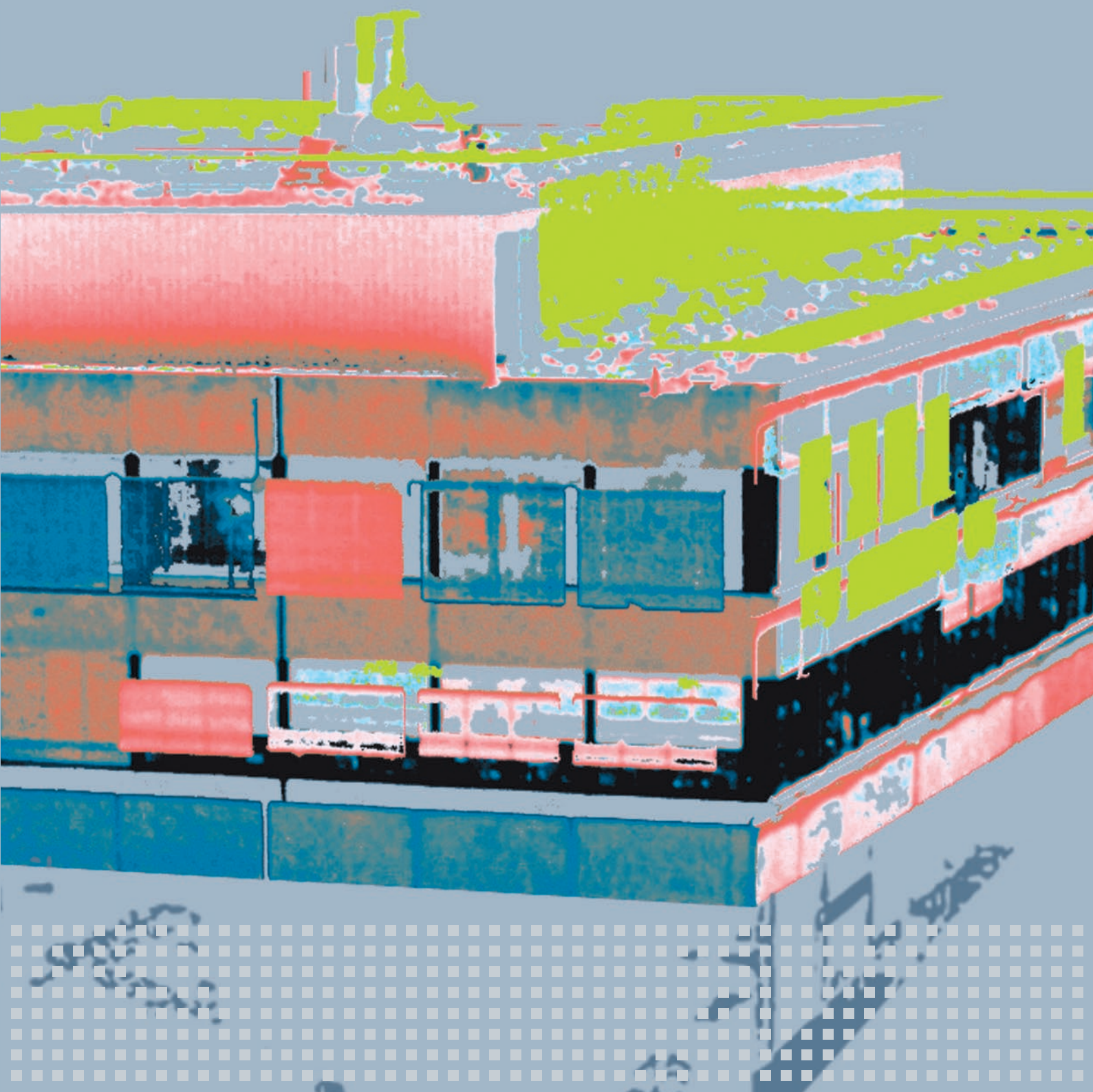


Department of Research
University Hospital Basel
A Portrait 1978–2005





Department of Research

A Portrait 1978–2005

Editorial

The Department of Research of the University Hospital Basel (Departement Forschung (DF), Kantonsspital/Universitätsspital Basel) celebrated its 25th anniversary in the autumn of 2003 and, after a few important changes in the last two years, presents itself in a new shape. This is an excellent occasion to publish the history of the last 27 years along with the current portrait of the DF.

The DF had been conceived in the early 1970s, when its founding fathers planned a new building right in the heart of the hospital grounds to serve as Centre for Teaching and Research (Zentrum für Lehre und Forschung, ZLF), housing the DF as well as teaching facilities and the medical library. The concept of a joint medical research facility for all laboratory-based research carried out by the different university clinics was novel for our country and far beyond and remained so ever since. The advantages of such a platform were manifold, most notably cost-effective sharing of expensive equipment and specialized laboratories as well as animal facilities; an increase in quality and impact through intensified scientific exchange and a marked broadening of experimental expertise; easy initiation of joint research projects and collaboration across the clinical boundaries; opportunities for young clinicians to get training in basic research and for young scientists to become exposed to biomedical projects and to collaborate with clinicians; joint continued education (lectures, seminars, project meetings), and last but not least a single administration for all research laboratories. The success of the DF is well illustrated by its steady growth in staff and scientific output over the past 25 years and also by the fact that various planning committees from other universities came to study the concept of the DF before founding similar research facilities. And finally, an increasing number of young PhD students and post-docs have been attracted by the research carried out at the DF.

When in the late 1990s, the medical faculties in Switzerland were urged to specialize in research and high-tech services in order to avoid too much overlap, the idea was born to integrate the DF and the preclinical institutes of the Medical Faculty of the University of Basel into one large department. This finally led to the foundation of the Department of Clinical-Biological Sciences (Departement für Klinisch-Biologische Wissenschaften, DKBW) in the year 2000. The formation of the DKBW was also the moment to alter the research structure and to form four so-called Schwerpunkte (focal groups) in the areas of immunology, oncology/genetics, cell plasticity/tissue repair, and neurosciences. With the opening of the new Biomedical Sciences building of the DKBW at the Mattenstrasse, some research groups left and new groups joined the DF at the beginning of this year.

This portrait of the DF summarizes the current research and reviews the history of the DF from 1978 to 2005, written by the former chair persons and the present chairman, as well as the events of the 25th anniversary of the DF, celebrated at the end of September 2003. Twenty seven high-impact papers published by teams of the DF over the 27 years were chosen as examples to illustrate the excellent quality of the research that continues to come out of the DF. Finally, many illustrations from laboratory work to social activities demonstrate that the DF has always been a place with an excellent atmosphere, both scientifically and socially, which is indispensable for fruitful research work.



Radek Skoda



Alex N. Eberle

Preface



The Department of Research (DF) is an ideal setting for research that addresses questions related to human disease. Located within the University Hospital Basel, it provides a haven where physician-scientists, declared an endangered species only a few years ago, can thrive. It offers state of the art equipment for cutting edge research. We will meet future challenges by increasing our interactions with the basic science institutes of the University, the new ETH institute in Basel and the research departments of the pharmaceutical companies. This portrait captures the spirit of this unique institution and describes the many transformations it went through to become what it is today.

Prof. Radek Skoda, M.D.
Chairman, Department of Research



To all our readers,
Twenty-seven significant years link the University Hospital Basel with the Department of Research. We can look back on a long period of intensive and high-quality cooperation, a period in which services, teaching and research have complemented one another in optimal fashion. The DF is an essential partner of the USB. Its broad spectrum of know-how is brought to bear at every level of USB, which, in turn, is of benefit to the patients. The DF can also look back with pride on the large number of its publications, which have appeared in well-known scientific journals. They are public testimony of international recognition accorded to the USB and its excellent reputation. May this long continue to be the case.

Rita Ziegler, lic. oec. HSG
Director, University Hospital Basel



A quarter of a century Department of Research represents a long period, a large scientific community and a huge amount of projects, but a unique concept: «from the bench to the bed side», the leading idea over the years. This success has three reasons: the proximity of the «ZLF» and the clinical departments, the mix of clinicians and experimental researchers as core of the research groups and the fact that people started the DF without waiting for total planning and financing, just trusting their peers and creating a favourable environment for research. By stepping in, taking opportunities and solving problems as they come, we will reach our goals and will inevitably receive the support we need.

Prof. André P. Perruchoud, M.D.
Dean, Medical Faculty, University of Basel

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Content

The Research Groups	11
Structure and Portraits in 2005	12
Chronological Index 1978–2005	24
25th Anniversary Events	29
25 th Anniversary Event 2003	30
Open Day 2003	34
History of the DF	37
Introduction	38
The First Steps. 1978–1988, Alfred Pletscher	40
The Maturation Phase. 1988–1992, Fritz R. Bühler	45
Growth and Autonomy. 1992–2000, Alex N. Eberle	48
A New Structure for the DF. 1995–1997, Werner Stauffacher	50
DF on the Move. 2000–2002, Regine Landmann	55
From Present to Future. Since 2002, Radek Skoda	58
Publications	61
27 Representative Articles 1978–2005	62
Epilogue	76

The Research Groups

Structure and Portraits in 2005

Department of Research

University Hospital Basel

Prof. R. Skoda

Experimental Critical Care Medicine

Prof. U. Eriksson

Transplantation Immunology & Nephrology

Prof. E. Palmer
Prof. J. Steiger

Clinical Immunology

Dr. M. Trendelenburg

Immunobiology

Dr. C. Hess

Experimental Immunology

Prof. G. De Libero

Infectious Diseases

Prof. R. Landmann
Prof. M. Battegay

Hepatology

Prof. M.H. Heim

Immunonephrology

Prof. J.A. Schifferli

Molecular Nephrology

PD Dr. B. Biedermann
Prof. R. Krapf

Neurosurgery

Prof. O. Gratzl

Neurobiology

PD Dr. N. Schaeren-Wiemers
Prof. A.J. Steck

Clinical Neuroimmunology

PD Dr. R. Lindberg
Prof. L. Kappos

Cell and Gene Therapy

Dr. A. Banfi
Prof. M. Heberer

Oncology Surgery

Prof. G.C. Spagnoli
Prof. M. Heberer

Medical Oncology

Prof. Ch. Rochlitz
PD Dr. M. Pless

Childhood Leukemia

Prof. J. Schwaller

Neurooncology

Prof. A. Merlo

Signal Transduction

Prof. Th.J. Resink
Prof. Dr. P. Erne

Vascular Biology

Prof. E. Battegay

Metabolism

Prof. U.O. Keller
Prof. Dr. B. Müller

Tissue Engineering

PD Dr. I. Martin
Prof. M. Heberer

CardioBiology

Prof. P. Buser
Prof. M. Brink

Cardiothoracic Surgical Research

Prof. H.-R. Zerkowski

Experimental Hematology

Prof. R. Skoda
Prof. A. Wodnar-Filipowicz

Pneumology

PD Dr. M. Roth
Prof. M. Tamm

Clinical Pharmacology

Prof. J. Drewe
Prof. St. Krähenbühl

Gynecological Endocrinology

Prof. Ch. De Geyter

Gastroenterology

Prof. Ch. Beglinger

Endocrinology

Prof. A.N. Eberle

Perioperative Patient Safety

Dr. S. Treves
Dr. T. Girard

Prenatal Medicine

PD Dr. S. Hahn
Prof. W. Holzgreve



Immunology



Neurobiology



Oncology



Cell Plasticity and Tissue Repair



UKBB-Group



External DF-Groups



CardioBiology

Prof. Marijke Brink, Prof. Peter Buser

In the heart, stress stimuli such as ischemia or hypertension cause the release of various factors that on the short term preserve cardiac function, but when acting for extended periods of time may change overall geometry of the heart such that cardiac output diminishes. Ultimately, when myocardial performance becomes insufficient to adequately supply blood to the various organs of the body, the disease is referred to as heart failure. We analyze molecular mecha-

nisms by which multiple stimuli (IGF, TNF- α , urocortin) change cell architecture and function, in particular that of the cardiomyocyte, the main building block of cardiac muscle, responsible for contraction. Physiological and therapeutic relevance of new findings is assessed *in vivo* in models of heart failure. Together with the analysis of hormonal expression patterns and detection of mutations in contractile and ion channel proteins in patients, our studies aim to improve the understanding of hormonal mechanisms in genetic as well as non-genetic forms of heart disease and should hopefully lead to novel strategies for its prevention and cure.



Cardiothoracic Surgical Research

Prof. Hans-Reinhard Zerkowski

We focus our research on surgical aspects of mechanisms and treatment of advanced heart failure. Gene expression, functional dysregulation and remodeling of human and animal samples are investigated regarding transition from compensation to end-stage heart failure: e.g. tissue from the left ventricular myocardium are obtained during implantation of ventricular assist devices and at cardiac transplantation. Using organ bath experiments, we are interested in functional differences between arterial and venous grafts for coronary bypass surgery, the impact of variable sur-

gical preparation techniques of the grafts and the influence of storage solutions on vascular function. Recently, we combine these investigations with proteome analysis. Proteomics might close the gap between genomic and physiological research. We perform 2-dimensional gel electrophoresis combined with mass-spectrometry. Since proteins are involved in most cellular processes, it might provide means for identifying novel diagnostic markers and therapeutic targets. We focus our research on proteome alterations in heart failure, the formation of aortic aneurysm, valve failure and the influence of drugs on arterial grafts.



Cell and Gene Therapy

Dr. Andrea Banfi, Prof. Michael Heberer

Our research focus is the understanding of the basic principles governing the growth of blood vessels and translating this knowledge into the development of therapies for ischemic diseases, such as myocardial infarction, peripheral ischemia and diabetic vascular complications. Our goal is to restore the blood supply by the delivery of growth factors that control the formation of new vasculature. We achieve this by genetically engineering precursor cells to express controlled levels and combinations

of angiogenic factors, and transplanting them into the ischemic tissue. This approach has the potential to provide both angiogenic stimulation and tissue regeneration, combining the specific advantages of cell therapy and gene therapy. We are developing novel methods to deliver the vascular endothelial growth factor gene alone or in combination with maturation factors to ischemic tissue, in order to increase safety and expand its therapeutic window *in vivo*. We are further interested in applying these methods to recently described progenitors that can be successfully delivered to the heart.



Childhood Leukemia

Prof. Jürg Schwaller

The main goal of our work is to understand genetic alterations underlying childhood acute leukemia. Elucidation of the critical molecular mechanisms involved may allow the design of targeted therapeutic approaches that are able to overcome limitations of current chemotherapy such as strong side effects as well as secondary malignancies. Starting from recurrent chromosomal translocations that are a hallmark of hematological malignancies, we are currently analyzing fusion genes that may exert their oncogenic activity by changing

target gene expression through epigenetic mechanisms like modification of cellular chromatin structure. Using various *in vitro* and *in vivo* models we hope to be able to dissect and to validate critical mediators of a chain of cooperative oncogenic events leading to the development of acute leukemia.



Clinical Immunology

Dr. Marten Trendelenburg

The aim of our research group is to understand mechanisms leading to autoimmunity. One major focus are autoantibodies against the first component of the classical pathway of complement (anti-C1q) which are mostly observed in patients with systemic lupus erythematosus (SLE). A major hypothesis of the pathogenesis of SLE assumes that the disease is driven by a defective clearance of apoptotic cells. Apoptotic cells could become antigenic and initiate an autoimmune response. C1q has been shown to play an important role in apoptotic cell clearance and C1q deficiency is strongly

associated with the development of SLE. However, most SLE patients have no primary complement deficiency but secondary hypocomplementemia that is most often associated with anti-C1q. In addition, the presence of anti-C1q in SLE patients strongly correlates with the occurrence of renal flares. Previous studies suggested that the occurrence of anti-C1q in SLE patients is necessary but not sufficient for the development of severe lupus nephritis. Anti-C1q might interfere with the normal function of C1q including the clearance of immune complexes and apoptotic cells.



Clinical Neuroimmunology

Prof. Ludwig Kappos, PD Dr. Raija Lindberg

Gene expression in multiple sclerosis (MS) on mRNA, protein and metabolite levels is our main research focus. Although significant progress in understanding MS pathogenesis has been made, valid and accurate diagnostic and prognostic markers are missing that would allow predicting important milestones in disease evolution. Our transcriptional analysis of blood samples of MS patients in different disease courses and after treatment with new therapeutic compounds revealed differentially expressed

genes, which we are currently validating as diagnostic markers for MS-course and therapeutic response. We are also evaluating the significance of myelin oligodendrocyte glycoprotein (MOG) and myelin basic protein (MBP) antibodies in plasma as predictive markers for conversion of clinically isolated syndromes to MS. Metabolite target analysis is used to assess if different disease patterns can be identified by NMR spectra of CSF samples. Our ultimate goal is to provide new tools for predictive monitoring, and hence individualized therapeutic decisions in MS.



Clinical Pharmacology

Prof. Stephan Krähenbühl, Prof. Jürgen Drewe

The Division of Clinical Pharmacology and Toxicology has two collaborating research groups. The laboratory of J. Drewe investigates the transport of drugs into several tissues, in particular brain and skeletal muscle. Besides the possibility of drug-drug interactions, the group is interested in genetic variants of the genes coding for the drug transporters. Such variants may represent important reasons for interindividual differences in drug action

and toxicity. The laboratory of S. Krähenbühl investigates adverse effects of drugs on the liver and other organs. Despite the fact that hepatic adverse effects are frequent, the mechanisms are known for only few of them. In order to make drug therapy safer, the group tries to find out mechanisms and possible risk factors of such adverse effects. Furthermore, the group develops *in vitro* systems suitable for screening drugs for toxic reactions.



