mice: prowess or relevant model? Transplantation 2002; 74(9): 1242-1246.
- Rudiger HA, Clavien PA. Tumor necrosis factor alpha, but not Fas mediates hepatocellular apoptosis in the murine ischemic liver. Gastroenterology 2002; 122(1): 202-210.

Dr. med.
Nazia Malekkiani
Selzner

Dr. med.
Mickael Lesurtel

Dr. med.
Stefan Heinrich

Liver regeneration

Dr. med. Nazia Selzner

The liver is the only solid organ with the ability to regenerate, 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 hepatectomies 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.

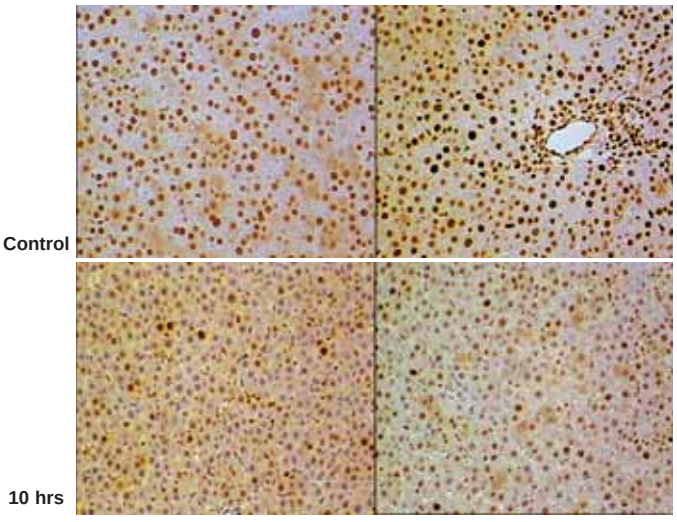
Animal studies in the steatotic liver indicated that the process of liver regeneration is significantly impaired at several levels of the pathway. This finding may open novel avenues for treatment of patients with hepatic steatosis.

Collaborations:

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

Selected references:

- Selzner N, Selzner M, Tian Y, Kadry Z, Clavien PA. Cold ischemia decreases regeneration after partial liver transplantation in the rat: a TNF-a/IL-6 dependent mechanism. Hepatology 2002; 36: 812-818.



Representative PCNA staining in rat livers two days after partial liver transplantation. PCNA positive hepatocytes were higher after 30 min of cold preservation when compared to the respective control groups (70 % liver resection alone), or after longer periods of cold preservation (10 & 16hr).

Dr. med.
Markus Selzner

Dr. med.
Daniel Dindo

Udo Ungethüm

Induction of cell death in tumors

Dr. med. Markus Selzner; Dr. med. Daniel Dindo

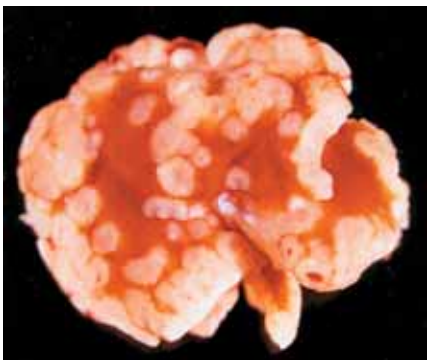
The development of cancer is the result of uncontrolled proliferation and the inability of the host to remove the unwanted cells. We are currently investigating several approaches to induce apoptosis in tumor cells to promote cell death. One approach using human colon cancer cells has opened promising insights:
Application of a synthetic form of the sphingolipid ceramide induced apoptosis and prevented tumor metastasis in the liver 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 to establish new therapeutic approaches.

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. 61(3):1233-40.



no treatment

ceramide treatment

Effect of ceramide treatment on the developement of liver metastases.

Achievements 2002

■ 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.

■ We now demonstrate that TNFa, and not Fas, induces apoptosis after normothermic ischemia and reperfusion (Gastroenterology). Blocking apoptosis was possible by up-regulation of the antiapoptotic mediator Bcl-2 resulting in decreased AST release and improved survival (J Hepatology).

■ We further investigated mechanisms of cold ischemia and reperfusion injury a mouse model representative of human liver transplantation was attempted. This would include arterialization of the hepatic artery in the recipient. With the development of a unique model of mouse liver transplantation including portal vein and hepatic artery reperfusion (Transplantation), we have been able to set a landmark in experimental transplantation research. We demonstrated that, in contrast to rat liver, the mouse liver strongly depends on the reconnection of the hepatic artery. Arterialization of the mouse liver graft decreased postoperative transaminases and improved survival with a normal histology already 2 weeks following transplantation. The dependence on a patent hepatic artery makes the mouse liver transplantation model more similar to the procedure of human liver transplantation.

■ Cold ischemia is today frequently combined with major tissue loss, e.g. during split or living related liver transplantation. We investigated the effects of cold ischemia on liver regeneration in a model of partial rat liver transplantation (Hepatology). Prolonged cold ischemia resulted in a dramatic decrease of the regenerative capacity of the liver, while short cold ischemia time increased liver regeneration. Prolonged cold ischemia was associated in decreased TNFa production and regeneration was normalized by the administration of rIL-6, which acts downstream of TNFa in the regenerative cascade.

4) The role of ATP and energy levels during organ preservation and transplantation is still controversial. Efforts to establish methods for the assessment of hepatic ATP levels were accompanied by a review of the literature, resulting in the publication of a special article in Hepatology including (Hepatology).

■ We organized the first Hepatobiliary and Gastrointestinal Research Retreat, February 3-6, 2002, Vulpera.

■ As part of our training program for the fellows in the laboratory, invited international scientists were hosted for discussion of the projects.

■ Prize of the Swiss Society of Surgery 2002 (Dr. M. Selzner)

■ This work was supported by grants from SNF, NIH, EMDO-Stiftung and by a private donation to support research and teaching.