Endocrinology

Prof. Alex N. Eberle

Current projects include: (1) Neuropeptide regulation of human adipocyte function in different body fat tissues of obese individuals, in particular bariatric patients (R. Peterli, T. Peters, M. Hoch), and analysis of mitochondrial activity and the mitochondrial proteome of normal and morbidly obese patients, with the aim of identifying predictors of obesity (P. Lindinger, V. Jägglin, U. Zumsteg). (2) Specific targeting of melanoma metastases with glycosylated radiopeptide analogs of melanocyte-stimulating hormone (α -MSH) containing chelators for ^{68}Ga , ^{111}In , and ^{90}Y , in order to reduce kidney uptake, a

limiting factor in the clinical application of internal radiotherapy (M. Calame-Christe, H. Tanner, J.-P. Bapst). (3) Quantitative analysis by ultrasensitive HPLC-mass spectrometry of transport processes and metabolism of peptides across biological membranes (R. Wenger); development of novel peptide tags for biomedical application (S. Knecht, B. Ernst). (4) Mitochondrial dysfunction in glaucoma patients (K. Wunderlich, J. Flammer). (5) Phenotypic effects of electromagnetic fields and other weak interactions on isolated cells (J. Burckhardt, K. Müller).



Experimental Critical Care Medicine

Prof. Urs Eriksson

As a clinical speciality, critical care medicine provides advanced and prolonged life support, as well as professional care to critically ill patients. Our research group focuses on inflammatory aspects of heart failure and coronary arterial disease, on the mechanisms of multiorgan failure in sepsis, on the pathogenesis of immune mediated lung injury, and explores the capacity of organ-derived stem cells to repair severely damaged tissues. Recently, we have developed a mouse model to study heart inflammatory mechanisms *in vivo*. Using this autoimmune myocarditis model we hope to refine

current therapeutic options and novel treatment strategies of inflammatory heart disease and heart failure. Another focus of our studies is the role of organ-derived pluripotent mesenchymal precursor cells in the regeneration of irreversibly damaged organs. At the moment, we focus our efforts on the characterisation and isolation of these cells. Although it is possible to isolate pluripotent precursor cell fractions from mesenchymal organs and direct them into cardiomyocytes *in vitro*, we do not know yet whether and how these precursor cells can also differentiate *in vivo*.



Experimental Hematology

Prof. Radek Skoda, Prof. Aleksandra Wodnar-Filipowicz

A large number of blood diseases, including leukemia, myeloproliferative disorders (MPD) and severe aplastic anemia, are now recognized as stem cell disorders. By examining loss of heterozygosity on chromosome 9p in patients with MPD we found that the gene for Janus kinase 2 (JAK2) carries a point mutation resulting in a unique valine to phenylalanine substitution in position 617 (V617F) of the JAK2 protein. This mutation provides a proliferative advantage to the cells and is present in about 50% of

MPD patients. We are now extending these studies to address the question at which stem cell / progenitor level the mutation occurs. Another focus of our studies is the role of the hematopoietic growth factor, flt3 ligand, in the regulation of stem cell function. These studies address the mechanism of flt3 ligand expression and function in the stem cell engraftment process. The third focus of our studies is the role of Natural Killer (NK) cells in the recognition of leukemic blasts. These studies address the interactions between NK receptors and their ligands on target cells as well as the genetic modification of NK cells in order to increase their specific cytotoxicity against leukemia.



Experimental Immunology

Prof. Gennaro De Libero

The Experimental Immunology research group is studying the T cell recognition of non-peptidic ligands such as glycolipids and phosphorylated mevalonate metabolites. We originally described T cells, which recognize self or bacterial glycosphingolipids (GSL) in autoimmunity, infection, cancer and atherosclerosis. We are currently studying this immune response in different disease models. Lipids are presented by CD1 molecules and we are also investigating the biology of CD1 molecules and the molecular mechanisms of CD1 loading with GSL. The goals of these studies are to un-

derstand the pathophysiological role of lipid-specific T cells and generate new vaccines based on self and microbial lipids. Our second main interest is antigen recognition by human $\gamma\delta$ T cells. We have described a major population of human $\gamma\delta$ T cells stimulated by small phosphorylated non-peptidic metabolites generated in the mevalonate pathway. By using *in vitro* immunoassays, *in vivo* response in T cell receptor $\gamma\delta$ transgenic mice and proteomics, we are currently investigating the molecular and cellular requirements for presentation of these metabolites as well as the potential use of this response in immunotherapy.



Gastroenterology

Prof. Christoph Beglinger

New information regarding appetite control and their hormonal regulation has extended our understanding of energy homeostasis. It is evident that either the amount of food consumed, the frequency of meals, or both, must be regulated if energy homeostasis is to be achieved. In addition to digesting and assimilating nutrients, the gastrointestinal tract plays a key sensing and signaling role in the physiology of energy homeostasis. The major determinant of meal size is the onset of satiety induced by various stimuli generated during food digestion that

leads to meal termination. Our understanding of the signaling molecules that influence the regulatory circuits has progressed rapidly in recent years, especially after the discovery of leptin and ghrelin. Humoral messengers include gut peptides such as CCK, GLP-1 and PYY which are released upon nutrient stimulation. The focus of our research group is the characterization of these satiety factors in healthy subjects and in patients with obesity. At the moment the focus is on the understanding of the interactions between mechanical gastric stimulatory factors and chemical satiety factors triggered by nutrients in the small intestine.



Gynecological Endocrinology

Prof. Christian De Geyter

Both the proliferation of cells and apoptosis are essential for the development of hormonally regulated tissue. Various genes and molecules, involved either in apoptosis or in the transduction of hormone signaling, are expressed both in breast and in ovarian follicular growth and are new discoveries in our unit: (1) Ovary-specific genes ADAMTS-16 (disintegrin and metalloproteinase with thrombospondin motifs) and EULIR, E3 ligase specific for inhibin binding protein. (2) Bcl-2 related proteins, human Bok and Bcl2L10. (3) Using cDNA gene array technology, gene expression patterns are es-

tablished in immortalized human granulosa cell lines during co-culture with human oocytes and in breast tissue from healthy postmenopausal women treated with or without estrogenic drugs. The ultimate aim of our research is to develop new diagnostic tools for the early prevention of breast cancer or for the detection of oocyte-mediated signaling in the ovarian follicle.



Hepatology

Prof. Markus Heim

The group works on intracellular signaling in liver disease and repair. The first project deals with the role of signaling through the Jak-STAT pathway in liver cell proliferation and differentiation. The role of Jak-STAT signaling in liver regeneration is investigated with the partial hepatectomy model in knockout and transgenic mice. The second project concerns the interference of hepatitis C virus (HCV) with interferon-(IFN)-induced intracellular signaling through the Jak-STAT pathway. Cells with inducible expression of HCV proteins, transgenic mice expressing HCV proteins in liver cells, and bi-

opsies from patients with chronic hepatitis C are investigated in regard to IFN-induced STAT signaling.



Immunobiology

Dr. Christoph Hess

HLA class I restricted CD8 T cells are an essential component of the protective immune response against a variety of viral infections. An effective host response to infection depends on production of functional CD8 T cells and their attraction to sites of viral replication. Our lab is interested in factors that determine an efficient CD8 T cell response in humans. Specifically we are investigating homing properties of CD8 T cell subsets formed during the process of activation and differentiation. The molecular mechanisms that control CD8 T

cell trafficking into sites of infection and inflammation are not well understood, but the chemokine/chemokine receptor system is thought to orchestrate this process. Efficient migration of cytotoxic CD8 T cells into sites of infection is intimately linked to their function. We are investigating expression, regulation and function of inflammatory T cell chemokine receptors (e.g. CXCR3, CCR5, CX3CR1, and CXCR1) expressed on antigen-specific and bulk CD8 T cell subsets with effector function.



Immunonephrology

Prof. Jürg A. Schifferli

Complement regulators/inhibitors have been found on the surfaces of human parasites, which spend at least a part of their life cycle in the host blood stream.

These proteins protect them against host complement attack. We described recently one such protein, which we called CRIT on the *Schistosoma* human parasite. Interestingly the same protein is found in humans and different data suggest horizontal gene transfer of CRIT from human to parasites. We are now studying the biology of CRIT in humans, and want also to find

out whether synthetically prepared component parts of this receptor may be used in reducing complement activation in *in vivo* models of disease. – In a separate project, we would like to get a better understanding of the mechanism(s) and role(s) of the release of microvesicles, so called ectosomes, by human cells. In particular, we are analysing the release and biological activity of ectosomes released by neutrophils and erythrocytes. Initial data indicate that ectosomes reduce inflammation and possibly the immune response.



Infectious Diseases

Prof. Regine Landmann, Prof. Manuel Battegay

We are interested in bacterial pathogenicity and host defense in *Streptococcus pneumoniae* meningitis and *Staphylococcus aureus* foreign body or systemic infection.

1. In pneumococcal meningitis we found the innate immune receptors toll-like receptor 2 (TLR2) and CD14 protective by augmenting bactericidal activity and decreasing neutrophil migration and inflammation. We are now investigating the defense mechanism by which TLR2/D14 affect bacterial clearance and inflammation in meningitis. We

search for the pneumococcal molecules, which interact with TLR2, by using mutants of *S. pneumoniae* with modified lipoproteins or lipoteichoic acids. 2. In staphylococcal foreign body infection we described a protective effect of TLR2. In this model we are interested in the mechanism of TLR2-antibacterial defense via antimicrobial peptides and reactive oxygen products. We further investigate staphylococcal virulence factors (genes for alpha-toxin and biofilm) in mouse foreign body infection, abscess, pneumonia and sepsis models. We aim at unraveling staphylococcal pathogenicity and the contribution of TLR2 to host response mechanisms.



Metabolism

Prof. Ulrich Keller, Prof. Dr. Beat Müller

A) Human adipose tissue as a source and a target of calcitonin precursors

and somatostatin in inflammation and sepsis: Calcitonin precursors such as procalcitonin (PCT) mediate deleterious effects in sepsis and inflammation, conditions also characterized by insulin resistance. We identified PCT and somatostatin as novel products of inflamed adipose tissue. We aim to characterize and sequence postulated response-elements within the gene promoters which, upon a specific stimulus, override the

neuro-endocrine tissue-selective expression pattern. In addition, using adipose tissue as a model, we attempt to unravel mechanisms for ectopic expression of hormones, e.g. occurring during inflammation, which may explain cardiovascular complications and result in adverse effects during sepsis. B) Stem cells as potential source of insulin producing cells (Project leader: Dr. H. Zulewski): Using adult stem cells from human islets of Langerhans we aim to generate *ex vivo* mature cells which adopt the capability to produce and secrete islet cell hormones. This would be an important step towards biological insulin replacement therapy in type-1 diabetes.



Molecular Nephrology

PD Dr. Barbara Biedermann, Prof. Reto Krapf

Project A. Vascular integrity is required for tissue homeostasis. Immune-mediated

vascular injury causes disease. Cytotoxic T lymphocytes are important effector cells of antigen-specific immune responses. We have shown that vascular endothelial cells have unique properties as targets of cytotoxic T lymphocytes, and we are in the process to identify the molecular basis of this observation. A mouse model of endothelial cell-restricted antigen expression will

be used to analyze the *in vivo* relevance of anti-endothelial, antigen-specific cytotoxic T lymphocytes for the development of vascular disease. Project B. Arteriosclerosis is a common disease. It leads to myocardial infarction, stroke and renal failure. Inflammation plays a key role in the pathogenesis of these events. We examine the proinflammatory role of cytotoxic T lymphocytes in arteriosclerosis in man. We have developed a human arterial tissue microarray and a data-based, clinical disease model to test scientific hypotheses regarding the pathogenesis of arteriosclerosis and to validate novel approaches to treat the disease in man.



Neurobiology

PD Dr. Nicole Schaeren-Wiemers, Prof. Andreas Steck

Investigation of molecular mechanisms of myelin formation, maintenance

and of demyelinating diseases: Multiple sclerosis and inflammatory demyelinating neuropathies are characterised by a degeneration of nerve cells in the brain or peripheral nervous system and often result in severe disability. Although the aetiology of these diseases is unknown, an immune-mediated damage of the protecting sheath around nerve fibres (myelin) is responsible for degeneration of nerve cells. We are currently in-

vestigating different aspects ranging from the basic molecular mechanism of myelin membrane formation and maintenance to the characterisation of brain and peripheral nerve biopsies in human diseases and their corresponding animal models. The knowledge of the selective function of each component of the complex myelin structure is essential to understand the multifactorial mechanisms, which may damage myelin but also promote remyelination in multiple sclerosis and inflammatory neuropathies. Possible protective therapies will depend on the understanding of myelin structure and function at the cellular and molecular level.



Neurooncology

Prof. Adrian Merlo

Our focus is to classify genetic alterations, which contribute to human brain tumorigenesis. Using our tumor bank, we performed somatic deletion mapping on

chromosomes 1 and 10, which harbor breakpoints of recombination at high frequency. Using electronic and classical cloning techniques, we have identified specific and consistent breakpoints, which are suspicious for the location of tumor suppressor genes. This way, we have defined a candidate gene, GPR26, on chromosome 10q25.3-26. GPR26 is an orphan G protein-coupled receptor, which functionally resembles seroto-

nin receptors. On chromosome 1p11, we identified a breakpoint at a locus that contains Notch2 and myomegalin. At present, we are sorting out which gene is involved in gliomagenesis. With regard to novel therapeutics, we have set up an *in vitro* assay system to test single and combinatorial strategies for glioblastoma, using protein kinase inhibitors against EGFR, KDR, PDGFR and mTOR as well as a histone deacetylase inhibitor and new highly potent cytotoxics (Novartis). Interesting synergistic effects have been detected which will be further explored by an orthotopic *in vitro* animal model.



Neurosurgery

Prof. Othmar Gratzl

Spinal cord injury (SCI) initiates a series of cellular and molecular events leading to further damage. The inflammatory response and the apoptosis of oligodendrocytes are of key interest. At present, there is no universally accepted treatment for SCI; the only pharmacotherapy used so far is the corticosteroid methylprednisolone. Estrogen is a natural sexual steroid hormone that has been shown to exert neuroprotective effects in stroke. Our laboratory has demonstrated that 17 β -estradiol is able to considerably decrease the ischemia-induced release of exci-

totoxic amino acids. Now, we study 17 β -estradiol effects in SCI focusing on the inflammatory response, apoptosis and angiogenesis in a rat model. SCI is induced by a clip compression of the spinal cord. 17 β -estradiol is injected at different time-points post-injury. Short and long term effects are observed by immunohistochemistry and assessment of locomotion. We could demonstrate that spinal cord compression induces a drastic recruitment of inflammatory cells at the site of injury three days after injury. This is accompanied by the activation of caspase-3, NF- κ B, MMP-9, and the glucose transporter GLUT-1 in capillaries within two weeks.



Medical Oncology

Prof. Christoph Rochlitz, PD Dr. Miklos Pless

A main topic of our research activities is focused on site-specific delivery of anti-cancer therapeutics. Encapsulation of these agents inside lipid-based carrier systems, or liposomes, results in passive targeting of liposomes to solid tumors due to a discontinuous microvasculature supporting the tumor and a significantly milder toxicity profile. Recently, we have increased the specificity of delivery further by attaching monoclonal antibodies or antibody fragments to the surface of liposomes (=immunoliposo-

mes). In fact, we demonstrated that by targeting the epidermal growth factor receptor (EGFR) using anti-EGFR immunoliposomes, the specificity and efficacy of various anticancer drugs was clearly improved. A first phase I clinical trial is designed and scheduled to start later in 2005. Furthermore, we are trying to develop vaccine strategies against malignant tumors. By using autologous tumor, theoretically all relevant tumor-associated antigens (TAA) should be present. Tumor cells are electrofused to dendritic cells from an unrelated donor for antigen presentation. A clinical study with this hybridoma cell vaccine is ongoing.



Oncology Surgery

Prof. Giulio Spagnoli, Prof. Michael Heberer

Immunotherapy might complement surgery, chemo- and radiotherapy in the treatment of advanced cancers. We are exploring antigen formulations and adjuvants of potential use in clinical immunotherapy. In particular we used inactivated recombinant vaccinia viruses encoding tumor-associated antigens and synthetic peptides in the immunization of metastatic melanoma patients. This treatment induces cytotoxic T lymphocytes (CTL) capable of killing tumor cells without toxic side effects but responses

are frequently of low extent and short lasting. Furthermore, synthetic peptides represent poor immunogenic materials, possibly due to fast degradation by serum and cell associated peptidases. Their bioavailability might be increased by inclusion into liposomes or virosomes. On the other hand, there is a paucity of adjuvants licensed for human use supporting the induction of cellular immune responses. We are investigating the possibility of using compounds triggering different Toll-like receptors (TLR) to promote CTL induction. In order to expand CTL, we are also studying the role of different cytokines in the absence of specific antigenic stimulation.



Perioperative Patient Safety

Dr. Susan Treves, Dr. Thierry Girard

Our research focuses on skeletal muscle excitation-contraction coupling

and how mutations in the genes encoding proteins involved in excitation-contraction coupling can result in neuromuscular disorders. We are studying the functional effects of mutations in the gene encoding the skeletal muscle ryanodine receptor, the calcium release channel present in the sarcoplasmic reticulum. Mutations in the ryanodine receptor (RYR1) gene have been linked to the

two neuromuscular disorders, namely central core disease (CCD) and multiminicore disease (MmD) and to malignant hyperthermia (MH), a pharmacogenetic disorder. Because MH is potentially lethal, presymptomatic diagnosis is important. As a national reference centre our lab is also involved in testing for MH susceptibility. Using a proteomic approach we have identified two novel proteins present in the skeletal muscle sarcoplasmic reticulum: junctate, a protein located in the endoplasmic/sarcoplasmic reticulum which is involved in intracellular calcium homeostasis, and JP-45, a protein present on the junctional face membrane of skeletal muscle.



Pneumology

Prof. Michael Tamm, Prof. Michael Roth

Airway remodeling with an increased mass of specific cells is observed

in patients with asthma, COPD and lung fibrosis. Our research focuses on the signaling pathways involved in proliferation and differentiation of lung fibroblasts, airway smooth muscle and epithelial cells and their modification by drugs. We have recently shown that asthmatic airway smooth muscle cells proliferate much faster than controls and that the enhanced proliferation is linked with a deregulation of the signaling molecule ERK1/2,

and a cell type specific lack of the transcription factor C/EBP- α . We further described that 2 β -adrenoceptor agonists exert their anti-proliferative action via the glucocorticoid receptor, and an interaction of the glucocorticoid receptor with C/EBP- α which controls proliferation explaining the clinically beneficial effect of combined drugs. We also investigate the interaction of bronchial epithelial cells with tissue structural cells and their modification by immunosuppressive agents. All our research is based on primary human cell cultures established from patients with lung diseases to gain better knowledge of the pathophysiology leading to new treatment options.