2.2.2 Islet Cell Laboratory

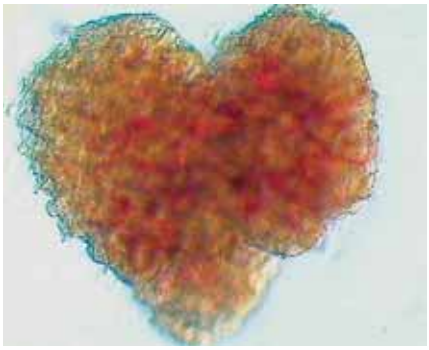
PD Dr. med.
Markus Weber

Dr.phil. II
Wolfgang Moritz

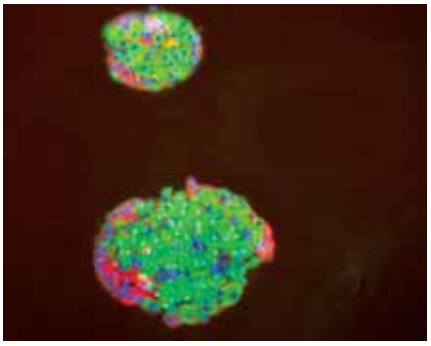
Improvement of cell survival in the immediate posttransplantation period

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.



Heart shaped isolated rat islet



Rat islets after in vitro cultivation at for 24 hours 1% oxygen: immunostaining for insulin (green), activated caspase-3 (red) and nuclei (DAPI, blue)

Achievements 2002

In the preceding year, our research project developed successfully and our lab became further established with extended knowledge in islet cell physiology in ischemic situations. We were able to demonstrate that isolated human islets undergo massive cell death upon exposure to hypoxic conditions that are similar to those which are expected after intrahepatic transplantation. The hypoxic damage is only observed in intact isolated islets, not so when islets where dispersed into single cells. Therefore we conclude that isolated islets are at specific risk to experience ischemic damage because of their spherical structure, which in a avascular state is aggravating the ischemic situation in the peri-transplant period. We are currently establishing a rat in vivo model in order to study the engraftment of hepatically transplanted islets with respect to the revascularization process and graft survival. Our aim will be to improve graft survival by modifying isolated islets by either specific pre-treatment and/or genetic approaches to reduce the minimal islet mass for a successful treatment of type 1 diabetes.

Collaborations:

The research project is also part of a close collaboration with PD Dr. Lehmann 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., Stroka D.M., Giuliani M., Kugelmeier P., Nett P.C., Lehmann R., Candinas D., Gassmann M., Weber M. (2002) Apoptosis in hypoxichuman pancreatic islets correlates with HIF-1alpha 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

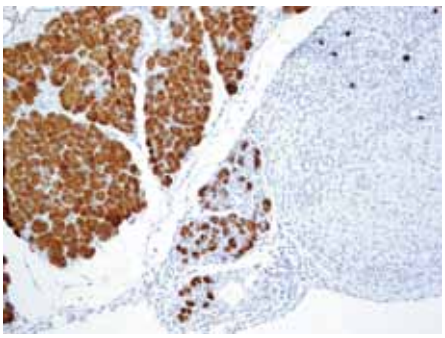
Dr. med.
Marc
Schiesser

Martha Bain

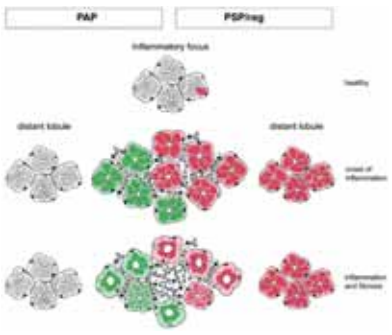
Analysis of secretory stress proteins during pancreatitis
PD Dr. med. Daniel Bimmler, PD Dr. Rolf Graf

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.



PSP/reg expression in a pancreas with extensive inflammation and fibrosis. Acinar cells on the left exhibit a high degree of PSP/reg; tubular complexes on the right lost ability to express PSP/reg.



Schematic drawing of an inflammatory focus in the pancreas. Expression levels of pancreatitis-associated protein (PAP, left) and pancreatitic stone protein (PSP/reg, right). Top: healthy tissue. Middle: onset of inflammation. Bottom:focus on inflammation and fibrosis. PAP expression indicated in green, PSP/reg in red.

Achievements 2002

- Scientific

We have cloned and expressed human pancreatic stone protein/ regenerating protein (PSP/reg).
With the recombinant protein we established a novel ELISA recognizing specifically human PSP/reg. Using this assay, we can determine PSP/reg-levels in serum samples of patients with acute and chronic pancreatitis.
To investigate the expression of the secretory stress proteins (PSP/reg and PAP) in mice we cloned the cDNA form mouse pancreas. The proteins will be expressed as recombinant fusion proteins to generate antisera for the immunohistochemical detection in mouse tissue. With this apporach, it will be possible to study inflammatory diseases in the mouse with the possibility to use mutant and knockout strains harboring modified genes for a variety of cytokines, matrix metalloproteases and other genes involved during inflammation and fibrosis.

- Personnel

Dr. Daniel Bimmler and Dr. Rolf Graf were promoted to Privatdozent
Severin Meili finshed his medical degree passing the Staatsexamen.

- Talks

R. Graf: A family of pancreatic stress proteins forms fibrils upon tryptic activation - a freak of nature? Joint meeting of the ECP and IAP, Heidelberg.

- Supported by the SNF and the Amelié Waring Stiftung.

Collaborations:

- Dr. Pia März & Prof. U. Otten, Physiologisches Institut, Universität Basel
- René Fischer, Biochemisches Institut, ETH Zürich
- Dr. George Scheele, Institute of Genomic Medicine, LaJolla, Ca, USA

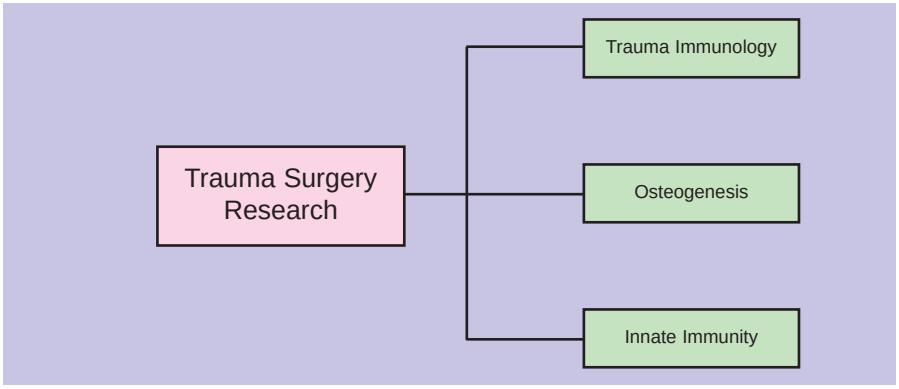
Selected references:

- Graf R, Schiesser M, Lüssi A, Went Ph, Scheele G.A. and Bimmler D. (2002). Coordinate regulation of secretory stress proteins (PSP/reg and PAP I, II & III) in the rat exocrine pancreas during experimental acute pancreatitis. J. Surgical Research, 105:136-144
- Graf R, Schiesser M and Bimmler D. (2002). Increased secretion of the pancreatic secretory trypsin inhibitor (PSTI) during development of chronic pancreatitis in the WBN/Kob rat Pancreatology, 2:108-115
- Graf R, Schiesser M, Scheele G.A, Marquardt K, Frick T.W., Ammann R and Bimmler D. (2001) A family of 16kDa pancreatic secretory stress proteins form highly organized fibrillar structures upon tryptic activation. J. Biol. Chem. 276:21028-21038

2.3 Trauma Surgery Research

Dr. med.
Marius Keel

Prof. Dr. med.
Otmar Trentz



2.3.1 Trauma Immunology

Dr. med.
Marius Keel

Dr. rer. nat.
Luc Härter

Dr. med.
Ludwig Labler

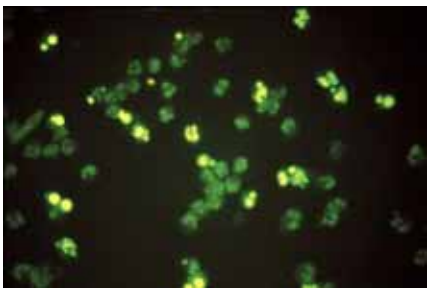
Dr. med.
Ladislav Mica

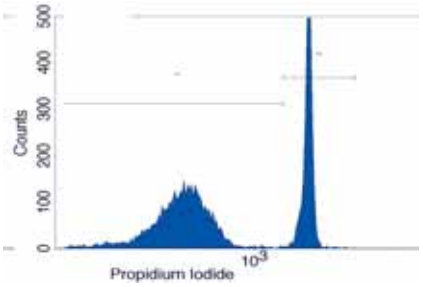
Ursula
Steckholzer

Immunomodulation in polytrauma patients
Dr. med. Marius Keel MD; Dr. Luc Härter

- Regulatory mechanisms of neutrophil apoptosis
- The Death-inducing Signaling Complex and leukocyte apoptosis
- Mechanisms of wound healing under vacuum-assisted therapy (VAC)

In patients with severe trauma the systemic inflammatory response syndrome (SIRS) correlates with a dysregulation of leukocyte and parenchymal cell apoptosis. This dysregulation adds to the pathogenesis of the multiple organ failure (MOF). Understanding the mechanisms that lead to this dysregulation will help to design a better therapy for patients with SIRS or MOF. Therefore, we investigate different signal transduction elements of the apoptosis pathways such as caspases, protein kinases, Bcl-2 proteins and molecules of the death-inducing signaling complex. Apoptosis of leukocytes isolated form septic patients or healthy controls is analysed by flowcytometry (FACS). Cytokine release is measured by ELISA and protein expression by Westernblot. Transcription of mRNA is monitored by RT-PCR and caspase-3 activity determined by DEVD-afc cleavage.
Furthermore, the mechanisms of wound healing and angiogenesis under VAC®-therapy are studied with histological and biochemical methods.





Quantification of apoptosis in neutrophil granulocytes (PMN) by TUNEL (left) or Propidiumiodine staining (right). PMN were stained by TUNEL (Terminal deoxynucleotidyl Transferase Biotin-dUTP Nick End Labeling) and counted under fluorescence microscope. Cells positive for the TUNEL apoptosis marker are seen as bright green cells. Alternatively, apoptotic PMN are counted after propidium iodide staining in FACS.

Achievements 2002

Talks:

- Ladislav Mica: USZ, Zürich: Reduced apoptosis of neutrophil granulocytes during sepsis (19. 04.2002).

66. Jahrestagung der DGU, Berlin: Bid und Bcl-2 regulieren nicht die Apoptose neutrophiler Granulozyten beim Patienten mit Sepsis (Preisträgersitzung 13.11. 2002)

- Marius Keel: 88. Clinical Congress of American College of Surgeons, San Francisco: Bcl-2 or Bid do not regulate neutrophil apoptosis in patients with sepsis (07.10.2002), & Toll-like receptor expression on leukocytes from septic patients (08.10.2002); 66. Jahrestagung der DGU, Berlin: Erhöhte Expression der Toll-like Rezeptoren-2 und -4 auf Leukozyten von Patienten mit Sepsis (Preisträgersitzung 13.11.2002)
- Luc Härter: 2. Swiss Apoptosis meeting, Bern: MAP kinases differentially regulate apoptosis in neutrophil granulocytes from patients with sepsis (23.08.2002)
- Ludwig Labler: 2. European meeting on VAC Therapy, Salisbury, UK, Poster: Mechanisms of granuloma formation in VAC systems
- Tag der Klinischen Forschung 2002, USZ, Zürich: 5 Posters
- Generous grants from UBS, Heubergstiftung 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:

- Härter L, Keel M, Hentze H, Steckholzer U, Ungethuem U, Trentz O, Ertel W. 2001 Spontaneous in contrast to CD95-induced neutrophil apoptosis is independent of caspase activity. J. Trauma 50:982-988
- Labler L, Oehy K. 2002 Vakuumversiegelung bei Problemwunden. Swiss Surg. 8(6):266-72.
- Härter L, Keel M, Hentze H, Leist M, Ertel W. 2001 Caspase-3 activity is present in cerebrospinal fluid from patients with traumatic brain injury. J Neuroimmunol. 121(1-2): 76-78
- Härter L, Keel M, Steckholzer U, Ungethuem U, Trentz O, Ertel W. 2002 Activation of Mitogen-Activated Protein Kinases During Granulocyte Apoptosis in Patients with Severe Sepsis. Shock 18(5): 401-406
- Keel M, Härter L, Platz A, Trentz O, Ertel W. 2002 Das Schädelhirntrauma dominiert die Systemische Entzündungsreaktion im Posttraumatischen Verlauf Langenbecks Arch. Chir. Forumband: 431-433

2.3.2 Osteogenesis Laboratory

Dr. med. Omana A. Trentz; Dr. Li K. Sun

Dr. med.
Omana A. Trentz

Dr. rer. nat.
Li K. Sun

Sonja Hemmi

Heterotopic Ossification

Heterotopic ossification is an unsolved problem in patients, especially after brain and spinal cord injury. It is defined as new 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. Measures of prevention are not very effective, matured ossifications can be resected, but with an high recurrency rate. HO induced by trauma may start within 2 to 3 weeks after the initial trauma, but its obvious onset has been described as late as several months after the precipitating event.

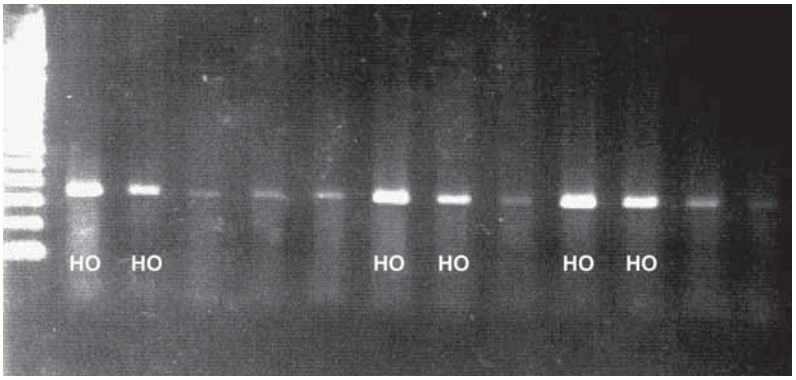
Aim of our study:

1. Comparison between phenotypic markers of primary human osteoblasts from iliac crest and from heterotopic ossification.
2. The expression and regulation of osteoblast specific gene "Osteocalcin".

Tissue Engineering

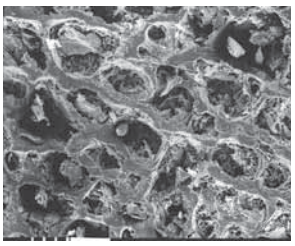
The repair of large osseous defects remains still an unsolved problem in bone surgery. The use of autogenous bone grafts is widely accepted and considered to be the golden standard in the treatment of bony defects. However the disadvantage of autogenous bone grafts are limited availability, harvesting 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.

Aim of our investigation is to test the bone substitutes with primary cultured human osteoblasts and to demonstrate the compatibility of these cells with bone substitutes.



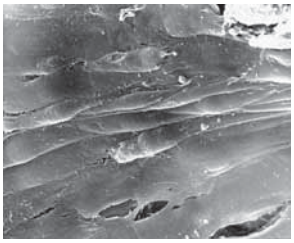
Alkaline phosphatase (ALP) (356 bp) expression by RT-PCR in Osteoblasts from iliac crest and heterotopic Ossification (HO)

Tutoplast Disc

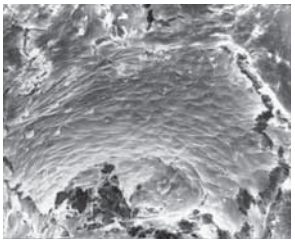


Tutoplast SEM (1000 m) without cells

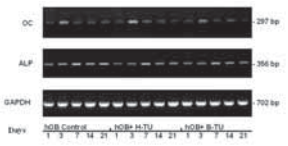
Angiogenesis in chicken embryo (in Chorio-allantoin-membrane (CAM)



Day 7 on Tutoplast



Day 21 on Tutoplast



RT-PCR: Osteocalcin (OC) and ALP

Achievements 2002

- Biocompatibility of allogenic and synthetic bone substitutes with primary human osteoblasts
- Differences between Osteoblasts markers in human osteoblasts from iliac crest and heterotopic ossification and the expression and regulation of osteoblast specific gene "Osteocalcin".

Collaborations:

- Department of Materials, Federal Institute of Technology, Zurich, Switzerland
- Institute for Clinical Chemistry, University Hospital Zurich, Switzerland (Prof. Dr. A. von Eckardstein, Lukas Bestmann)
- University Hospital Nijmegen, Netherlands Prof. Dr. Jan Goris
- General Hospital Chur, Switzerland (Prof. Dr. A. Leutenegger)

Selected references:

- O A Trentz, R Zellweger, MG Amgwerd, GK Uhlschmid (1997) Testung von Knochenimplantaten auf Zellinien und humanen Osteoblasten Unfallchirurg 100; 39-43
- B Saad, S Matter, GK Uhlschmidt, T Hirt, OA Trentz, P Neuschwander, UW.Suter (1995) In vitro Charakterisierung der Biokompatibilität eines neuen Polyesterurethans für chirurgische Anwendung: 1995 Chirurgisches Forum f. experim. u. klinische Forschung
- OA Trentz, A Platz, N Helmy, O Trentz (1998) Verhalten von Osteoblastenkulturen auf Titan-, Stahl- und Hydroxylapatit-Implantaten Swiss Surg. 1998;4: 203-209
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- OA Trentz, N Helmy, LK Sun, GK Uhlschmid (2001) Proliferation of human osteoblast and osteoblast-like cell line on Tutoplast European Cells and Biomaterials Vol.1. Suppl.2, 2001
- Osteoblasts Response to Human and Bovine Tutoplast in vitro OA Trentz et al (2002) Biomaterials (In Press)