Prenatal Medicine

PD Dr. Sinuhe Hahn, Prof. Wolfgang Holzgreve

A major focus of our research remains the development of non-invasive risk-

free methods for the prenatal examination of fetal genetic traits. We had originally worked towards this goal by using rare fetal cells enriched from maternal blood, now by the PCR analysis of cell free fetal DNA in maternal plasma. The feasibility of these approaches has been the subject of a large-scale study conducted under the auspices of the NIH. By the use of the latter approach, we have recently been able to demonstrate that this

method is already suitable for clinical applications such as the determination of the fetal RhD status in pregnancy with a Rhesus constellation, or fetal sex, in pregnancies at risk for an X-linked genetic disorder or compound heterozygotes for β -thalassemia, in that the required levels of sensitivity (>98%) and specificity (100%) can be attained. We have also recently detected that fetal material from the placenta is involved with the pathophysiology of pregnancy. Further research in this arena is fostered by the EU funded SAFE Network, where our group is acting as scientific coordinator.



Signal Transduction

Prof. Thérèse Resink, Prof. Paul Erne

Cell adhesion molecules in tissue remodeling: We study the role of T-cadhe-

rin (T-cad), an unusual member of the cadherin family of calcium-dependent surface adhesion molecules, in cardiac and vascular tissue remodeling. T-cad expression is markedly increased in endothelial and smooth muscle cells under pathological conditions associated with abnormal migration and growth such as atherosclerosis and restenosis after balloon angioplasty. We hypothesize that T-cad importantly modulates vascular cell beha-

avior in the context of vessel repair and formation of new vessels. To examine how T-cad influences vascular cell behavior *in vitro* we use cultures of vascular cells and exploit adenoviral/lentiviral gene transfer for loss- and gain-of-function models. There is much to be understood regarding how changes in T-cad expression occur, and how T-cad affects vascular cell function at the molecular level. Angiogenesis in plaque instability: In another project we aim to identify novel lipids and inflammatory cell-derived soluble factors within the atherosclerotic plaque that can induce neovascularization of atheromas and delineate key signal transduction mechanisms underlying the angiogenic response.



Tissue Engineering

PD Dr. Ivan Martin, Prof. Michael Heberer

Research of the tissue engineering group focuses on the *in vitro* genera-

tion of cartilage, bone and meniscus substitutes based on autologous cells and 3D scaffolds. The questions addressed are related to the identification of appropriate cell sources (mature, progenitor, stem cells), the selection of suitable growth factors and hormones, the use of 3D scaffolds in different compositions and geometries (synthetic or natural, meshes or foams) and the

development of bioreactors to apply physical stimuli (perfusion, compression) under controlled conditions. These projects are at the interface between fundamental and applied research and are based on a tight collaboration between biologists, engineers and surgeons. Results obtained so far have led to the identification of specific cocktails of molecules, scaffold parameters and regimes of physical stress supporting the expansion and differentiation of human chondrocytes and mesenchymal progenitor cells into cartilaginous and bone-like tissues of clinically relevant sizes.



Transplantation Immunology and Nephrology

Prof. Ed Palmer, Prof. Jürg Steiger

The laboratory of Transplantation Immunology and Ne-

phrology is investigating the basic biology of T lymphocytes and is applying this expertise to improve the success of organ transplantation. We are interested in several aspects of T cell biology and are working towards a better understanding of how T cells differentiate, how they function, and how they die. The focus of our research is the T cell antigen receptor (TCR), which dictates how T cells respond. We have identified 2 amino-acid motifs

within the TCR: one controls thymocyte differentiation and a second regulates T cell apoptosis. Our goal is to understand how the TCR is able to transduce a number of qualitatively different signals. We are using our knowledge of T cells to study the biology of graft rejection in a mouse model system and in transplanted patients, with the aim of developing a clinical test to detect a rejection reaction at an early stage.



Vascular Biology

Prof. Edouard Battegay

Angiogenesis, the formation of micro-vascular networks from existing ones, is a highly regulated process that arises in response to hypoxia and other stimuli

and that relieves tissue ischemia in patients with ischemic heart and peripheral vascular disease. The renin-angiotensin-system (RAS) plays an essential role in the maintenance of vascular homeostasis. Several lines of evidence suggest a role of angiotensin II and bradykinin in angiogenesis. We are therefore investigating the RAS system to understand its role in angiogenesis of the heart and hypertension-induced left ventricular hypertrophy.

In connection with these projects we examine specific signaling pathways via the molecule mTOR. This mTOR-dependent pathway appears to be driven by hypoxia and enhances the response of vascular wall cells and angiogenesis to PDGF and other growth factors. Thus, altered signaling plays a role in mediating the angiogenic response during ischemia in heart disease and peripheral vascular disease.

Chronological Index

1978–2005

Research Groups and Research Group Leaders, 1978–2005

Research Groups

Research Group Leaders

Anesthesiology (Research Lab) Bioengineering, later continued as Perioperative Patient Safety <i>Dept. of Anesthesiology</i>	Dr. Richard G. Buckles Prof. Myron B. Laver Prof. Dick Thompson Prof. Daniel Scheidegger	1979–1981 1978–1983 1984–1987 1988–1993
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Biochemistry/Endocrinology [Molecular Tumor Biology from 1997] <i>Women's Hospital, later DF Group</i>	Prof. Urs Eppenberger	1979–2003
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Cardiothoracic Surgery <i>Clinic of Cardiothoracic Surgery</i>	Prof. Hans-Reinhard Zerkowski	1999–
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Cardiovascular Research <i>Dept. of Int. Medicine, Div. of Cardiology</i>		
• Hypertension	Prof. Fritz R. Bühler	1978–1992
• Signal Transduction	Prof. Thérèse Resink Prof. Paul Erne	1994– 1998–
• Cardiology/CardioBiology	Prof. Peter Buser Prof. Marijke Brink Prof. Matthias Pfisterer PD Dr. Christian Zaugg	1988– 2004– 1998–2000 2000–2004
• Vascular Biology <i>Dept. of Int. Med., Policlinic</i>	Prof. Edouard Battegay	1998–

Research Groups and Research Group Leaders, 1978–2005

Research Groups

Research Group Leaders

Cardiovascular Genetics

*Dept. of Int. Medicine, Div. of Endocrinology, Diabetology
and Clinical Nutrition*

PD Dr. André Misérez

1998–2002

Cell and Gene Therapy (ICSF)

Dept. of Surgery

Dr. Andrea Banfi

2004–

Prof. Michael Heberer

1998–

Childhood Leukemia

Getrude-von-Meissner Foundation

Prof. Jürg Schwaller

2004–

Clinical Immunology

Dept. of Int. Medicine, Clinic B

Dr. Marten Trendelenburg

2005–

Clinical Neuroimmunology

Clinic of Neurology

Prof. Ludwig Kappos

1990/1998–

PD Dr. David Leppert

1998–2003

PD Dr. Rajja Lindberg

1998–

Clinical Pharmacology

Dept. of Int. Medicine, Div. of Clinical Pharmacology

Prof. Luzius Dettli

1978–1982

Prof. Ferenc Follath

1978–1989

Prof. Thomas F. Lüscher

1990–1997

Prof. Walter Haefeli

1998–1999

Prof. Stephan Krähenbühl

2000–

Prof. Jürgen Drewe

1998–

Dermatology

Clinic of Dermatology

Prof. Rudolf Schuppli

1979–1983

Prof. Theo Ruffli

1998–2005

Dr. Mei Bigliardi

2002–2005

Dermatology–Allergology

Clinic of Dermatology, Pollen Analysis Service

Dr. Ruth Leuschner

1979–2004

Diabetology

*Div. of Endocrinology/Diabetology, and later
Pediatric Endocrinology/Diabetology*

Prof. Willy Berger

1979–1993

PD Dr. Urs Zumsteg

1998–2004

Endocrinology

Pediatric Endocrinology/Diabetology & DF Group

Prof. Jürg Girard

1979–1992

Prof. Alex N. Eberle

1982–

Enzyme Biology

Dept. of Int. Medicine, Policlinic

continued as Policlinic Research Lab

Prof. Ulrich Dubach

1978–1992

Research Groups and Research Group Leaders, 1978–2005

Research Groups

Research Group Leaders

Experimental Critical Care Medicine

Prof. Urs Eriksson

2004–

Experimental Hematology*Dept. of Int. Medicine, Div. of Hematology*

Prof. Bruno Speck

1978–1993

Prof. Catherine Nissen

1978–2002

Prof. Alois Gratwohl

1994–2002

Prof. Radek Skoda

2002–

Prof. Aleksandra Wodnar-Flipowicz

2000–

Experimental Immunology*DF Group*

Prof. Gennaro de Libero

1990–

Experimental Nephrology**Transplantation Immunology***Dept. of Int. Medicine, Div. of Nephrology*

Prof. Gilbert Thiel

1978–1999

Prof. Felix Brunner

1978–2001

Prof. Jürg Steiger

2000–

Prof. Ed Palmer

2002–

Gastroenterology*Dept. of Int. Medicine, Div. of Gastroenterology*

Prof. Niklaus Gyr

1978–1987

Prof. Georg A. Stalder

1986–1993

Prof. Christoph Beglinger

1994–

Gynecological Endocrinology*Women's Hospital, Div. of Gynecological Endocrinology*

Prof. Christian de Geyter

1999–

Hepatogastroenterology*Dept. of Int. Medicine, Division of Gastroenterology**continued as Hepatology*

PD Dr. Cornel Sieber

1995–1999

Prof. Markus Heim

1997–

Human Genetics*Human Genetics of the University Children's Hospital*

Prof. Hansjakob Müller

1979–2004

Immunobiology*Dept. of Int. Medicine, Clinic B*

Dr. Christoph Hess

2004–

Immunonephrology*Dept. of Int. Medicine, Clinic B*

Prof. Jürg Schifferli

1994–

Infectious Diseases*Dept. of Int. Medicine, Div. of Infectiology*

Prof. Werner Zimmerli

1988–2001

Prof. Regine Landmann

1997–

Prof. Manuel Battegay

2002–

Research Groups and Research Group Leaders, 1978–2005

Research Groups

Research Group Leaders

Membrane Receptors*DF Group*

Prof. Matthias Staehelin

1984–1987

Metabolism/Liver Research*Dept. of Int. Medicine, Div. of Nephrology*

Prof. Heinrich Thölen

1978–1987

Metabolism*Dept. Int. Medicine, Div. of Endocrinology, Diabetology
and Clinical Nutrition*

Prof. Ulrich Keller

1978–

Prof. Beat Müller

2003–

Molecular Endocrinology*Dept. of Int. Medicine, Clinic A*

PD Dr. Jürg Schwander

1986–1993

Prof. Werner Stauffacher

1986–1993

Molecular Nephrology*Dept. of Int. Medicine, Bruderholzspital*

PD Dr. Barbara Biedermann

1999–

Prof. Reto Krapf

1999–

Molecular Tumor Biology*Women's Hospital*

Prof. Alfonso C. Almendral

1988–1996

Molecular Oncology*Internal Medicine of the St. Claraspital*

Prof. Christian Ludwig

1994–2001

Neurobiology*Clinic of Neurology*

Prof. Conrad G. Honegger

1978–1989

Prof. Heinrich E. Kaeser

1978–1992

Prof. Hugo Besedovsky

1989–1992

Prof. Andreas Steck

1993–

PD Dr. Nicole Schaeren-Wiemers

1998–

Neurooncology*Clinic of Neurosurgery*

Prof. Adrian Merlo

1994–

Neurosurgery*Clinic of Neurosurgery*

Prof. Othmar Gratzl

1990–

PD Dr. Aminadav Mendelowitsch

2000–2003

Neurotransmitters*DF Group*

Prof. Alfred Pletscher

1978–1988

Oncology (Medicine)*Dept. of Int. Medicine, Div. of Oncology*

Prof. Jean-Paul Obrecht

1978–1990

Prof. Richard Herrmann

1991–2001

Prof. Christoph Rochlitz

1998–

Research Groups and Research Group Leaders, 1978–2005

Research Groups

Research Group Leaders

Oncology (Surgery)*Dept. of Surgery*

Prof. Giulio Spagnoli

2000–

Prof. Michael Heberer

1998–

Pediatric Immunology*University Children's Hospital*

Prof. Georg A. Holländer

1995–2004

Pediatric Surgery*University Children's Hospital*

Prof. Dietrich Von Schweinitz

2000–2003

Perioperative Patient Safety*Dept. of Anesthesiology*

Prof. Albert Urwyler

1994–2003

Dr. Thierry Girard

2003–

Dr. Susan Treves

2003–

Pneumology*Dept. of Int. Medicine, Div. of Pneumology*

Prof. André Perruchoud

1988–2002

Prof. Michael Roth

2000–

Prof. Christoph Tamm

2002–

Policlinic (Research Lab)*Dept. of Int. Medicine, Policlinic*

continued as Heptaogastroenterology

Prof. Niklaus Gyr

1992–1997

Prof. Markus Heim

1996–1997

Surgery (Research Division)*Dept. of Surgery*• **Biochemistry (Surgery)**

1978–1985

Prof. Martin Allgöwer

1978–1985

Prof. Guido A. Schönenberger

1978–1985

• **Oncology, Metabolism, Reperfusion,****Trauma, Transplantation** 1986–1997

continued as Oncology (Surgery) and Tissue Engineering

Prof. Felix Harder

1986–1994

Prof. Michael Heberer

1986–

Tissue Engineering*Dept. of Surgery*

PD Dr. Ivan Martin

1998–

Prof. Michael Heberer

1998–

Transplantation Biology*Dept. of Surgery*

Prof. Georg L. Floersheim

1979–1990

25th Anniversary Events

Scientific Symposium

The 25th anniversary celebrations began on Friday, September 19, 2003 with a scientific symposium featuring renowned invited speakers from US and European institutions and group leaders from the DF.

On the occasion of this event, the founder and former chairman of the DF, Professor Dr. Alfred Pletscher received heart-

felt praise for his essential role in creating and developing the DF and his far-reaching contributions to the development of biomedical research in Basel. The director of the Kantonsspital (now renamed «University Hospital»), Rita Ziegler, and the Dean of the Faculty of Medicine, André Perruchoud, addressed the audience and emphasized the significance of the DF for the future.





Rita Ziegler, Director of the University Hospital Basel

The DF was conceptualized and planned with wide support from the Department of Health and the Department of Education as well as the Kantonsspital and the Medical Faculty of the University of Basel. The particular idea behind the DF was to centralize and bring together basic and applied medical research. Since then, the DF has facilitated the efficient translation of new medical knowledge from basic science to clinical practice and has evolved to an ideal link between the Medical Faculty and the hospital. The Kantonsspital will do all it can to ensure that the DF has a bright future.



André Perruchoud Dean of the Medical Faculty

The Department of Research is one of the key factors, which will assure the future of the Medical Faculty. It brings together clinical and basic researchers, making the bridge between the patient and the lab. This door to door and day to day working close together allows an effective scientific cross fertilization. For the Medical Faculty small is synonyme of success. The concept of the DF has directed further developments in our faculty. The Department of Clinical and Biological Science will have to follow the same line taking full advantage of an extensive exchange with clinicians involved in research.

Friday, september 19, 2003

Hörsaal 1, Pharmazentrum, Klingelbergstrasse 70, Basel

Welcome address and closing words: Rita Ziegler, André Perruchoud

- 13.30** Pathogenesis of Myeloproliferative Disorders
Radek Skoda, Department of Research, Basel
- 14.05** PTEN Tumor Suppressor Gene
Ramon Parsons, Columbia University, New York
- 14.40** Cartilage Regeneration
Ivan Martin, Department of Research, Basel
- 15.45** Genetic Screens in Cancer Research
Philip Leder, Harvard Medical School, Boston
- 16.20** Gene Therapy for Human Severe Combined

- Immunodeficiencies
Marina Cavazzana-Calvo, Hôpital Necker, Paris
- 17.20** Jak/Stat Signaling and Hepatitis C
Markus Heim, Department of Research, Basel
- 17.55** Small G-protein Signaling
Tobias Meyer, Stanford University, Stanford
- 18.30** T Cell Receptor Signaling and Immunological
Tolerance; Ed Palmer, Department of Research,
Basel



Radek Skoda Experimental Hematology, DF

The Pathogenesis of Myeloproliferative Disorders. Myeloproliferative disorders (MPD) are a group of diseases characterized by aberrant proliferation of one or more blood cell lineages. They represent clonal stem cell disorders of unknown etiology with an inherent tendency towards leukemic transformation. Mitotic recombination on chromosome 9p is a frequent chromosomal alteration in MPD and likely harbors a gene involved in disease progression. Mapping of the recombination breakpoints is applied to search for the gene involved. In addition, transgenic mouse models for MPD were generated to study molecular aspects of MPD pathogenesis.



Ramon Parson Columbia University, New York

PTEN Tumor Suppressor Gene. The tumor suppressor gene PTEN is frequently mutated in human malignancies. PTEN is the primary phosphatase of the lipid messenger PIP3 and exerts a central role in the control of cellular homeostasis by counteracting the PI-3 kinase network. Cells deficient for PTEN are unable to restrict PI-3 kinase signaling, which stimulates cell proliferation and oncogenesis. To develop rational therapies for PTEN-deficient tumors, the negative effect of the inhibitor CCI-779 on PI-3 kinase signaling was tested. CCI-779 significantly suppressed tumor growth by blocking PI-3 kinase signaling.



Ivan Martin Tissue Engineering, DF

Cartilage Regeneration. After highlighting the clinical need for functional cartilage grafts, a proof-of-principle study in rabbits was presented to demonstrate the utility of engineered cartilage for the repair of large osteochondral defects. The presentation illustrated several strategies that are being applied to improve the quality of engineered cartilage starting from human chondrocytes, in particular the use of regulatory molecules during cell expansion, the selection of instructive scaffolds, and the application of physical forces to the developing tissues in dedicated bioreactors.



Philip Leder Harvard Medical School, Boston

Genetic Screens in Cancer Research. To identify novel oncogenes, transgenic mice that are prone to develop breast tumors were infected with the mouse mammary tumor virus (MMTV). By analyzing the site of MMTV integration in mice with a shortened latency for tumor formation, a novel member of the wingless (Wnt) family was identified as the proto-oncogene responsible for the acceleration of tumor formation. A high throughput screening with 16,000 compounds led to the identification of a small molecule, F16, that specifically inhibited the proliferation of breast cancer cells by inducing cell cycle arrest and apoptosis.

Marina Cavazzana-Calvo Hôpital Necker, Paris

Gene Therapy for Human Severe Combined Immunodeficiencies. Severe combined immunodeficiencies (SCIDs) are caused by different molecular genetic defects that lead to the arrest of T-cell differentiation and early death in the absence of therapy. Results of gene therapy show the correction of two SCID conditions, suggesting that gene therapy could overcome the long-term recurrence of the T-cell immunodeficiency. However, integration of retroviral vectors carries the risk of insertional mutagenesis. Two SCID patients treated with gene therapy developed aberrant clonal proliferation of lymphoid cells due to enhanced protooncogene expression.



Markus Heim Hepatogastroenterology, DF

Jak/Stat Signaling and Hepatitis C. Many viral infections induce the expression of interferon alpha and beta (INF α / β). INF α signaling activates the Jak/STAT signaling pathway, which was found to be impaired in patients with chronic hepatitis C. The data presented indicate that the hepatitis C virus (HCV) induces hypomethylation of STAT1. Importantly, hypomethylated STAT1 associates with PIAS1, which inhibits the binding of STAT1 to DNA. Therefore, restoring STAT1 methylation by therapeutic interventions might increase INF α responsiveness and could facilitate the eradication of HCV in chronically infected individuals.



Tobias Meyer Stanford University, Stanford

Small G-Protein Signaling. Signaling proteins from the same family can play markedly different roles. This phenomenon is evident in the control of cell shape; the expression of different constitutively active, small GTPases induced distinct classes of cell morphologies. Functional specificity among GTPases has been explored by creating switch-of-function mutants. This approach was used to study chemotaxis, a cellular sensing mechanism that guides immune cells to sites of infection. We propose a model in which chemotaxis is a stochastic process triggered by individual signaling events.



Ed Palmer Transplantation Immunology, DF

T Cell Receptor Signaling and Immunological Tolerance. The repertoire of T lymphocytes depends on positive and negative selection processes, which occur in the thymus. In the presented study, the influence of the T cell receptor (TCR) on thymocyte and T cell biology was investigated by focusing on how the TCR «reads» ligand affinity and how the initial receptor engagement leads to the initiation of early receptor signals. An extremely sharp affinity threshold was observed, which distinguishes positive and negative selection. Studies on a mutant receptor were performed to learn how the TCR differentially signals proliferation and death.



Open Day

When in 1998 the DF celebrated its 20-year anniversary with a three-day event by opening its doors to the scientific community, the local and national «politics», to the media and the public, the response was so overwhelming that for the 25-year anniversary a similar event for the general public was planned. On 27 September 2003, the DF opened its doors again and offered an attractive program with lectures about important medical topics, visits to the laboratories and scientific posters and information stands in the entrance hall of the ZLF building.

Many visitors enjoyed this multifaceted program: Eleven 20-min lectures from *immunization against cancer* to *resistance against heart attack* gave them a tour d'horizon about the themes covered by the different research groups. In more detail, the visitors could experience the forefront of biomedical science by watching experiments in the twenty laboratories that were especially prepared for the lay public. Demonstrations included separation of different cell types by fluorescence-activated cell sorting, visualization of structures within individual cells and in brain tissue by confocal microscopy, manipulation of input signals to isolated beating hearts, new avenues to defend the body from hepatitis virus, the cultivation of natural cartilage and bone implants, new insight into body fat as source of hormones and other modulating molecular signals and much more. After absorbing all this new information, the visitors needed a relaxing pause in the entrance hall where they could taste the delicious food from Turkey and China prepared by scientists and technical staff of the DF and have a beer at the bar, before taking a last health advice in the poster area, e.g. about reducing the risk of acquiring melanoma or other deadly diseases, or stopping by at the info stand of the

PhD students to learn more about the fascinating experience to undertake a doctoral thesis in the field of biomedical sciences. Meanwhile the younger generation was taught «computer sciences» in a computer corner and, in a temporary *kindergarden* in the cafeteria of the hospital, the youngest generation was exposed to the «breeze of enthusiasm» in a house of science.

Samstag, 27. September 2003

Labors und Eingangsbereich des Zentrums für Lehre und Forschung (ZLF), Hebelstrasse 20, 4031 Basel

- 10.30** Christian De Geyter: Das Gespräch mit der Eizelle
- 11.00** Miklos Pless: Impfen gegen Krebs? – Immuntherapien in der Krebsbehandlung
- 11.30** Adrian Merlo: Löst die Krebsgenetik den gordischen Knoten bei Hirntumoren?
- 12.00** Petra Duda: Immunsystem und Multiple Sklerose – Was gibts Neues?
- 12.30** Barbara Biedermann: Blutgefässe: Ein Bewässerungs- und Kanalisationssystem der besonderen Art
- 13.00** Hans Hirsch: Aids gebannt, HIV im Griff, Ziel erreicht?
- 13.30** Dirk Schaefer: Gelenkknorpel aus dem Labor
- 14.00** Aleksandra Filipowicz: Die verschiedenen Gesichter der blutbildenden Stammzellen
- 14.30** Christian Zaugg: Resistenz gegen Herzinfarkt
- 15.00** Beat Müller: Was der Diabetes von der Sepsis lernen könnte
- 15.30** Albert Urwyler: Kalte und heisse Patienten während der Operation – wie Forschung die Patientensicherheit in der Anästhesie erhöht



History

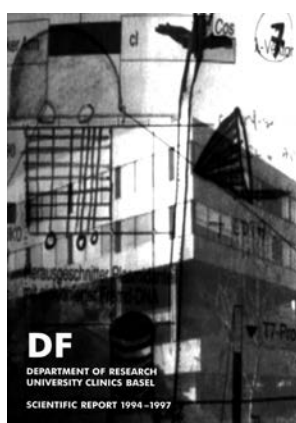
Introduction

When the DF celebrated its 25th anniversary in the autumn of 2003, it found itself in the unique situation that a well-sized group of members of the founding generation were still actively pursuing their research at the DF and, even more importantly, that all former chair persons of the DF were present and willing to write up the history of the DF. This group of seven chair persons spans an entire generation with an enormous wealth of experience in organizing medical and pharmaceutical research at the local and national (international) level. The photograph opposite was taken in the hospital gardens in the autumn of 2003.

The history of the DF can be divided into five phases, and these five phases are mirrored by the appearance of the biannual reports published during these periods. In *The First Steps* the founding chairman Prof. Alfred Pletscher (1978–88) describes the building of a new type of departmental structure for hospital-based laboratory research. His biannual reports were presented in decent blue colour. In 1987, Alfred Pletscher's 70th birthday

was celebrated together with the (somewhat early) «10 years DF» event; the proceedings of the scientific symposium on the «The Platelet in Pathophysiological Research», which was held on March 20, 1987, were published in *Experientia* (vol. 44, no. 2, 1988).

The next period (*The Maturation Phase*) summarized by the second chairman Prof. Fritz R. Bühler (1988–91/92) was devoted to making the DF well-known beyond the Swiss boundaries, to attracting the interest of young clinicians in laboratory-based research and to create a DF Fund with the help of industrial sponsors in order to strengthen its financial basis. The colour of the biannual reports in yellow reflected better visibility. This colour continued well into the third phase (*Growth and Autonomy*), but was later replaced by a different format, language and appearance with illustrations and art. This third phase headed by Prof. Alex N. Eberle (deputy chairman 1986–91 and 1995–97, chairman 1992–95 and 1997–2000) and by Prof. Werner Stauffacher (chairman 1995–97) was the most complex one as it





**The chair persons of the DF 1978–2003 (from left to right):
Prof. Alfred Pletscher, Prof. Fritz R. Bühler, Prof. Werner
Stauffacher, Prof. Alex N. Eberle, Prof. Regine Landmann,
Prof. Jürg Schifferli, Prof. Radek Skoda**

was originally meant to be a transition period of short duration. By contrast, the DF experienced a substantial growth for eight years, and through a new structure of the Kantonsspital it gained more autonomy. The fourth period (*The DF on the Move*) chaired by Prof. Regine Landmann (deputy chair 1997–2000 and 2002–03; chairwoman 2000–2002) and Prof. Jürg Schifferli (co-chair 2000–2002) fell into the phase when the DF took its initial steps as part of the newly formed DKBW (Department of Clinical and Biological Sciences) while continuing its independent growth and development. The latter is reflected by the newly formed DF logo shown on the biannual report 2000/01. The fifth and present period (*From Present to Future*) represents that part of the DF's history, in which a full integration of the DF into the DKBW is being planned and this period will also be remembered by multicolour reports: Prof. Radek Skoda (chairman since 2002) gives an account on the present and future developments of the DF.

Alex N.Eberle

The First Steps

1978–1988 Alfred Pletscher

Professor Alfred Pletscher was the founding chairman of the Department of Research. Holding an MD and PhD, he came to Basel in 1948 where he was first resident at the Medical University Clinic. In 1955 he joined F. Hoffmann-La Roche to become director of biomedical research and later the global head of research of the Roche group. He was also the first Professor of Pathophysiology of the Medical Faculty, co-founder of different research institutions and President of the Swiss National Science Foundation. In 1978 he returned to the University Hospital to build up the DF.

The Department of Research (DF) was founded as part of the Centre of Teaching and Research (ZLF) which was built in the course of the third building phase of the Cantonal Hospital Basel (KBS). In a memorandum dated 6th August 1969, which was sent to the members of the Cantonal Parliament (Grosser Rat), the section «2.4.2. Research» specifies the necessity for the hospitals to add a «special organisational structure for research, separate from the clinical organisation».

After approval of this memorandum, a commission of the Medical Faculty of the University of Basel chaired by Prof. Aurelio Cerletti was entrusted with the setting up of a provisional statute of organization for the DF. Another faculty commission chaired by Prof. Heinrich G. Haas performed a preliminary inventory of the laboratories of the KBS which were involved in clinical research. Both these commissions were later replaced by one provisional commission, assigned to make a proposition for the organization of the ZLF. It consisted of 8 faculty members as well as the Medical Director of the KBS. I had the honour to be its chairman. This commission decided to take care only of the

research carried out in the DF (including the animal quarters of the KBS), whereas the responsibility for teaching was transferred to the Dean of Studies of the Medical Faculty.

After numerous discussions with the governmental heads of the Health and Education Departments, the building commission, the management of the KBS, and the Medical Faculty, a practicable concept for the organisation and running of the DF was formulated. I was then asked whether I would take over the chair of the DF. This offer interested me, being a former resident (1948–1954) of the Medical University Clinic in Basel and a lecturer in pathophysiology in the Medical Faculty. I realised above all that this was a challenge to support clinical research, which was not optimally promoted in our country. In addition, a fresh start after more than 20 years in research in the pharmaceutical industry was tempting. Thus, I accepted the position (in 1978) which included space for a personal research laboratory, a secretary and a personal technician as well as a parking space in the underground garage in lieu of a salary.

I will now describe the development of the DF that took place during my period of office (1978–1988).

General Conditions

The following general conditions of the KBS had to be met:

- The DF had to report to the management of the KBS and thus belonged to the Department of Health of Basel-Stadt.
- Within the KBS, the DF had the status of an independent department, like all the clinical departments.
- A curatorium consisting of representatives from the Health and

Education Departments, the KBS, the Medical Faculty and the conference of the departmental heads of the KBS should act as a coordinating body.

- The present and future research groups of the University Clinics of the KBS should all be admitted to the DF.
- The clinical research groups that were to be settled in the DF continued to belong administratively to the individual clinics and were dependent for most of their research funds on the clinics' budgets.
- The DF could not expect additional financial means from the government. Funds necessary to build up the new department and its research had to be recruited from foundations and industrial sources.

More detailed guidelines concerning the field of activity of the DF and conceptions concerning the aim to be achieved were drawn up in a supplement to this document.

Field of Activity and Objectives

The research in the DF should be directed towards human disease, but independent of the presence of patients. Thus, both basic and applied laboratory-based medical research was to be encouraged, the importance lying in the relevance for human disease. The individual projects for the research should come from the clinics which in turn should benefit from the results. In this way there was a clear distinction from the recently established Biocenter of the University of Basel whose objective it was to cover basic research in the entire spectrum of biology.

By concentrating the laboratory part of clinical research in the DF, we aimed at:

- improving the cooperation between research groups working in the KBS;
- improving the quality of the research;
- increasing the attractiveness of research for the coming medical generation, e.g. by encouraging research activities in their further education;
- optimal use of the expensive infrastructure (e.g. special rooms) and apparatus;
- improvement in the financial transparency of the research expenditure.

Relocation of the Research Groups

The architecturally completed laboratories had to be distributed among the clinical research groups which had before been



Prof. Alfred Pietscher, the founding chairman of the DF

scattered around the area of the KBS. This took place after numerous «site visits» with the different groups and discussions with their departmental heads. The oncologist at that time, Prof. Gerd Nagel, as well as a lawyer for financial questions Dr. Robert Egger were of considerable help. This was essential, as it was not always easy to persuade the groups to move. Many were afraid, for example, of forfeiting space and independence. Finally, however, it was possible to persuade almost all the research groups of the advantages they would benefit from, after relocation to the DF. The move to the DF followed step by step and began in the second half of 1978. The groups with related topics were located as near as possible to each other. At the end of 1979 when the occupation was complete, about 20 research groups were working in the DF. This number underwent minor

fluctuations but did not alter significantly until the completion of the early developmental period (1987).

Cooperation

The concentration of the research groups in the DF alone was an important prerequisite for improvement in the transparency of their activities and encouragement of their cooperation. A further supporting measure were the regular internal colloquia which were open to all and in which the researchers reported on their ongoing work and presented it for discussion. In addition, we organized external half-day meetings near Basel to which all members of the DF were invited and in which the researchers reported on their progress over the past months and year. Methodology was also discussed here in the hope of exchange of know-how between the groups. The DF regularly invited well-known external speakers to seminars to talk on subjects of general interest. Today, such measures are taken for granted but in those days were not yet customary in Basel's University Clinics. It was also expected that they would help to extend the horizon of the co-workers beyond that of their specific fields which, in view of today's specialisation in research, is a cultural concern.

Quality

The promotion of quality was a priority for which the conditions were not the best because of the requirement that all research groups from the KBS were to be incorporated into the DF regardless of their standard. It was not possible to make a selection. The groups were of varying size and worked in different areas of medicine. The heads of the various clinics were alone responsible for the topics and their realisation. Formation of priorities by «top-down» planning was, for example, not possible so that an improvement in quality had to be made by the «bottom-up» principle. This was attempted with the following measures:

Specialised Advice and Support

It was regarded as important that the research in the DF which was directed by clinicians should have the support of scientists (biochemists, molecular biologists etc.) who actually took part in the research and/or advised and supported the groups. The long-term objective was to have positions in the DF for such scientists. This was only partly successful (see below).

Subsidiary Financial Support

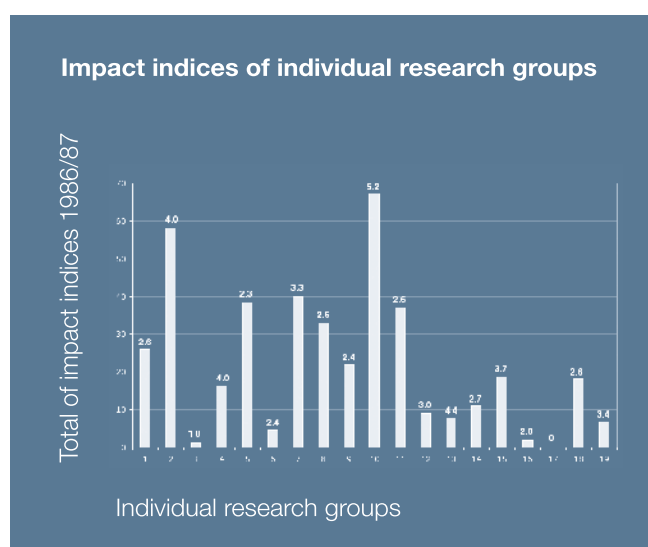
It was arranged that a small budget would be assigned to the

DF for subsidising successful research groups. This also set the stage for creating «centres of gravity» (*Schwerpunkte*).

Quality Control

The introduction of indicators for quality control was thought of as an incentive for the researchers to scrutinise and if necessary improve the quality of their work. The quality of each group was assessed as follows:

- A Scientific Advisory Board made up of independent, external experts met with the research group leaders at least twice a year for one to two days to be informed about the state of their work and further planning. The members of the Advisory Board also had admittance to the research groups between the meetings if deemed necessary. Once a year, the Advisory Board prepared a written report for the Curatorium and the chairman of the DF. The leaders of the research groups also received a copy of the corresponding report for their group. With the institution of an advisory board, the DF followed the successful example of the Basel Institute of Immunology, which in Basel was one of the first to set up such a body.
- The impact indices of the journals in which the individual research groups had published over the years were added up for each group. The differences between the groups revealed a broad variation, e.g. for the years 1986 plus 1987 from 0 to 67 (Fig. below). These measures at first gave rise to vehement criticism by some research group leaders but were accepted with time as just one of the quality criteria.