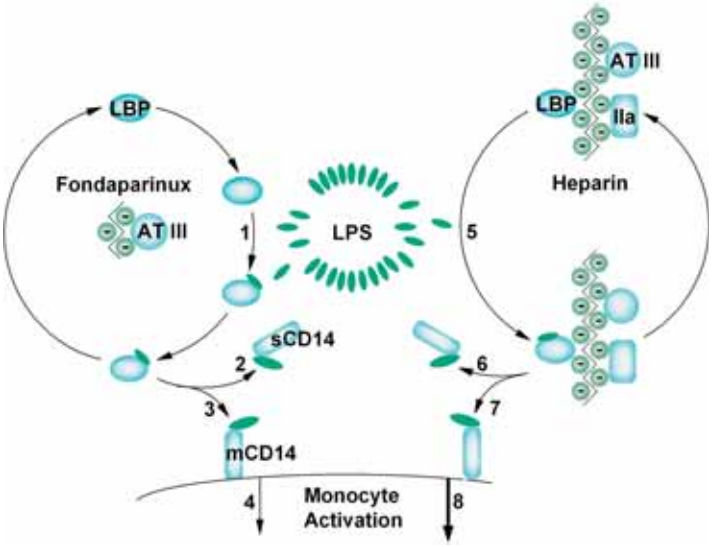
2.3.3 Innate Immunity Laboratory

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.



A model for the interaction between heparin and LBP. LPS micelles inefficiently activate CD14+ monocytes. LBP disaggregates LPS (1) and catalyses the transfer of LPS monomers to either soluble (2) or membrane-bound CD14 (3). Subsequent activation of monocytes (4) is thought to occur through a physical interaction between membrane-bound CD14-LPS and MD2-TLR4 complexes. We propose that binding of LBP to heparin enhances the catalytic ability of LBP to transfer LPS (5, 6, 7), thereby resulting in the amplification of LPS signaling (8). Other heparin-binding plasma proteins such as antithrombin III (AT III) or thrombin (Factor IIa) will also bind to heparin. Plasma concentrations of heparin, LPS, LBP and soluble (sCD14), as well as expression levels of membrane-bound CD14 (mCD14) may determine to what extent LPS signals are amplified. Fondaparinux, which is identical to the AT III-binding pentasaccharide sequence in heparin, does not interfere with LPS-induced monocyte activation.

Achievements 2002

We have identified LPS-binding protein (LBP) as a novel heparin-binding plasma protein. Using a fluorescence-based assay, we have shown that clinically used heparin preparations significantly enhance the ability of LBP to 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 proinflammatory cytokines. Fondaparinux, which is identical to the antithrombin III-binding pentasaccharide 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 anticoagulation.

LPS-enhancing effects are not unique to heparin or heparin-like structures. We have 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 fundamental 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 the transfer of LPS to the surface of peripheral blood monocytes.

Collaborations:

- Hans Flodgaard, Leukotech, Fruebjergvej 3, Box 8, 2100 Copenhagen - Denmark
- Hans-Peter Beck, Swiss Tropical 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 polypeptides amplify lipopolysaccharide-induced monocyte activation. Infect Immun. 2002; 70: 6904-6910.
- Heinzelmann M, Bosshart H. Fondaparinux sodium lacks immunomodulatory effects of heparin. 2003, Am J Surg, in press.
- Heinzelmann M, Bosshart H. Heparin binds to lipopolysaccharide (LPS)-binding protein, facilitates the transfer of LPS to CD14, and enhances LPS-induced activation of peripheral blood monocytes. 2003, submitted.

2.3.4 Computer Assisted Trauma Surgery

PD Dr. med.
Guido Wanner

Dr. med.
Marius Keel

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, Universitätsspital Zürich
- Dr. Paul A. Grützner, Berufsgenossenschaftliche Unfallklinik Ludwigshafen, Unfallchirurgische Klinik der Universität Heidelberg
- PD Dr. Peter Messmer, Departement Chirurgie, Abteilung Traumatologie, Kantonsspital, Universitätskliniken Basel

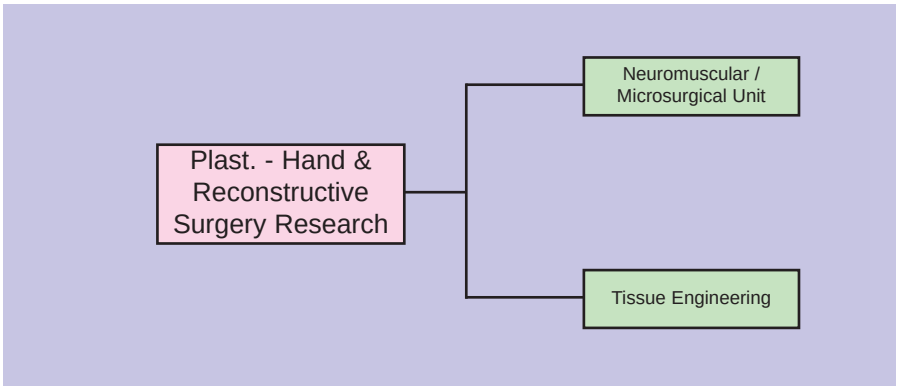
Selected references:

- Grützner PA, Vock B, Schulte-Bockholt D, Wentzensen A: Computerassistierte Operationsverfahren in der Unfallchirurgie. Trauma Berufskrankh 4:S145-S152, 2002.
- Gebhard F, Kinzl L, Arand M: Computer-assisted surgery. Der Unfallchirurg 103:612-617, 2000.
- Maresceaux J, Soler L, Ceulemans R, Garcia A, Henri M, Dutson E: Bildfusion, virtuelle Realität, Robotik und Navigation. Chirurg 73: 422-427, 2002.

2.4 Plast. - Hand & Reconstructive Surgery Research

Dr. med.
Gertrude Beer

Prof. Dr. med.
Viktor Meyer



2.4.1 Neuromuscular / Microsurgical Unit

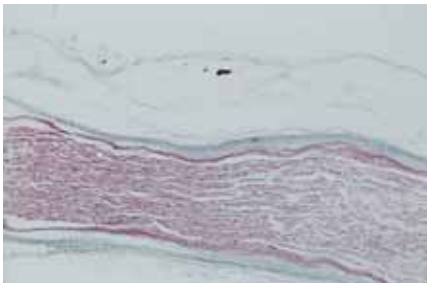
Dr. med.
Doris Burg

Dr. med.
Gertrude Beer

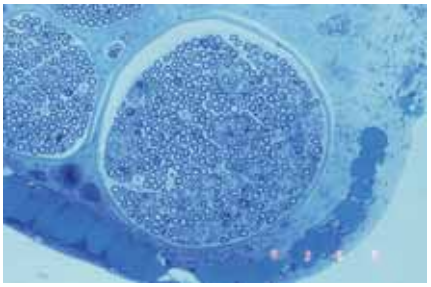
Functional, Electrophysiological and Morphometric Evaluation of Nerve Regeneration from Coaptation on Regenerated Nerve Fibres – Experimental Studies on the Peroneal Nerve in the Rabbit

Dr. med. Gertrude M. Beer, Dr. med. Doris Burg, Prof. Dr. Viktor E. Meyer

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 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. The present studies are conducted to evaluate reinnervation of the peroneal nerve of New Zealand White rabbits after coaptation on recently regenerated axons in comparison to coaptation at either the same site or on more proximal sites, on unscathed nerve fibres. Nerve regeneration is assessed by intraoperative neurography, histomorphological analysis and functional results; functionality counting as the ultimate parameter of nerve regeneration.



Longitudinal section of the peroneal nerve of the rabbit, silverstain (x100)



Cross-section through the peroneal nerve of the rabbit, toluidinblue (x100)

Achievements 2002

- Workshop: Hands - on Demonstration of the intraoperative neurography on the peroneal nerve of the rabbit, 7. November, University Hospital Zürich.
- Development of a new crush-clamp (G.M. Beer) and stimulating and recording electrodes (D. Burg).

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
- PD Dr. Th. Stallmach, Institute for Neuropathology, University Hospital Zürich
- Mag. Dr. Dr. J. Steurer, The Institute of Industrial Electronics and Material Sciences, University of Technology, Vienna, Austria

Selected references:

- Beer GM, Burg D, Meyer VE. (2001) Standardizing nerve crushes with a non-serrated clamp. J. Reconstr. Microsurg. 17 (7) : 531 - 534
- Beer GM, Burg D, Meyer VE. (2001) Tattooing agents for nerve marking in experimental surgery. J. Reconstr. Microsurg. 17 (6) : 437 - 440
- Cristina Schmitz H, Beer GM. (2001) The toe-spreading reflex of the rabbit revisited - functional evaluation of complete peroneal nerve lesions. Lab. Anim. 35 : 340 - 345
- Cristina Schmitz H, Beer GM. (2001) Muscle-sparing approach to the peroneal nerve of the rabbit. Lab. Anim. 35 : 334 - 339
- Beer GM, Burg D, Zehnder A, Seifert B, Steurer M, Grimaldi H, Meyer VE. (2002) Functional, electrophysiological and morphometric evaluation of nerve regeneration from coaptation on regenerated nerve fibres - an experimental study in the rabbit. J. Reconstr. Microsurg., in press

2.4.2 Hand - Plastic & Reconstructive Surgery

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 joints

Dr. med. Volker Wedler; Dr. med. Maria Schneller-Gustafsson

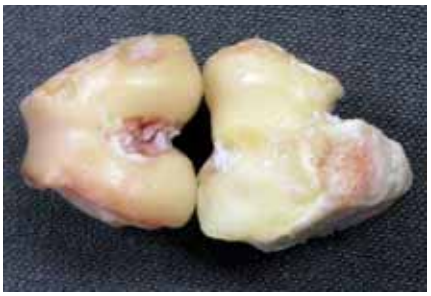
Background

The regenerative capacity of cartilage is known to be very poor and is therefore a major problem in traumatic injuries or cartilage defects secondary to tumorsurgery and in several diseases with severe cartilage loss - such as osteoarthritis and rheumatoid arthritis.

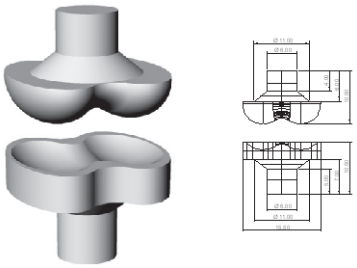
The reconstruction of a destroyed joint has remained a difficult problem. Although prosthetic replacement has made significant progress, many obstacles remain, especially with children and young adults.

Pilot study

The purpose with this study is to replace a complete articular defect in the distal knee joint of twenty White New Zealand Rabbits with autologous chondrocytes cultured on a synthetic biodegradable copolymer scaffold. The project extends for a timeperiod of two years.



Dissected rabbit knee joint



Designed scaffold 3D computer model

Achievements 2002

- Installation of a new laboratory for tissue engineering.