Abcissa: Individual research groups, anonymous, in alphabetical order. **Ordinate:** Total of impact indices of journals with publications of the individual research groups in 1986/87. **Numbers:** impact points per paper.

Early pioneers of the DF who
are still working at the DF.

Front row (from left): Gerdien
Gamboni, Alex Eberle, Regine
Landmann, Alfred Pletscher,
Fabrizia Ferracin, Werner
Krenger. *Centre:* Doris Lutz.
Back row: Denise Biemann,
Verena Jäggin, Thérèse
Resink, Monika Hermle,
Kathrin Cencier, Nicole
Chiodetti. Missing on the
photograph is Paul Erne.



- The success in acquiring external financial means, particularly from the Swiss National Research Foundation (based on scientific assessment) as well as the award of scientific prizes was also taken into account.

Ethical Measures

An Ethics Commission for Animal Experimentation was set up early on, i.e. before there were official regulations. It was made up of external and internal participants to which the research groups had to submit their plans for animal experiments. The decisions of the commission and the necessary modifications of the proposed experiments were generally well accepted by the applicants. With the introduction of the Swiss Law for Animal Protection, the internal commission was dissolved.

Problems

A major problem was the double affiliation of the researchers working in the DF. Most of the research groups belonged to the clinics of the KBS who also provided the greater part of their budgets. On the other hand, their research activities took place in the DF where the infrastructure and apparatus as well as expert advice was built up. This resulted in problems of identity building and integration, particularly at the beginning. The fact that in the first years the DF had very little financial means and in particular lacked its own positions for scientists also contributed to the problem of insufficient support for the clinical research groups. Certainly, there were competent scientists in some of the groups but with two exceptions (see below) these were all financed by private means (for limited time periods) and their

number was too small for a qualitative «quantum leap» of the DF.

The question to which governmental department the DF should belong to was also a problematic issue. The opinions were divided. I myself felt that it should be transferred from the Health Department to the Education Department as the latter was responsible for teaching and research at the University. This change however did not take place during the time period described here.

Per aspera ad astra

It could not be expected that the aims for the DF would be achieved within the first period of its existence; their realisation should rather be a long-term project. As a consequence, only partial success could be recorded. Thus the new infrastructure and the centralisation of apparatus was generally regarded as progress. In addition the internal communication between the research groups improved, resulting in cooperation between groups which later formed the basis for subsequent «centres of gravity» (*Schwerpunkte*). The quality control was a partial success. For example, it led to the spontaneous withdrawal of less successful groups without necessitating direct interference from the DF management.

The realisation of two state positions for scientists belonging to the DF who, apart from their own research supported other groups with their know-how, was also important for the quality of the work. One of these two staff positions was occupied by Dr. Alex Eberle who also functioned as Deputy Head of the DF, the other



Some more pioneers of the first period. *Front row:* Alfred Pletscher, Willi Küng, Sebastiano Sansano, Luisa Baselgia, Sibylle Bertschin. *Middle row:* Silvia Sendelov, Elli Christen, Susi Vosmeer, Heidi Bodmer, Catherine Meyer, Felix Brunner. *Back row:* Armin Bieri, Thomas Aerni, Liliane Todesco, Verena Dalle Carbonare, Thomas Woodtli, Markus Wenk, Heinz Kuenzi, Gilbert Thiel.

by Dr. Ernst Bürgisser. A further advance was the nomination of a technical assistant for the DF (Betriebsassistent: Armin Bieri) for the administrative and technical issues.

A good social climate is a prerequisite for a successful enterprise. Festivities, expeditions etc. organised with enthusiasm and imagination by members of the DF contributed substantially to the identity building (see photos). The markedly positive attitude of the directors of the KBS (Aldo Buser, Prof. Walter Schweizer, Prof. Hanspeter Rohr) to the DF also contributed to the good climate.

The DF slowly became known in wider circles, e.g. through a series of 14 articles over a period of time in the Basler Zeitung in which researchers presented their projects. Discussions with politicians were also organised, e.g. on the occasion «Researchers meet politicians» to which members of the cantonal parliament (Grosser Rat) and other prominent politicians from the region were invited to the DF for information and discussion. The DF also seemed to attract the younger generation interested in disease-oriented research. Thus, it is my impression (although exact statistical records are lacking) that an increasing number of doctoral and postdoctoral students have been working in the different research groups of the DF.

Since the first steps described here, the DF has developed in an impressive manner thanks to the efforts of my successors and their crew. So may the DF be granted further creative success under its present direction.



10th anniversary of the DF (Basler Zeitung)

The Maturation Phase

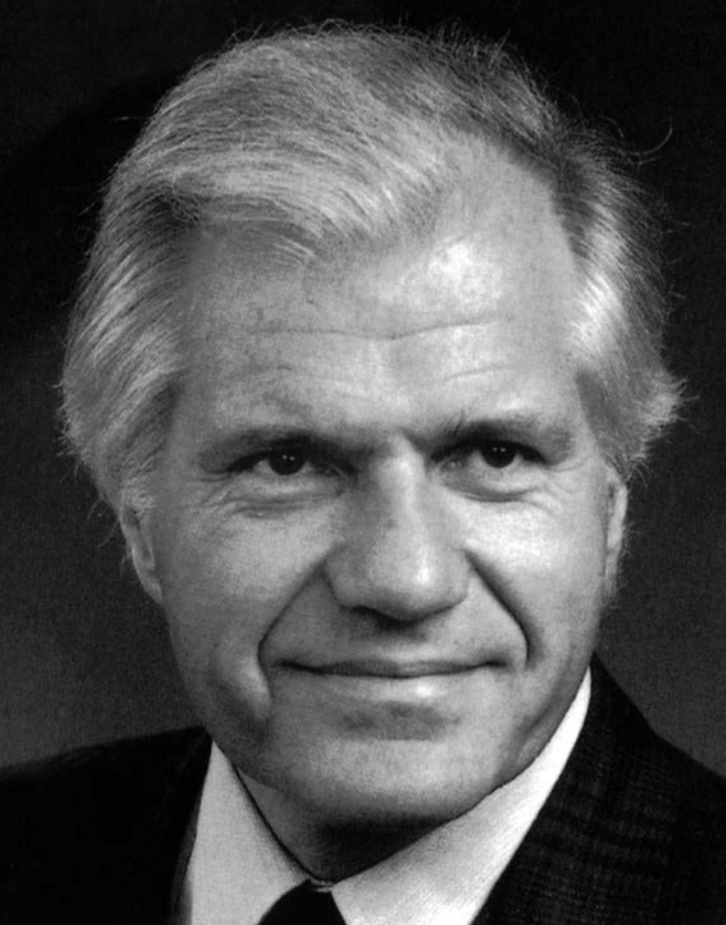
1988–1992 Fritz R. Bühler

Professor Fritz R. Bühler, a cardiologist at the University Hospital Basel since 1977 and leading expert in basic and clinical hypertension research, was heading a large research group at the DF when he was elected as its chairman and Professor of Pathophysiology in 1988. Within three years, he succeeded in establishing a large fund for the DF, raising the impact of basic medical research and integrating the DF into new networks with other universities, in particular of the upper Rhine valley (EUCOR), and with industry. In 1991 he was recruited by Hoffmann-La Roche as Head of Global Clinical Research and Development and Chief Medical Officer.

After solid foundation building in the first decade of the DF to create a unique disease-oriented research platform of the Medical Faculty and the University Hospital Basel, the DF now underwent a maturation process, leading to greater international recognition through further quality enhancement and controlled expansion. A major challenge was to match the impact of comparable national and international institutions performing similar disease-oriented research. Therefore, the «maturation process» aimed at strengthening the foundations for successful bench-based research, along with better defined research objectives addressing medical needs. The Medical Faculty and the higher authorities paved the way for these goals in that they promoted the Chairman's position of the DF to the more prestigious status of Ordinarius (o-Professor) of Pathophysiology and thus emphasized the dual role of the DF as a centre for teaching medical students and as a hub of disease-oriented research for the University Hospitals.

Clinicians in Research

In the early nineteen seventies, laboratory-based disease-oriented «clinical research» was greatly underdeveloped in Basel, relative to comparable university settings in Switzerland and elsewhere in Europe – not to speak of Anglo-Saxon countries. For example, in the mid-eighties Basel had only four full-time equivalent clinicians at the chief resident (*Oberarzt*) level with work time designated for disease-related bench work whereas Geneva had sixteen. Notwithstanding the great and laudable efforts of the Swiss National Science Foundation (SNF), young investigators had a difficult time in finding lab space and developing their own research in Basel's hospital environment. Success in (clinical) research was not vital to an MD career, and peers viewed the domain rather suspiciously. The lack of research by young clinicians was attributed to the preponderance of clinical duties and often also to insufficient laboratory skills. Thanks to the existence of the DF, bench-based clinical research has gained fresh appreciation in Basel. However, the actual research work was performed by the lone scientist in the lab, who depended upon financial sponsorship by the clinical team leader and who often lacked significant scientific input from that authority. The point was (and still is) that clinicians interested in research are distracted by primary patient care and in addition by time-consuming managerial tasks and numerous hospital committees. Thus, clinical bench-based research was greatly neglected, and modern functional biology was the domain of the Biocenter. The DF was Basel's strategic hope to enable faster patient access to basic medical science.



Prof. Fritz Bühler, second chairman of the DF

The description in 1979 by Wyngaard of «the clinical investigator as an endangered species» was especially appropriate in the setting of the Basel Cantonal Hospital (where even the name «University Hospital» encountered resistance!): There were too few positions permitting clinicians to integrate serious research with their clinical duties. The relatively small scale of our University Hospitals, the demand for superior clinical performance and the shortage of MD research positions resulted in neglect of the clinical scientist. Even numerous attempts for improvement at the local and national level from 1970–1995 failed to overcome the deficit in positions and financing. The basic scientific community is imperfectly acquainted with the difficulties associated with applied clinical bench-based research, as compared to basic science.

Financing Clinical Research: The DF Fund

While a broader management structure of the DF that included the positions of chairman, deputy chairman, technical assistant (Betriebsassistent; the latter two established previously) and secretary as well as larger funds for equipment and running costs were facilitated by the KBS, Medical Faculty and local government, positions for both clinical and full-time PhD scientists remained limited. There was also a lack in representation of certain important fields, e.g. immunology, and an obvious need in progress of informatics. As the DF gained momentum, the

heads of research of Basel's pharmaceutical industries could be persuaded to assist with financial support in order to help the DF to reach the goals of modern disease-oriented research. Through negotiations with their joint Contact Group for Research Issues (KGF, Kontaktgruppe für Forschungsfragen) a well-structured DF Fund of CHF 4.5 million to be applied over five years was established. This new fund enabled strategic creation and supplementation of research positions in immunology, surgery, gynecology, infectious diseases and, most importantly, for an informatics expert. Incidentally, these funds were never applied to the cardiovascular research sector! The DF was very thankful for and proud of this timely impulse which facilitated the maturation of the DF. The input from pharmaceutical industry remains as decisive today for the presence of key scientists and for maintaining a sustained level of research impact.

The DF Publication Impact Factor Doubled

Several measures to improve the quality of the research at the DF led to yearly analyses based on quality indices established in the Department's early days. Without overrating «impactitis», the International Citation Index is an internationally used standard. It was therefore a rewarding discovery that the impact factor of the DF consistently improved, almost doubling in the early nineties.

Another indication of quality was provided by the research team's financial support from the SNF, which is based on peer-review of research plans. Virtually all DF research teams were now funded by the SNF. Also, important prizes were awarded to DF members, e.g. the Theodor-Nägeli Prize to Thomas F. Lüscher in 1990 and the Robert-Wenner Prize (Swiss «Cancer Research Prize») to Alex N. Eberle in 1991.

The Department Head Walks a Tightrope

The dual function of Professor of Pathophysiology and Chairman of the DF was not an easy one: once elected – and this was a slow process – the new professor was asked to teach at least one third of the annual course, to further enhance the teaching in pathophysiology and to keep Basel on the inside track in Swiss examination results. As chairman of the DF the new professor also had full responsibility for all affairs, with the fortunate assistance of the deputy chairman, Prof. Alex N. Eberle, as well as other staff members, and he became member of numerous committees. For example, he interacted with the Curatorium, the Scientific Advisory Board, as well as a large departmental conference and a small executive committee. Certainly there

were plenty of checks and balances, and little room for creative strategic work. In spite of, or perhaps because of these constraints, a lively growth and maturation phase resulted in internal consolidation and enhanced external visibility. The chairman of the DF was probably the best-controlled professor in Europe at the time.

Important Achievements

Partnerships between physicians and PhD scientists were nurtured, yielding a new critical mass of PhDs in the Department. This greatly impacted the quality and stability of bench-based clinical research. Quality of research has been systematically benchmarked and encouraged, as for example in the monthly DF newsletter.

Scientific conference platforms were supplemented with project meetings, and DF seminars were combined with clinical research conferences. Guest professorships and lectures, as well as regular interactions with the clinical and scientific societies, and lunch meetings with students and young investigators, were promoted. The presentation of the «15-years DF» symposium formed the climax of these activities.

Research networking within the tri-national EUCOR (European Confederation of Upper Rhine Universities), as well as Europe and the United States, was encouraged and esteemed. A number of regional collaborations in basic and clinical research were fostered in oncology, infectious and cardiovascular diseases as well as drug trials. A EUCOR master course in clinical research

(MD-PhD) was started jointly with the Universities of Freiburg i.Br. and Strasbourg. There were also a number of interactions with Eastern European countries, e.g. with institutions in Moscow.

An integrated training and education program has been started in a concerted effort to maximise the Basel branch of the Swiss National Science Foundation, and in this a system for sponsoring young investigators with «only» one half of a grant was created, requesting that the second half be contributed by another Basel-based foundation. Predictably, the system was disliked by some, but it helped to support training, mostly in the United States, for twice the number of students. This «half-tax system» is still up and running.

Along with the evolution of the DF Fund, in a healthy «two way street» mode, we also accepted the visiting professorship of Prof. Robert O'Neil of Georgetown University, Department Head of Biostatistics at the U.S. Food and Drug Administration. He spent a sabbatical at the DF, in the golden triangle of the Basel pharmaceutical industry, in the heart of Europe. Over eight Thursday evenings he held the so-called TITER course, Topics In Therapy Evaluation and Review. Some 40 participants were expected, but 350 attended, with the result of a very positive effect on the DF Fund. This demonstrated the great need for a systematic postgraduate training course in integrated drug development, and thus the European Centre for Pharmaceutical Medicine course was born, and is alive and well today.

On many more occasions, the DF functioned as an excellent neutral platform for communication and scientific interaction, and hence despite all its «pathophysiological» ups and downs, the DF was and is a success story and model for laboratory-based clinical research. We hope that in ten years' time the DF will have sustained its high scientific standards, while opening further to entrepreneurship. Some may have the courage to take this road in their own enterprise, applying good ideas and results to a medical need. Who better to translate basic research information into clinical practice than the clinical scientist? I remain a DF member «de coeur» and wish everybody at the DF great scientific success, personal satisfaction and a lot of fun.



Robert-Wenner Prize 1991: Franz Buchegger, 42 (Lausanne), Jean-Claude Reubi, 46 (Bern) und Alex N. Eberle, 46 (Basel) received the Robert-Wenner Prize of the Swiss Cancer League in recognition of their leading research on new treatment strategies. The prize of 210,000 Swiss Francs was awarded in the castle Ebenrain in Sissach/BL on 31 January 1991 (Schweizer Illustrierte, February 4, 1991).

Growth and Autonomy

1992–2000 Alex N. Eberle

Professor Alex N. Eberle, a biochemist and molecular biologist trained at the ETH in Zurich and the MRC Laboratory of Molecular Biology in Cambridge, England, joined the DF in 1982 to head the Laboratory of Endocrinology and to help building up a modern infrastructure for molecular and cellular biomedical research at the DF. As deputy chairman from 1986, he succeeded Prof. F.R. Bühler as chairman for three and a half years, was again deputy chairman and visiting professor in California and then served for another three years as chairman from 1997–2000. During the 1990s, the DF experienced a marked growth in personnel, infrastructure and autonomy.

When the DF's second phase ended prematurely with Prof. Fritz R. Bühler accepting a prestigious position in pharmaceutical industry in 1991, the deputy chairman – taking over half of the head's responsibilities in the autumn of 1991 and the other half in spring 1992 while maintaining his own duties – was expected to continue the new course of the DF and at the same time paving the way for new developments. A number of projects at the DF had just been started, e.g. the establishment of the European Master in Clinical Research (EMCR), a one-year practical and theoretical training course preparing medical doctors for PhD; other practical block courses held at the DF, e.g. in molecular biology; the introduction of new rules for radiosafety, biosafety and animal experimentation, based on new federal laws; the broadening of the DF infrastructure, e.g. the purchase of large instruments and the establishment of informatics; continued fund raising and many more. All this was continued with great effort, except for fund raising at the departmental level, which appeared an important asset for the search committee



Prof. Alex N. Eberle, third and fifth chairman of the DF

itself when it tried to nominate a well-known successor to the chair of pathophysiology. Therefore, the new acting chairman guided the DF through a smooth transition from the second

phase with its external activity and visibility to the third phase characterized by internal growth and more autonomy.

Internal Growth

Internal growth and broadening of the experimental competence was the most important priority for the DF at the beginning of the 1990s when numerous new techniques originating from cellular and molecular biology and analytical biochemistry were introduced to biomedical science. Not only was it necessary to obtain new apparatus, the continued training and further education of the staff, intensified exchange and internal collaborations as well as the recruitment of promising young lab heads were the most important factors for the DF to fulfil its role as a first-class research platform for the different clinics of a university hospital with their diverse needs and expectations. By offering the different research groups an optimized structure and well-working services for efficient experimentation, they could increase their productivity and hence generate more funds. Broadening of this type of fund raising at the DF indeed was very successful, and over the years, this development was gradually matched by the additional support of the Kantonsspital and the Health Department, despite the economically «difficult» times. The measures taken for internal growth were manifold:

- First, the DF needed more transparency in the decision making and participation at all levels. The conferences of research group leaders and of the DF staff served as platform of discussion and participation in the planning process. An apparatus planning committee was installed with representation of all laboratories in order to achieve a consensus with respect to spending investment money.
- Second, as different federal laws were newly implemented, the DF needed new safety and laboratory rules: a bilingual folder (German/English) explaining and regulating all necessary details was published (*Betriebsreglement*), unique and exemplary for academic institutions. Regular instruction courses in the different areas complemented these efforts.
- Third, the «culture» of collaboration amongst individuals and between laboratories, including reducing boundaries between labs, using general equipment in the proper way, taking over small departmental duties, helping out scientifically and socially, was further encouraged and improved. Through an efficient management at the personal/social and the technical levels the «association» of laboratories was gradually transformed into the «federation» of today's DF.



EMCR course 1992: Students from Strasbourg, Freiburg i.Br. and Basel attending the first EUCOR Master in Clinical Research (EMCR) course during practical training at the DF in November 1992.

- Gradually, the central services provided by the DF were expanded to different new areas, e.g. to informatics support, cell analysis and sorting, confocal microscopy, peptide synthesis and analysis. Novel cell and molecular biology methods were introduced and the technical staff further educated in special technical training courses. Finally, purchases in specific sectors were centralized for reasons of fast and cheaper availability of biological reagents and other material, leaving however much freedom to the research teams.
- The number of postdocs and PhD students at the DF increased steadily to 57 and, respectively, 46 in the year 2000, along with this the number of publications and their impact.
- Through persistent negotiations, five new research professorships could be generated (Catherine Nissen, Regine Landmann, Gennaro De Libero and Georg Holländer) or integrated (Urs Eppenberger) in the DF.
- The budgets for investment and running costs could almost be duplicated in the period from 1992 to 2000. The distribution of the running costs to the different labs followed clear and transparent rules.
- Regular supervision by the Curatorium and the External Advisory Board were an important factor for the control of the DF's head and the DF as a whole.

continued on p. 52

A New Structure for the DF

1995–1997 Werner Stauffacher

Professor Werner Stauffacher, head of the Department of Internal Medicine of the University Hospital from 1976–95 and member of the DF Curatorium since 1978, joined the DF as chairman in 1995 to implement a new structure compatible with the reforms at the University Hospital. His wide network through his many responsibilities, e.g. as former Vice President of the Swiss National Science Foundation's Research Council and later President of the Swiss Medical Academy, was decisive for the future direction of the DF, in particular for the early steps in establishing «molecular medicine» at the DF.

In 1993, the Hospital Board entrusted a commission consisting of mainly KBS members of the medical, nursing and administrative sectors and some external advisors with an extensive analysis of the organizational structure of the Kantonsspital which resulted in the Nabholz report («Nabholz-Bericht») in 1994. This report suggested various improvements for a future organization of the KBS, the three most relevant being (1) to increase the degree of organization of the KBS as a whole, (2) to give the nursing sector more weight in decision-making at the hospital-level, and (3) to delegate as much power as necessary to the newly formed «super»-departments (Bereiche). At the beginning of 1995, several variants for merging different clinics/institutes/departments were discussed, and finally seven areas (Bereiche) were chosen, one each for internal medicine, the surgical disciplines, the women's hospital, the smaller clinics, the diagnostic and medical service departments, the technical and supporting services and finally, the Department of Research. It was fortunate that research kept its independence in this structure.



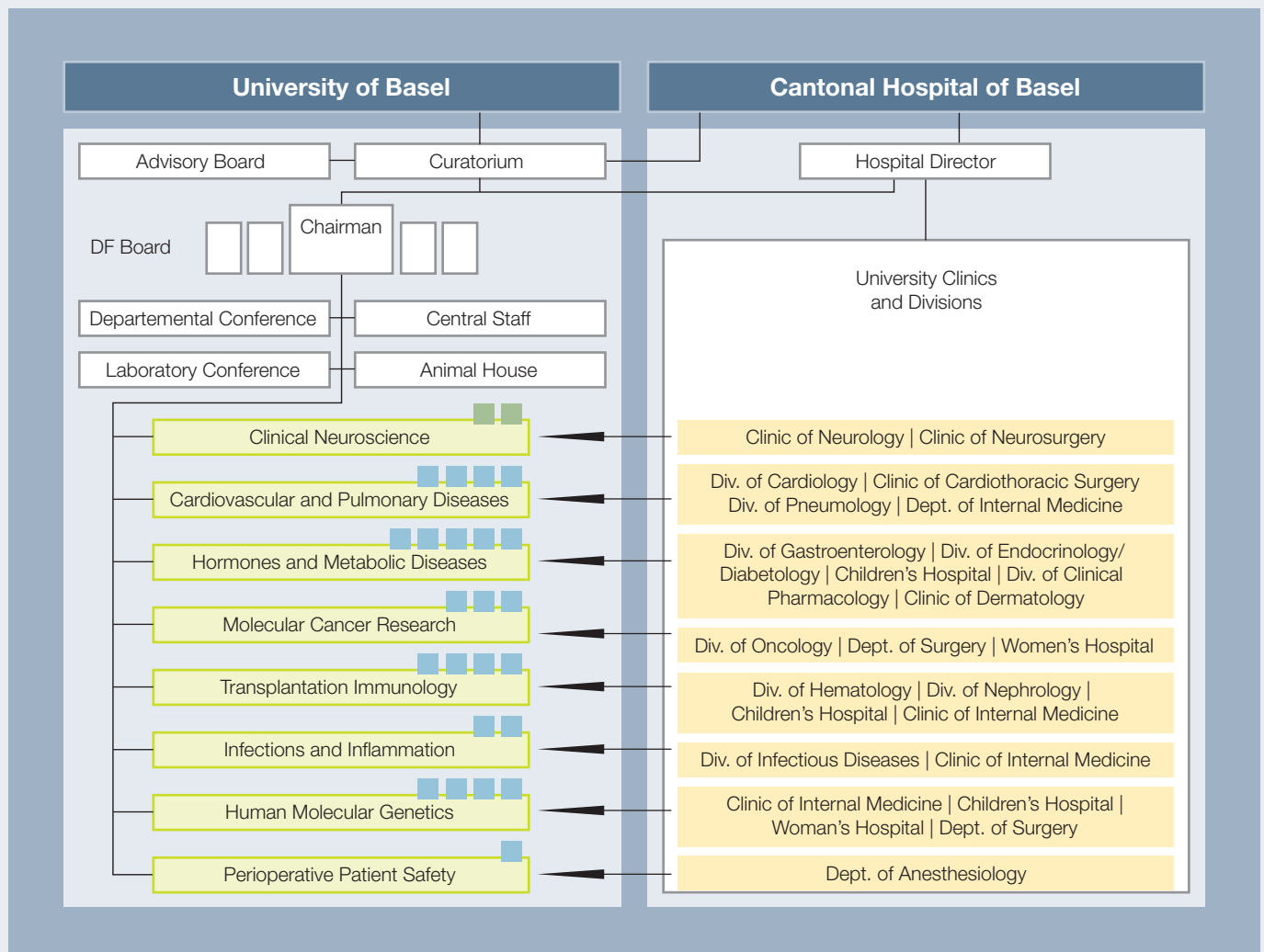
Prof. Werner Stauffacher, fourth chairman of the DF

A new DF Statute that had to consider a certain degree of democracy and rotation of board members was worked out and approved by the higher authorities. It defined the composition of the departmental board with a chairman, a deputy chairman, an administrator for personnel and finance, and a representative of the research group leaders and of the technical staff. The

supporting staff of the board was kept relatively small (secretary, technical assistant, informatics supporter). The departmental conference (Bereichskonferenz) played the role of a «parliament». The chairman was elected jointly by the Health Department and the University Council. The Laboratory Conference included all members of the DF and was called in 2–3 times each year. The DF Statute also defined the categories of research groups, originating from the different university clinics and other hospitals. The Curatorium of the DF with its nine members from the Medical and Science Faculties, the Kantonsspital, from other hospitals, and (one) from industry acted as the supervisory board which was elected jointly by the Health Department and the University Council. The Curatorium elected an external Advisory Board which comprised 16 professors from Swiss and foreign universities; it met in 1998 and 1999 when it carried out site visits from which a very valuable and detailed report originated in 1999. In

the year 2000, when the DF became part of the DKBW, both the Curatorium and the Advisory Board discontinued their activities.

Adaptations to the DF structure were made in 1997 when the research teams were grouped into focal areas (Schwerpunkte) and again at the end of the year 2000 when the departmental board was reduced to chairman and deputy chairman, with all staff functions (i.e. head of personnel, finance, organization and security, service assistance, informatics support, and secretaries) integrated into an enlarged and permanent staff. With this organization the DF was better equipped to fulfill the many different requirements imposed on it by new rules and legislations and to play its part in the newly formed DKBW. At the same time, the research teams of the DF were regrouped into the four newly defined focal areas of the DKBW (see present DF structure on page 12).



New organigram of the DF in 1997. The DF Board consisted of five persons: Prof. Alex N. Eberle (chairman, Prof. Regine Landmann (deputy chair person), Andrea Künnell (head of personnel and finances), Prof. Christoph Beglinger (representative of the research group leaders), Monika Hermle (representative of the technical staff). The Curatorium was headed by Prof. Felix Harder and the Advisory Board by Prof. Hubert Blum (Freiburg i.Br.). The Schwerpunkte (focal areas; yellow) were coordinated by research group leaders.



The DF staff on an autumn hiking tour to the Feldberg (Germany).

- The grouping of the 24 research teams into eight focal divisions (see below) fostered methodological collaboration and exchange, resulting in a growing number of joint projects which was another factor for the ever increasing productivity of the DF.

«Journée de Réflexion»

On August 25, 1993, the DF organized a *Journée de Réflexion*, at which – and this was unique for a department of the Kantonsspital – all categories of collaborators (research group leaders, postdocs, PhD students, technicians) and the different boards (Curatorium, Advisory Board, former DF chairmen, the Hospital Board) first discussed within their group and then brought the essence to the attention of everybody in a plenary assembly, mainly addressing the future structure of the DF and its organisation, research topics, collaboration and aspects from the social and employee's side. The ensuing report about this event served the Cantonal Health Department to fix specific guidelines for the future structure of the administration of the DF.

A New Structure

When Prof. Alex N. Eberle started his sabbatical leave in the winter of 1995, he was succeeded as chairman by Prof. Werner Stauffacher who – as head of the Department of Internal Medicine – had been a member of the DF Curatorium right from its beginning. He arrived at the DF at the time when the Kantonsspital began to regroup its clinics, institutes and departments by forming seven «super»-departments (*Bereiche*), all of which obtaining greater autonomy and responsibility in the management of finances, positions and internal affairs. Although the



DF was the smallest of these departments, it was probably the most complex to lead, as it had to meet the requirements of the «*unité de doctrine*» with respect to legal rules, the distribution of its resources (space, money and staff) and the flexibility needed to guarantee as much freedom to the research groups that received their scientific input from their clinics and were, in part, directed by clinic and division heads. Very experienced in managing a large medical department and with a chairman status of an independent «commissioner», Prof. Werner Stauffacher worked out the new DF structure (see inset on p. 50/51) and the DF bylaws, in close collaboration with a small team of research group leaders, staff members and administrative specialists. After another type of «*Journée de réflexion*» held in Muttensz in 1996, the first proposal for the introduction of focal areas was added (see figure in the inset). Altogether, with this new structure, the DF gained more autonomy in administering its positions and finances: whereas until the mid-1990s it was virtually impossible to convert a position from one category into another (e.g. hiring a scientist instead of a technician), the number of the (missing) scientist's positions could now be increased and some badly needed positions for the service and management staff of the DF formed.

From Pathophysiology to Molecular Medicine

Between 1992 and 1998, two attempts to find a successor for Prof. Fritz R. Bühler to the chair of pathophysiology had failed and in the meantime, the organization of teaching the pathophysiology courses as well as the research area favoured for this chair had changed. Molecular medicine was the new discipline that received considerable attention by the end of the

1990s, because the focus of this discipline is the understanding of health and disease at the cellular and molecular level and the use of this information for the design of new approaches for the diagnosis, treatment and prevention of disease. As molecular medicine is based on very modern methodologies such as gene therapy, DNA-based testing, novel vaccine design, genetically modified animal models for specific diseases, proteomics and advanced techniques of structural analyses at the molecular and cellular level, a well-known expert was sought and found in the person of Prof. Radek Skoda who finally joined the DF at the beginning of 2002. The excellent state of equipment and the multifaceted ongoing research of the DF, much of it in close vicinity to molecular medicine, certainly helped to integrate his and other new groups active in this new discipline.

The long duration of this recruitment had the negative consequence for the DF Fund, established in 1990, that it was not continued by the industrial donators: in the meantime, the founders were all retired and the sponsoring preferences of pharmaceutical industry changed insofar that now the most attractive projects of individual groups within an institution were

supported, rather than the institution as a whole. This reduced the chairman's possibilities to set priorities. Nevertheless, along with the increasing productivity of the DF, the total of sponsor and grant income by all research groups reached as much as eight million Swiss Francs in the year 2000.

The DF Celebrates 20 Years

In September 1998, the DF celebrated its 20th anniversary. This occasion was marked with a three-day event *Medical Research at the Turn of the 21st Century* and a big party: (1) The «local politics», i.e. members of government and parliaments of Basel-Stadt and Baselland, the president and rector of the University, the director of the Kantonsspital, the former DF chairmen, the DF Curatorium and Advisory Board, well over 400 members, of the University and Hospital as well as interested colleagues from Switzerland and abroad attended a short presentation of the DF, followed by lectures on the impact of medical research on clinical science and more generally on science politics at the turn of the 21st century. The president of the government of Basel, *Regierungspräsidentin* Veronica Schaller, finally demonstrated

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Neues Forschungszentrum im Medizin-Bereich

Die Universität Basel, das Sanitätsdepartement des Kantons Basel-Stadt und das Universitäts-Kinderspital beider Basel haben gestern einen Vertrag zur Bildung eines neuen «Departements Klinisch-Biologische Wissenschaften» abgeschlossen.



how much a small canton like Basel can do to support flourishing research centers and where its limitations lie. A lively apéro opened the door for new concepts (see below). (2) A scientific symposium with invited and in-house speakers was held the following day, with the DF Curatorium and Advisory Board present; this gave an excellent overview on the state of the different projects pursued at DF. (3) Finally, on the third day of the event, the DF opened its doors to the general public who came in large numbers to listen to the latest news from clinical frontiers, presented by experienced clinicians, and to study posters and attend demonstrations in the laboratories. The DF received a lot of attention in the local newspapers during these days. Needless to say how much the big party that followed the time-consuming preparations by the DF members was appreciated by them.

A Novel Concept of Integrating Medical Research and Teaching

Towards the end of the 1990s, almost all professors of the pre-clinical institutes of the Medical Faculty were about to retire and a new generation had to be appointed to take over the responsibilities for preclinical teaching and research. In view of the relatively small size of the preclinical institutes and in the attempt to assemble the whole laboratory-based research of the Medical Faculty «under one umbrella», the DF chairman proposed, publicly for the first time in his address on the occasion of the 20 years DF event, that one large department be formed containing about eight to ten different teaching units, each of which would have a specific research focus and consist of several research groups. Such a department would represent the experimental medicine section of the University and link basic biosciences of the Biocenter and Pharmacenter with bedside research of the University clinics. The idea was first dismissed by Regierungspräsidentin V. Schaller, but later taken up again, and together with the President of the University Council, Dr. Rolf Soiron, the head of Pathology, Prof. M. Mihatsch and the DF chairman, she worked out a first concept. Numerous negotiations at all levels took place, until in spring 2000 a contract between the University of Basel, the University Hospital Basel and the University Children's Hospital (*UKBB*) was signed, to start an experimental phase for a such a «super»-department, now called *Department of Clinical and Biological Sciences (DKWB)*, that contained only 3-4 focal research areas. Teaching was organized separately, because of a major reform of the study programs that was started at about the same time.

After almost 15 years in charge of management of the DF as deputy chairman and chairman, it was time for Alex N. Eberle to entrust the management duties into the hand of the next generation whose task it would be to build up the new department and plan the new site for the DKWB next to the Biocenter and Pharmacenter. As at the end of 2000, the new professor had not yet arrived at the DF, Prof. Regine Landmann and Prof. Jürg Schifferli took over the chair of the DF for one and a half years.

DF on the Move

2000–2002 Regine Landmann

Professor Regine Landmann joined the DF in 1978, was a research group leader in the Laboratory of Infectious Diseases since 1996 and elected deputy chairwoman of the DF in 1997. She succeeded Prof. A.N. Eberle in 2000 to become the first chairwoman of the DF, which she headed jointly with Prof. Jürg Schifferli, clinical head in internal medicine, whose task it was to take over strategic responsibilities in the newly formed Department of Clinical and Biological Sciences (DKBW) of the Medical Faculty. During the time of their joint chairs, the DF was formally integrated into the DKBW, received additional research laboratories for new teams and experienced a substantial growth.

The takeover of the DF chair by Jürg Schifferli and me in October 2000 was shortly after the founding of the DKBW. For the first time the DF was integrated in a larger university structure, together with the preclinical institutes of Biochemistry, Physiology, Anatomy and Microbiology. The previously active Curatorium of the DF was replaced by the DKBW Council and the rights and duties of the DF were fixed by two authorities, on the one hand the DKBW Board and Council – of which Jürg Schifferli was a member – and on the other hand the board of the Kantonsspital where I took a seat. The aim of the new DKBW was, and remains, the integration of the DF into the University. By the end of the year 2000, the DKBW Board had defined 4 major fields of research – immunology, oncology/genetics, cell plasticity/tissue repair and neurosciences – into which the research themes of the majority of groups could be accommodated. Thus, the foundation for improved communication and more project links between the various groups was laid. This restructuring process began during the time of our chairmanship and was marked by newly

appointed professors as heads of the Biochemistry, Physiology and Anatomy institutes. In addition, Ton Rolink was selected for the Professorship in Immunology sponsored by Roche.