Collaborations:

- Dr. Jens Riesle and Tim Woodfield, Cartilage Tissue Engineering Group, IsoTis, Bilthoven, Netherlands
- Dr. Peter Neuenschwander, Department of Materials, Institute of Polymers, ETH Zürich
- Dr. Theo Tervoort, Department of Materials, Polymer Technology, ETH Zürich
- Dr. Frank Bootz, Institut für Labortierkunde, Universität Zürich-Irchel

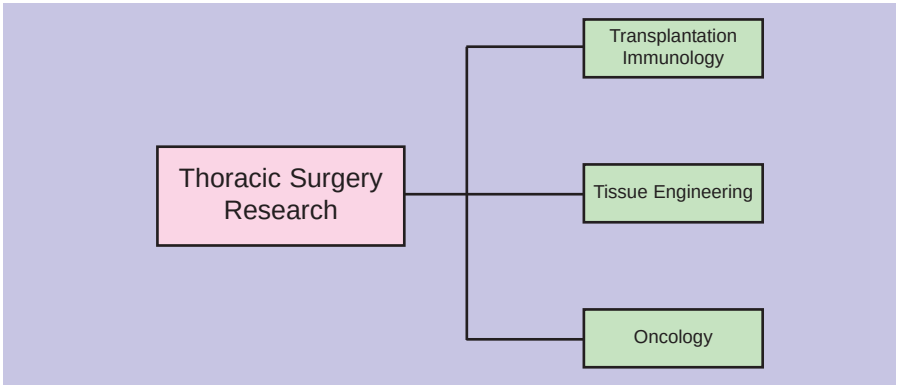
Selected references:

- Risbud M V, Sittinger M. Tissue engineering: advances in in vitro cartilage generation. Trends in Biotechnology. 2002;20(8):351-356.
- Ochi M, Uchio Y, Kawasaki K, Wakitani S, Iwasa J. Transplantation 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 RS, 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.

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

Immunomodulatory and Organ-preserving-Effect of Melatonin in Models of Perfused Lung and Heart Transplantation

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

We have previously shown that melatonin protects lungs from ischemia-reperfusion injury follo-wing transplantation. In addition, ist immunomodulatory effect will be assessed in various models of acute perfused organ graft rejec-tion.

Dr. med. Florian Jung

Vlasta Strohmeier

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

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

The lymphocyte surface glycopro-tein CD26 is a heterogenous mole-cule, characterized by an array of diverse functional properties. It belongs to an unique class of mem-brane-associated proteases, pos-sessing dipeptidyl peptidase IV (DPP IV) enzymatic activity. Accumulating evidence indicates a central role for CD26 in allogeneic antigen-mediated immune path-ways and during the memory T cell response. Based on our previous observations during acute and accelerated cardiac allograft rejec-tion, we want to investigate the role of CD26/DPP IV in a different model of perfused allograft rejec-tion.

Achievements 2002

- SNF grant (principal investigator: S. Korom): The T Cell Costimulatory Antigen CD26/Dipeptidylpeptidase (DPP IV) in Acute Rejection of Lung Allograft

Collaborations:

- Dr. I. De Meester & Prof. Dr. S. Scharpé from the Dept. of Pharmaceutical Sciences, University of Antwerp, Antwerp, Belgium.

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.

2.5.2 Tissue Engineering

Dr. med.
Lin Yang

Dr. med.
Florian Jung

Manfred Welti

Trachea Reconstruction using Novel Tissue Engineered Constructs
Dr. med. Lin Yang; PD Dr. med. Stephan Korom; Dr. med. Florian Jung

The problem of reconstructing long segmental tracheal defects remains unsolved, despite the recent progress in the field of in vitro cartilage tissue engineering. Yet, employing chondrocyte-seeded polymer constructs, may serve as an emerging concept to overcome those difficulties. In the previous experiments with several types of chondrocytes (including human tracheal chondrocytes) culture in static culture condition, we have demonstrated neocartilage-like tissue can be fabricated through seeded cells grew in a novel polymer scaffold – DegraPol. Biochemical test, histological test with Alcian blue staining and SEM validate component of cartilage and extracellular matrix are produced.

Achievements 2002

- Establishment of a tissue engineering laboratory
- SNF grant (principal investigator: L. Yang): Trachea Reconstruction using Novel Tissue Engineered Constructs

Collaborations:

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

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 2002

- Grant from Cancer League Zurich and Hartmann-Müller Foundation

Collaborations:

- Radio-Onkologie (V. Vuong, M. Pruschy, S. Bodis)
- Onkologie (R. Stahel)
- Pathologie (P. Vogt)
- Chemische 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

3. Events at the Surgical Research Division in 2002

Zurich Cardiac Technical Course, 29 / 30 August 2002

ATLS - Course , 30 January 2003

Cardiac Technical Course 29 November 2002
The Second Swiss Workshop on Temporary Ventricular Assistance

Hands-on, Demonstration of intraoperative Neurography
7 November 2002

4. Publications 2002

■ Bosshart H. and Heinzelmann M. 2002. Arginine-rich cationic polypeptides amplify lipopolysaccharide-induced monocyte activation. Infect Immun. 70: 6904-6910.

■ Graf R., Schiesser M., Lussi A., Went P., Scheele G.A. and Bimmler D. 2002. Coordinate regulation of secretory stress proteins (PSP/reg, PAP I, PAP II, and PAP III) in the rat exocrine pancreas during experimental acute pancreatitis. J Surg Res. 105: 136-144.

■ Graf R., Schiesser M. and Bimmler D. 2002. Increased secretion of the pancreatic secretory trypsin inhibitor (PSTI-I, monitor peptide) during development of chronic pancreatitis in the WBN/Kob rat. Pancreatology. 2: 108-115.

■ Harter L., Keel M., Steckholzer U., Ungethuem U., Trentz O. and Ertel W. 2002. Activation of mitogen-activated protein kinases during granulocyte apoptosis in patients with severe sepsis. Shock. 18: 401-406.

■ Hoerstrup S.P., Kadner A., Melnitchouk S., Trojan A., Eid K., Tracy J., Sodian R., Visjager J.F., Kolb S.A., Grunenfelder J., et al. 2002. Tissue engineering of functional trileaflet heart valves from human marrow stromal cells. Circulation. 106: I143-150.

■ Hoerstrup S.P., Kadner A., Breymann C., Maurus C.F., Guenter C.I., Sodian R., Visjager J.F., Zund G. and Turina M.I. 2002. Living, autologous pulmonary artery conduits tissue engineered from human umbilical cord cells. Ann Thorac Surg. 74: 46-52; discussion 52.

■ Hoerstrup S.P., Zund G., Cheng S., Melnitchouk S., Kadner A., Sodian R., Kolb S.A. and Turina M. 2002. A new approach to completely autologous cardiovascular tissue in humans. Asaio J. 48: 234-238.