New Space and New Research Group Leaders

The foundation of the DKBW also allowed us to relieve the long-standing space problem in the DF. The DKBW was allotted lab and office space in the Pharmacenter and in the Vesalianum. Thus the start of our chairmanship was also marked by the relocation of several laboratories. The groups working in neurobiology found room in the Pharmacenter, next to the Biocenter where the focus of the Basel Neuroscience is located. The groups of cardiovascular and human genetics moved to the Vesalianum, the same building where in spring 2001 the newly elected Professor of Biochemistry was placed. As a consequence, space in the DF became free for those groups who had until then worked under extremely narrow conditions (about 6 m² per person): Pediatric Immunology, Experimental Immunology, Hepato-Gastroenterology and Pneumology could spread out. It was our aim to group laboratories with related interests close to one another. We reached this aim within a year. This was made possible in part by the generous decision of the Hospital Board to allow us the use of our budget for laboratory reconstruction rather than machines.

Jürg Schifferli and I were chosen to head the DF, paving the way for the future until the Professor for Molecular Medicine was formally elected. By the end of 2000 it became clear that Radek Skoda, at that time research group leader at the Deutsche Krebsforschungszentrum Heidelberg, was the most promising candidate for the Professorship for Molecular Medicine. We in-

cluded in our planning space for the group of Radek Skoda and thus an extension of the Experimental Hematology lab. During this planning phase it became clear that the Basel Institute of Immunology would close its doors by the end of 2001. We were very interested in bringing at least one of the excellent immunologists to the DF. Therefore, under the leadership of Prof. Klaus Gyr, who succeeded to interest Novartis Pharma in financing a 5-year professorship, the DF was able to bring Ed Palmer and his group to the DF. In order to accommodate this group we had to find additional space. With the help of the secretary of the Health Department of Basel-Stadt, it was possible to obtain space, which had previously been used by the Laboratory School on the 4th floor of the ZLF building. It was therefore possible during the period of relocating labs, to prepare the laboratory for Ed Palmer for his start in October 2001.

Jürg and I had ideas for all of these changes, but they wouldn't have been possible without the help of our excellent staff. Monika Hermle with her gift of organization was irreplaceable. Armin Bieri was ready to help with all of the moves and with connecting new computers at any time of day or night. His cooperative attitude was very much appreciated by everyone in the DF. We are also thankful to Heidi Hoyer mann, our head of human resources who not only kept track of all changes of personnel but also let the collaborators feel secure and gave out advice when needed. Finally our controller, Hans Schreiber, kept track of all our expenses in an efficient and simple way.

The Focal Areas of the Research at the DF

The time of our chairmanship can be characterized by «on the move». The reorganization of many laboratories brought dynamic and the feeling of a new start for many groups. The number of employees in our department increased by 56 persons. Apparently the changes of room and people in the DF formed a good ground for a quantitative and qualitative increase of our activities in the four major research fields:

- Research in Immunology concentrated on the function of $\gamma\delta$ T cells, antigen recognition by CD1 molecules, thymus development, endothelial-specific cytotoxic T lymphocytes and Jak-Stat signal transduction. Inflammation research focused on complement inhibitors and Toll-like receptors of the natural immune system.
- Oncology/Genetics was concerned with genetic changes in colon carcinoma, blood tumors of platelets and erythrocytes, growth factors in bone marrow, and the function of natural kill-



Prof. Regine Landmann, sixth chairperson of the DF

er cells in defense against cancer. In addition the relevance of tumor markers in the prognosis of breast cancer has been investigated and confirmed in a large number of patients. The geneticists were also interested in fat metabolism and carried out extensive investigations in affected families to elucidate risk factors. Surgical research concentrated on immunotherapy of melanoma with tumor antigen and co-stimulatory molecules.

- Tissue Repair and Cell Plasticity included groups that worked in the cardio-pulmonary-vascular field. Matrix structures in the lungs, as well as vascular cell adhesion molecules such as T-cadherin or signal transduction molecules such as mTOR were investigated. Research in cardiology and cardiac surgery was concerned with molecular changes and magnetic resonance spectrometry in rhythm disturbances, and with ischemic heart failure. Surgical research also investigated new growth and regeneration in cartilage. The group of Prenatal Medicine of the University Women's Hospital, whose research focused on the importance of fetal DNA in human blood in pre-eclampsia and in prenatal diagnostics, was also included in this field. Finally,

the OMEN group (obesity-metabolism-nutrition) comprising the teams of clinical pharmacology, endocrinology, gastroenterology, metabolism, and part of the pharmacology of the Biocenter, jointly concentrated on the regulation of body weight and energy metabolism.

- The groups Neurobiology specialized in the pathogenesis of multiple sclerosis (MS). They investigated the function of myelin proteins in mouse models and carried out microarray gene analyses on brain tissue from people who had died of MS. In neurosurgery, an ischemia model in rats was used to evaluate novel therapeutic approaches for stroke.



Prof. Jürg Schifferli, the sixth co-chairman of the DF

The research of Anesthesiology in the DF concentrating on the syndrome of malignant hyperthermia was not included in any of the special fields. It was however strongly supported by the DF since the distribution of the resources followed qualitative criteria.

The DFacts

Research activities in the DF have been published in a quarterly cycle since October 2000, using the newly created «DFacts». With the DFacts we were able to create a PR outlet for the research publications of the DF. Each edition contained the title pages of new publications from the DF and a longer report on

one special research subject. Upcoming activities, non-research activities of members of the DF and new collaborators introduced with photos were also included. DFacts was distributed to a wide audience including the officials of the cantonal administration, the University, professors with a special link to the DF, clinicians in the University Hospital and other hospitals of Basel and every member of the DF. It soon became clear that everyone wanted space for his or her publications in DFacts. The realization of such a journal requires editing and journalistic skills, which was successfully carried out by Heidi Hoyermann. Verena Jäggin was responsible for a highly professional layout.

At the close of a 1½ year chairmanship, Jürg Schifferli and I felt that we had laid the foundations to allow the new Professor of Molecular Medicine a good start with which to lead the DF to further scientific success. The period was often marked by hectic, but it also stimulated many colleagues as new ideas were developed and realized in a non-conventional pragmatic and direct way. It was fun, but it was also good to hand this task to a younger colleague with great scientific and organizational visions and to be able to look quietly into the future of the DF.



Number one of the newly established DF-magazine, DFacts.

From Present to Future

Since 2002 Radek Skoda



Prof. Radek Skoda, the seventh chairman of the DF

Professor Radek Skoda is chairman of the DF since 2002. He obtained his M.D. degree from the University of Zurich Medical School and trained in internal medicine and hematology at the University Hospital Basel, joined the Department of Genetics at Harvard Medical School, Boston, as a postdoctoral fellow between 1989 and 1993, returned to Basel as a group leader at the Biozentrum with a SCORE career development award from the Swiss Na-

tional Science Foundation, was head of the Division «Molecular Hematology/Oncology» at the German Cancer Research Center (DKFZ) in Heidelberg from 2000-2002 and has been appointed Professor of Molecular Medicine at the University of Basel in 2002.

During the 1990's, while I completed my clinical training in the Division of Hematology of the Kantonsspital and established my research as a group leader at the Biozentrum in Basel, I observed the DF from a distance. During this time the DF expanded with an influx of young scientists and new group leaders. I always envied the ideal location of the laboratories within the hospital campus. Since I was interested in applying basic research methodology to solve clinical problems, the DF seemed to be the ideal place for it. When I was appointed to the DF in 2002, I realized how well my predecessors had organized the department to become an institute that provides an excellent environment for competitive bio-medical research. I found a highly competent staff of management assistants who organize everyday work from maintenance and repair of the equipment to animal care and administration. Two staff members, Heidi Hoyermann and Verena Jäggin, in their spare time, write, compose and publish the Dfacts newsletter, which appears three times per year and is tremendously popular. The DF has grown to an organization of more than 320 people. Remarkably, two thirds of the financing relies on soft money, more than at any other research institute of the University of Basel. In a recently performed portfolio analysis by the Faculty of Medicine of the University of Basel, the DF received top scores. The clinicians endorse the concept of the DF and some of them cite the DF as being one of the reasons why they came to Basel. Most of the research groups at the DF



DKBW-Project-Seminar

Speaker: **Bernhard Bettler**
Molecular Neurobiology, Inst. Physiology

Title: **"Genetic dissection of GABA-B receptor physiology"**

Date: **Tuesday, 11th November 2003**

Time: **12:30 –13:30 h**

Place: **Seminar Room 313**
Zentrum für Lehre und Forschung (ZLF),
Hebelstrasse 20 (3rd floor), Kantonsspital Basel

The traditional project seminars of the DF were extended to the new platform DKBW-Project-Seminar.

are headed by clinicians. However, the DF has also a growing number of group leaders who work as full time scientists without clinical obligations. In increasing numbers, the clinical research groups are run by a «tandem» team consisting of a clinician and a full time scientist. I consider this a model for the future for the DF, since both sides can profit from each other to identify important clinical problems and find ways to their solution.

New Achievements

During the first two years of my tenure I focused on facilitating the communication and interaction between the research groups. We held two retreats where the DF group leaders presented their current research and their plans for the future. Diversity is one of the hallmarks of the DF, which can be a burden but also an asset. In some areas of research, a critical mass of scientists working on related problems is emerging, e.g. in immunology, which has become one of the strong points of the DF, but also in oncology-hematology and stem cell research. DF-Groups working in the field of neuroscience profit from their interactions with

the Basel Neuroscience Program, which unites research groups from the Biozentrum, the Friedrich Miescher Institute and the DKBW. An important step to improve communication was to integrate groups from the basic science institutes of the DKBW into our regular weekly Project-Seminars. Thereby, a new platform was created that helps promoting the exchange of ideas between clinicians and basic scientists. The number of graduate students, working on their PhD theses at the DF, has steadily increased over the years. Many of them have received their undergraduate training at the Biozentrum. To reward highly motivated students and postdocs, a new DF-prize has been awarded each year starting 2003 to the first author of the best DF-publication, which is selected by a committee of three outside experts.

The second focus of my activities was to participate in defining the future place of the DF within the DKBW and the University. The DKBW unites all experimental research of the Faculty of Medicine within one department. The idea behind the DKBW was to increase our critical mass and add flexibility that could allow us to adjust to the rapid changes in bio-medical research and to create a center of excellence with an international reputation. The DKBW should build a bridge between the basic science institutes and the clinical units. The DKBW was founded in 2000 and was foreseen to evolve in three steps: the first step was to create a political platform with a centralized board. Being part of the DKBW has helped the DF acquire new laboratory space, a constant problem for us. DF research groups, in particular those working in the field of neurobiology, have been accommodated in the Pharmacenter, a research building of the university. Conversely, a new professor in cardiac physiology, Marijke Brink, was appointed as the head of the cardiology research at the DF. The second step, planned for 2007, will be to combine the financial resources of the DKBW institutes, the DF and the research laboratories of the Children's Hospital. The third step, projected for the next decade, will be to unite all DKBW research laboratories in one location. This will involve the construction of a large new research building. In preparation for the upcoming second step, which involves creating a new structure and leadership and the transfer of the DF and UKBB finances from the hospital to the university, several retreats were held between key representatives of the three organizations. A new board with a stronger representation of the clinical units will take over by the end of 2005.

The ties between the DF and the University are not limited to the DKBW. Together with the Biozentrum, the DF and the DKBW have established important new core facilities, such as the

«Transgenic Mouse Core Facility» for generating knockout and transgenic mice and the «Life Sciences Training Facility», which allows DF researchers to perform gene expression microarray experiments using the Affymetrix platform. The University Computing Center (URZ) headed by Prof. Fritz Rösler provides the internet and email access for the DF and has recently established a server for our data storage. The IT support of the DF collaborates with the team of the Biocenter-Pharmacenter-IT group (BioPhIT) headed by Roger Jenni. Nanotechnology, which in some aspects was pioneered in the Department of Physics at Basel University, is being integrated into life-sciences projects. Finally, the new ETH institute for systems biology in Basel will undoubtedly bring further impulses and push the limits.

Outlook

One of the challenges for the future will be how to improve research in times of stagnant or shrinking budgets. It is clear that the government support alone will not be sufficient for keeping pace with the rapid developments in the life sciences sector. Sponsors and private donations will undoubtedly become a more important factor in Europe and Switzerland. A generous donation by the Gertrude von Meissner Foundation made it possible to appoint Jürg Schwaller as the new professor in childhood leukemia, further strengthening leukemia and cancer research at the DF. We hope to attract similar donations in the future.

Reorganization and movement is important, but science also needs a quiet corner, where new ideas can develop. When people in the hallways and during coffee breaks discuss science and not politics, I know we are on the right track. We should not forget that providing the environment for creative science is essential, but scientific progress cannot always be planned. Real innovation often comes from areas that were not expected to provide breakthroughs. Research is a fascinating enterprise, because an unexpected breakthrough in one field can change the research in a large number of disciplines. We have to be prepared to meet these opportunities and challenges in the future.

Publications

Publications

27 Representative Articles 1978–2005

Between 1978 and 2005, the research groups of the DF contributed a total of 2444 original publications and numerous review articles as well as book chapters. Also, several DF members authored and/or edited books and conference proceedings. In this period, the average impact of the publications from the DF was steadily rising, which was a key factor for the greater «visibility» and recognition of the DF achieved at the national and international level over the last twenty seven years. The scientific output of the DF also played an important role for the reputation

of the University Clinics of the University Hospital as a place of excellence. In the following, twenty seven representative publications were chosen which had been published between 1979 and 2005. For each year (except for 1988/1992), one paper was selected whose experimental part was entirely or primarily done at the DF and whose authors were members of the DF. Many more papers of equivalent or similar quality could not be considered; they are all listed in the biannual scientific reports of the DF.

Histochemistry

63, 245–251, 1979

Quantitative Distribution of Lysosomal Hydrolases in the Rat Nephron

M. Le Hir, U.C. Dubach and U. Schmidt

Abstract: The activities of N-acetyl- β ,D-glucosaminidase (NAG, EC 3.2.1.30), β , D-galactosidase (β -gal, EC 3.2.1.23) and acid phosphatase (ac-Pase, EC 3.1.3.2) were measured in the glomeruli, five segments of the proximal and four segments of the distal tubule of normal male Wistar rats. The activities of NAG and β -gal are 3- to 5-fold higher in the first part of the proximal tubule than in other segments and very low in glomeruli. We

propose that the distribution of these two glycosidases reflects the contribution of the different tubular segments to the reabsorption of glycoproteins. The maximal activity of ac-Pase was found in the straight part of the proximal tubule. It was only 1.5-fold higher than in the distal tubule. Moreover, the activity in glomeruli is rather high. We conclude that ac-Pase is not primarily involved in the handling of reabsorbed molecules.

Peripheral Blood Cells from Patients with Aplastic Anaemia in Partial Remission Suppress Growth of Their Own Bone Marrow Precursors in Culture

Catherine Nissen, Pierre Cornu, Alois Gratwohl and Bruno Speck

Abstract: In 12 patients with severe aplastic anaemia who had achieved self-sustaining autologous bone marrow function after treatment with antilymphocyte globulin, or with cyclophosphamide given for attempted bone marrow transplantation, colony formation by all haemopoietic precursors remained far below normal. Precursors from peripheral blood, erythroid precursors in particular, failed to form a normal number of colonies. This paucity of colony formation does not reflect a true lack of precursor cells but is due to circulating cells which impair maturation. Addition of low density peripheral blood cells to autologous bone marrow cultures diminished colony formation by granulocyte-macrophage precursors (GM-CFC) and abolished «burst» formation by BFU-E. Strong auto-inhibition preceded relapse in four of eight patients. The phenomenon was not observed in five

normals, in five aplastic anaemia patients with stable haemopoietic grafts and in three polytransfused control patients. The T-cell poor subpopulation of peripheral blood cells, containing mainly B-cells and macrophages, was especially inhibitory. Accordingly, removal of plastic adherent cells from bone marrow cell suspensions improved plating efficiency in aplastic anaemia patients, but not in normals. Isolated E-rosette positive cells had no negative effect. Inhibition could only be demonstrated in the autologous situation. Colony formation by normal allogeneic peripheral blood precursors was not impaired by patient cells. The phenomenon is likely to reflect residual disease activity which is compensated *in vivo* but can be demonstrated *in vitro*. It may be of help in early recognition of patients who are at risk of relapse after autologous bone marrow reconstitution.

The Release of Pancreatic Polypeptide by CCK-Octapeptide and Some Analogues in the Dog

F. D. Meyer, K. Gyr, W. H. Häcki, C. Beglinger, L. Jeker, L. Varga, L. Kayasseh, D. Gillessen and G. A. Stalder

Abstract: In dogs with gastric and pancreatic Thomas fistulas the effect of different cholecystokinin-like peptides upon pancreatic polypeptide (PP) release was studied in three ways: (a) Plasma PP concentrations were determined by radioimmunoassay in response to 135 pmol/kg/h of the synthetic C-terminal octapeptide of cholecystokinin (CCK-OP) (A), of three of its analogues (B, C, D) where methionine has been replaced by methoxinine, and in response to 45 pmol/kg/h of caerulein. The greatest rise in plasma PP concentration expressed as Δ PP was achieved with caerulein (327 ± 37 pM), when taking into account the threefold smaller dose used, followed by CCK-OP (536 ± 67 pM) and analogues B (343 ± 51 pM), C (87 ± 46 pM), and D (32 ± 15 pM). The order of potency with respect to stimulation of exocrine pancreatic secretion was the same: E and A precede B, C, and D. Δ PP correlated linearly with the pancreatic

protein output ($r = 0.98$, $P < 0.01$). (b) CCK-OP was infused in four doses of 35, 70, 135, and 270 pmol/kg/h, and plasma PP concentrations and exocrine pancreatic secretion were monitored. The correlation between pancreatic protein output and Δ PP was very close ($r = 0.98$, $P < 0.01$). (c) Atropine sulfate (0.1 mg/kg, i. v.) reduced the PP response to the 135 pmol/kg/h dose of CCK-OP by 61%. We conclude from this that CCK-OP and related peptides do release PP and that their effect on exocrine pancreatic secretion is closely correlated with their PP-releasing capacity. The PP release may therefore be used as an indicator of the CCK-like activity of CCK fragments and analogues. CCK-OP may well represent one of the humoral stimulatory factors contributing to the release of PP, but this action appears to depend on a cholinergic background.