■ Inci I., Inci D., Dutly A., Boehler A. and Weder W. 2002. Melatonin attenuates posttransplant lung ischemia-reperfusion injury. Ann Thorac Surg. 73: 220-225.

■ Jockenhoevel S., Zund G., Hoerstrup S.P., Schnell A. and Turina M. 2002. Cardiovascular tissue engineering: a new laminar flow chamber for in vitro improvement of mechanical tissue properties. Asaio J. 48: 8-11.

■ Kadner A., Hoerstrup S.P., Tracy J., Breymann C., Maurus C.F., Melnitchouk S., Kadner G., Zund G. and Turina M. 2002. Human umbilical cord cells: a new cell source for cardiovascular tissue engineering. Ann Thorac Surg. 74: S1422-1428.

■ Kadner A., Hoerstrup S.P., Zund G., Eid K., Maurus C., Melnitchouk S., Grunenfelder J. and Turina M.I. 2002. A new source for cardiovascular tissue engineering: human bone marrow stromal cells. Eur J Cardiothorac Surg. 21: 1055-1060.

■ Kadner A., Viirre E., Wester D.C., Walsh S.F., Hestenes J., Vankov A. and Pineda J.A. 2002. Lateral inhibition in the auditory cortex: an EEG index of tinnitus? Neuroreport. 13: 443-446.

■ Keel M., Härter L., Platz A., Trentz O. and Ertel W. 2002. Das Schädelhirntrauma dominiert die Systemische Entzündungsreaktion im Posttraumatischen Verlauf. Langenbecks Arch. Chir. Forumband. 431-433.

■ Korom S., De Meester I., Maas E., Stein A., Wilker S., Jung F., Weimer R., Brendel M.D., Ernst W., Friemann S., et al. 2002. CD26 expression and enzymatic activity in recipients of kidney allografts. Transplant Proc. 34: 1753-1754.

■ Labler L. and Oehy K. 2002. Vakuumversiegelung bei Problemwunden. Swiss Surg. 8: 266-272.

■ Maurus C.F. and Seebach J.D. 2002. Seilschaften am immunologischen Checkpoint. Swiss. Med. Forum. 41: 967-977.

■ Moritz W., Meier F., Stroka D.M., Giuliani M., Kugelmeier P., Nett P.C., Lehmann R., Candinas D., Gassmann M. and Weber M. 2002. Apoptosis in hypoxic human pancreatic islets correlates with HIF-1alpha expression. FASEB J. 16: 745-747.

■ Rabkin E., Hoerstrup S.P., Aikawa M., Mayer J.E., Jr. and Schoen F.J. 2002. Evolution of cell phenotype and extracellular matrix in tissue-engineered heart valves during in-vitro maturation and in-vivo remodeling. J Heart Valve Dis. 11: 308-314; discussion 314.

■ Rudiger H.A. and Clavien P.A. 2002. Tumor necrosis factor alpha, but not Fas, mediates hepatocellular apoptosis in the murine ischemic liver. Gastroenterology. 122: 202-210.

■ Rudiger H.A., Kang K.J., Sindram D., Riehle H.M. and Clavien P.A. 2002. Comparison of ischemic preconditioning and intermittent and continuous inflow occlusion in the murine liver. Ann Surg. 235: 400-407.

■ Schurr U.P., Lachat M.L., Reuthebuch O., Kadner A., Mader M., Seiffert B., Hoerstrup S.P., Zund G., Genoni M. and Turina M.I. 2002. Endoscopic saphenous vein harvesting for CABG -- a randomized, prospective trial. Thorac Cardiovasc Surg. 50: 160-163.

■ Selzner M., Rudiger H.A., Selzner N., Thomas D.W., Sindram D. and Clavien P.A. 2002. Transgenic mice overexpressing human Bcl-2 are resistant to hepatic ischemia and reperfusion. J Hepatol. 36: 218-225.

■ Selzner N., Selzner M., Tian Y., Kadry Z. and Clavien P.A. 2002. Cold ischemia decreases liver regeneration after partial liver transplantation in the rat: A TNF-alpha/IL-6-dependent mechanism. Hepatology. 36: 812-818.

■ Sindram D., Rudiger H.A., Upadhya A.G., Strasberg S.M. and Clavien P.A. 2002. Ischemic preconditioning protects against cold ischemic injury through an oxidative stress dependent mechanism. J Hepatol. 36: 78-84.

■ Sodian R., Lemke T., Fritsche C., Hoerstrup S.P., Fu P., Potapov E.V., Hausmann H. and Hetzer R. 2002. Tissue-engineering bioreactors: a new combined cell-seeding and perfusion system for vascular tissue engineering. Tissue Eng. 8: 863-870.

■ Sodian R., Loebe M., Hein A., Martin D.P., Hoerstrup S.P., Potapov E.V., Hausmann H., Lueth T. and Hetzer R. 2002. Application of stereolithography for scaffold fabrication for tissue engineered heart valves. Asaio J. 48: 12-16.

■ Tian Y., Rudiger H.A., Jochum W. and Clavien P.A. 2002. Comparison of arterialized and nonarterialized orthotopic liver transplantation in mice: prowess or relevant model? Transplantation. 74: 1242-1246.

■ Vajdova K., Graf R. and Clavien P.A. 2002. ATP-supplies in the cold-preserved liver: A long-neglected factor of organ viability. Hepatology. 36: 1543-1552.

5. Awards 2002

- C. Walton Lillehei Award, European Association of Cardiothoracic Surgery (PD Dr. S. Hoerstrup)

- Ethicon-Prize, German Society of Thoracic and Cardiovascular Surgery (PD Dr. S. Hoerstrup)

- 1st Clinical Day of Research Price, University Hospital Zurich (PD Dr. S. Hoerstrup)

- Young Investigator Award, European Association of Cardiothoracic Surgery (Dr. A. Kadner)

- Prize of the Swiss Society of Surgery 2002 (Dr. M. Selzner)