Diabetes

31, 630–633, 1982

Quantitation of Glycosylated Hemoglobin

Elimination of Labile Glycohemoglobin During Sample Hemolysis at pH 5

Emanuel Bissé, Willi Berger and Rudolf Flückiger

Abstract: A simple method for the elimination of labile glycohemoglobin in the chromatographic quantitation of glycosylated hemoglobin is described. Use is made of the instability of Schiff base adducts in acidic solution. Erythrocytes are lysed with a pH 5 buffer. At this pH dissociation reaches completion during sample preparation.

Science

221, 564–566, 1983

The Immune Response Evokes Changes in Brain Noradrenergic Neurons

Hugo Besedovsky, Adriana Del Rey, Ernst Sorkin, Mose Da Prada, Roland Burri and Conrad Honegger

Abstract: A decreased noradrenaline turnover in the hypothalamus of rats was observed at the peak of the immune response to sheep red blood cells. The decrease in noradrenergic neuronal activity was mimicked by injection of soluble mediators released by immunological cells activated in vitro. Noradrenaline also ten-

ded to decrease in the brainstem but not in the residual brain. It is suggested that products released from activated immunological cells during the immune response may induce the previously described autonomic and endocrine mechanisms that contribute to immunoregulation.

The New England Journal of Medicine

310, 1084–1088, 1984

Correlation of Platelet Calcium with Blood Pressure

Effect of Antihypertensive Therapy

Paul Erne, Peter Bolli, Ernst Bürgisser and Fritz Bühler

Abstract: Intracellular free calcium has been implicated in vascular smooth-muscle contraction and in the pathophysiology of essential hypertension. We studied free calcium levels in blood platelets, which have many features in common with vascular smooth-muscle cells. With use of an intracellularly trapped fluorescent dye, the free calcium concentration in platelets was found to be elevated in 9 patients with borderline hypertension and 45 patients with established essential hypertension, who were compared with 38 normotensive subjects. There was a close correlation between the free calcium level and both sys-

tolic and diastolic blood pressure ($n = 92$; $r = 0.883$ for systolic pressure and 0.931 for diastolic pressure; $P < 0.001$ for both). Antihypertensive treatment with calcium entry blockers ($n = 15$), beta-adrenoceptor blockers ($n = 12$), or a diuretic ($n = 6$) resulted in a reduction in free calcium, and this correlated with the fall in blood pressure ($P < 0.001$). The intracellular free calcium concentration in platelets may be determined by the same humoral or pharmacologic factors that determine the height of blood pressure.

Journal of Clinical Investigation

75, 1471–1476, 1985

Pancreatic Enzyme Response to a Liquid Meal

and to Hormonal Stimulation

Correlation with Plasma Secretin and Cholecystokinin Levels

Christoph Beglinger, Michael Fried, Ian Whitehouse, Jan B. Jansen, Cornelis B. Lamers and Klaus Gyr

Abstract: Pancreatic trypsin output and plasma secretin and cholecystokinin (CCK) levels were measured in five healthy volunteers to investigate the mechanisms involved in regulating postprandial pancreatic secretion. The pancreas was stimulated by a liquid test meal or by either intravenous secretin ($1\text{--}82\text{ pmol/kg per h}$) or caerulein, a CCK analogue ($2.3\text{--}37\text{ pmol/kg per h}$), or by a combination of secretin and caerulein. Pancreatic secretion was assessed by a marker perfusion technique (polyethylene glycol [PEG 4000]), plasma secretin, and CCK by specific radioimmunoassays. Increasing doses of secretin produced increasing bicarbonate output ($P < 0.01$), whereas trypsin was not stimulated over basal. Graded caerulein produced a stepwise increase in trypsin and bicarbonate output ($P < 0.01$). Potentiation occurred for bicarbonate secretion between secretin and

caerulein, but not for trypsin output. Postprandial trypsin secretion averaged 29.1 IU/min over 150 min (equal to 55% of maximal response to caerulein). The peak trypsin response amounted to 90% of maximal caerulein. Significant increases of plasma secretin ($P < 0.05$) and CCK ($P < 0.01$) were observed after the meal. Comparison of enzyme and CCK responses to the test-meal or to exogenous caerulein suggested that the amount of CCK released after the meal could account for the postprandial trypsin secretion. We conclude that (a) the postprandial enzyme response in man is submaximal in comparison to maximal exogenous hormone stimulation; (b) CCK is a major stimulatory mechanism of postprandial trypsin secretion, whereas secretin is not involved; and (c) potentiation of enzyme secretion is not a regulatory mechanism of the postprandial secretory response.

The New England Journal of Medicine

315, 533–537, 1986

Atrial Natriuretic Peptide and Atrial Pressure in Patients with Congestive Heart Failure

Anthony E.G. Raine, Paul Erne, Ernst Bürgisser, Franco B. Müller, Peter Bolli, Felix Burkart and Fritz R. Bühler

Abstract: To define the relation between atrial pressures and the release of atrial natriuretic peptide, we measured plasma concentrations of the peptide in 26 patients with cardiac disease – 11 with normal atrial pressures and 15 with elevated atrial pressures (11 of these 15 had elevated pressures in both atria). Mean peptide levels (\pm SEM) in the peripheral venous blood were increased in the 11 patients with cardiac disease and normal atrial pressures, as compared with 60 healthy controls (48 ± 14 vs. 17 ± 2 pmol per liter). In the patients with elevated atrial pressures, peptide concentrations were increased twofold in peripheral venous, right atrial, pulmonary arterial, and systemic arterial plasma, as compared with the concentrations in the patients with normal atrial pressures. A step-up in peptide concentration was seen between the venous and right atrial

plasma ($P < 0.002$) and between the pulmonary and systemic arterial plasma ($P < 0.01$), suggesting release of the peptide from the atria. A linear relation was found between right atrial pressure and right atrial peptide concentration ($r = 0.835$, $P < 0.001$) and between pulmonary wedge pressure and the systemic arterial peptide concentration ($r = 0.866$, $P < 0.001$). Right atrial pressure and the peptide concentration both increased with exercise testing in the nine patients evaluated. We conclude that the release of atrial natriuretic peptide is at least partly regulated by right and left atrial pressures. Distinguishing the relative contributions of the two atria and defining the role of peptide release in the pathogenesis of heart failure will require further investigation.

Proc. Natl. Acad. Sci. USA (PNAS)

84, 1277–1281, 1987

Altered Protein Kinase C in a Mast Cell Variant Defective in Exocytosis

Nachman Mazurek, Romano Regazzi, Christopher Borner, Rudolf Wyss, Jean-François Conscience, Paul Erne, Urs Eppenberger and Dorian Fabbro

Abstract: The murine mast cell line PB-3c is dependent on interleukin 3 (IL-3) with respect to survival and proliferation. These cells also require IL-3 to display antigen-mediated serotonin release, which is coupled to a transient increase of cytosolic free calcium ($[Ca^{2+}]_i$). The antigen-mediated exocytosis is inhibited by phorbol 12-tetradecanoate-13-acetate (PTA), an activator of phospholipid/ Ca^{2+} -sensitive protein kinase. In contrast, the malignant mast cell variant PB-1 is IL-3 independent with respect to proliferation but is unable to undergo antigen-mediated exocytosis. Yet this cell line exhibits basal levels of $[Ca^{2+}]_i$, serotonin content, and numbers of IgE receptors comparable to those of PB-3c cells. Subcellular distribution studies revealed that the specific activity of cytosolic protein kinase C of PB-1 cells was only 40% of that found in PB-3c cells. Furthermore,

the PB-1 cells showed a significantly higher specific activity of membrane-bound protein kinase C than PB-3c cells. Scatchard plot analysis of $[^3H]$ -phorbol-12,13-dibutyrate binding to intact PB-1 cells demonstrated the presence of 20% high-affinity ($K_d = 6$ nM) and 80% low-affinity ($K_d = 60$ nM) phorbol ester receptors, whereas PB-3c cells displayed only the low-affinity phorbol ester binding. Immunological characterization of protein kinase C from both cell lines revealed the presence of a normal 77-kDa protein kinase C holoenzyme in both cell lines. In addition, a 72-kDa protein kinase C-related protein band was found mainly in the membrane fraction of the PB-1 variant. It is suggested that this altered and membrane-bound form of protein kinase C may be involved in the blockage of the antigen-mediated exocytosis of PB-1 cells.

Nature

334, 703–705, 1988

Calcium Channels in Thrombin-Activated Human Platelet Membrane

A. Zschauer, C. van Breemen, F. R. Bühler and M. T. Nelson

Abstract: Platelet-activating factor, 5-hydroxytryptamine, thromboxane A_2 , adenosine diphosphate and thrombin are known to activate platelets by stimulating calcium entry, but the nature of the entry pathways is unknown. We present the identification of single divalent cation channels from thrombin-activated human platelets. Membrane vesicles from unstimulated and thrombin-stimulated human platelets were incorporated in planar bilayers and unitary currents through single channels were measured. Divalent cation selective channels could only be demonstra-

ted in thrombin-stimulated preparations. These channels share a number of properties in common with voltage-dependent calcium channels: a high degree of selectivity for divalent cations, a single channel conductance of about 10 pS (in 150 mM Ba^{2+}) and sensitivity to blockade by inorganic calcium channel blockers such as Ni^{2+} . In other respects, these channels are different as they are not voltage-dependent and are not blocked by 1,4-dihydropyridine calcium channel antagonists.

The New England Journal of Medicine

319, 462–467, 1988

Difference Between Endothelium-Dependent Relaxation in Arterial and in Venous Coronary Bypass Grafts

Thomas F. Lüscher, Dennis Diederich, Robert Siebenmann, Kurt Lehmann, Peter Stulz, Ludwig von Segesser, Zhihong Yang, Marko Turina, Erich Grädel, Erika Weber and Fritz Bühler

Abstract: Both the internal mammary artery and the saphenous vein are used to construct coronary-artery bypass grafts. We hypothesized that the release or production of endothelium-derived relaxing factor, which regulates blood flow and inhibits platelet function, may differ in venous and arterial grafts. We therefore studied endothelium-dependent relaxation in internal mammary arteries, internal mammary veins, and saphenous veins obtained from 58 patients undergoing coronary bypass surgery. Vascular rings with and without endothelium were suspended in organ chambers, and isometric tension was recorded. Acetylcholine (10^{-8} to 10^{-4} M), thrombin (1 U per milliliter), and adenosine diphosphate (10^{-7} to 10^{-4} M) evoked potent endothelium-dependent relaxation in the mammary artery but weak response in the saphenous vein ($P < 0.005$; $n = 6$ to 27). In the mammary artery,

relaxation was greatest in response to acetylcholine (86 ± 4 percent reduction in norepinephrine-induced tension), followed by thrombin (44 ± 7 percent) and adenosine diphosphate (39 ± 8 percent). In the saphenous and mammary veins, relaxation was less than 25 percent. Relaxation was unaffected by indomethacin but was inhibited by methylene blue and hemoglobin ($P < 0.005$ and 0.01, respectively), which suggests that endothelium-derived relaxing factor was the mediator. Endothelium-independent relaxation in response to sodium nitroprusside was similar in arteries and veins. We conclude that endothelium-dependent relaxation is greater in the mammary artery than in the saphenous vein. The possibility that this contributes to the higher patency rate among arterial grafts than among venous grafts will require further study.

Characterization of Receptors for α -Melanocyte-stimulating Hormone on Human Melanoma Cells

Walter Siegrist, Flavio Solca, Sibylla Stutz, Laura Giuffrè, Stefan Carrel, Jürg Girard and Alex N. Eberle

Abstract: Receptors for α -melanocyte-stimulating hormone (α -MSH) on human malignant melanoma cell lines were investigated with a specific binding assay and characterized with structural analogues of α -MSH and adrenocorticotrophic hormone and by photoaffinity cross-linking of the hormone-receptor complex. Specific binding of high-performance liquid chromatography-purified, monoiodinated α -MSH in the presence of 1 mM 1,10-phenanthroline as protease inhibitor was highest after a 2-h incubation at 37°C. The nonspecific binding was <20% and dissociation of the ligand-receptor complex was relatively slow. Ten out of 12 human cell lines showed specific binding sites for α -MSH with K_D values ranging from 0.195 to 2.87 nM and the sites/cell being ~400 to ~1600. Virtually identical results were obtained in an as-

say where the cells remained attached to the culture dishes during the entire experiment. The study of hormone analogues with the D10 cell line showed that oxidized α -MSH had an ~40-fold lower affinity than α -MSH whereas [Nle⁴,D-Phe⁷]- α -MSH displayed a threefold and the adrenocorticotrophic hormone fragments (1–17) and (1–24) a 20- and 8-fold higher affinity. Cross-linking of the α -MSH-receptor complex of three cell lines using monoiodinated [Nle⁴,D-Phe⁷, Trp(2-nitro-4-azidophenylsulfenyl)⁹]- α -MSH as photo-affinity label revealed a major M_r 45,000 protein band on sodium dodecyl sulfate-polyacrylamide gels, analogous to the MSH receptor of mouse B16 melanoma cells.

Release of Endothelin from the Porcine Aorta Inhibition by Endothelium-derived Nitric Oxide

Chantal Boulanger and Thomas F. Lüscher

Abstract: This study was designed to examine whether endothelin is released from the intima of intact arteries, and whether endothelium-derived nitric oxide regulates its production. Endothelin was detected in the incubating medium of unstimulated pig aortae with, but not in those without endothelium. In preparations with endothelium, thrombin (2–6 U/ml) and the calcium ionophore A23187 (10^{-6} M) stimulated the release of the peptide. The basal and thrombin-stimulated production of endothelin were prevented by the protein synthetase inhibitor cycloheximide (10^{-6} M). The production of endothelin upon stimulation

with thrombin (4 U/ml) was potentiated by L-N^G-monomethyl arginine and methylene blue and reduced by superoxide dismutase and 8-bromo cyclic guanosine 5'-mono-phosphate (GMP), while the basal release of the peptide was unaffected. Thus, (a) endothelin is released from the intimal layer of intact blood vessels, both under basal conditions and after stimulation with thrombin and the calcium ionophore A23187, and (b) endothelium-derived nitric oxide released during stimulation with thrombin inhibits the production of the peptide via a cyclic GMP-dependent pathway.

Proc. Natl. Acad. Sci. USA (PNAS)

88, 1888–1892, 1991

Expressions of the Low Density Lipoprotein Receptor and 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Genes are Stimulated by Recombinant Platelet-Derived Growth Factor Isomers

Michael Roth, Lyman R. Emmons, André Perruchoud and Lutz H. Block

Abstract: The plausible role that platelet-derived growth factor (PDGF) has in the localized pathophysiological changes that occur in the arterial wall during development of atherosclerotic lesions led us to investigate the influence of recombinant (r)PDGF isomers -AA, -AB, and -BB on the expression of low density lipoprotein receptor (LDL-R) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [(S-mevalonate:NAD⁺ oxidoreductase (CoA-acylating), EC 1.1.1.88] genes. In addition, we clarified the role of protein kinase C (PKC) in expression of the two genes in human skin fibroblasts and vascular smooth

muscle cells. The various rPDGF isoforms are distinct in their ability to activate transcription of both genes: (i) Both rPDGF-AA and -BB stimulate transcription of the LDL-R gene; in contrast, rPDGF-BB, but not -AA, activates transcription of the HMG-CoA reductase gene. (ii) All recombinant isoforms of PDGF activate transcription of the *c-fos* gene. (iii) While rPDGF-dependent transcription of the LDL-R gene occurs independently of PKC, transcription of the HMG-CoA reductase gene appears to involve the action of that enzyme.

Journal of Clinical Investigation

92, 1903–1909, 1993

Comparison of the Effects of Recombinant Human Insulin-like Growth Factor-I and Insulin on Glucose and Leucine Kinetics in Humans

Roland Laager, Ronald Ninnis and Ulrich Keller

Abstract: To compare the metabolic effects of elevated plasma concentrations of IGF-I and insulin, overnight-fasted normal subjects were studied twice, once receiving IGF-I and once insulin at doses that resulted in identical increases in glucose uptake during 8-h euglycemic clamping. Recombinant human IGF-I or insulin were infused in one group at high doses (30 $\mu\text{g/kg}$ per h IGF-I or 0.23 nmol/kg per h insulin) and in another group at low doses (5 $\mu\text{g/kg}$ per h IGF-I or 0.04 nmol/kg per h insulin). Glucose rate of disappearance (measured by [6,6- D_2]-glucose infusions) increased from baseline by $239 \pm 16\%$ during high dose IGF-I vs $197 \pm 18\%$ during insulin ($P = 0.021$ vs IGF-I). Hepatic glucose production decreased by $37 \pm 6\%$ during high dose IGF-I vs $89 \pm 13\%$ during insulin ($P = 0.0028$ vs IGF-I). IGF-I suppressed whole body leucine flux ([1- ^{13}C]-leucine infusion technique) more than insulin (42 ± 4 vs $32 \pm 3\%$ during high

doses, $P = 0.0082$). Leucine oxidation rate decreased during high dose IGF-I more than during insulin (55 ± 4 vs $32 \pm 6\%$, $P = 0.0001$). The decreases of plasma concentrations of free fatty acids, acetoacetate, and β -hydroxybutyrate after 8 h of IGF-I and insulin administration were similar. Plasma C-peptide levels decreased by $57 \pm 4\%$ during high doses of IGF-I vs $36 \pm 6\%$ during insulin ($P = 0.005$ vs IGF-I). The present data demonstrate that, compared to insulin, an acute increase in plasma IGF-I levels results in preferential enhancement of peripheral glucose utilization, diminished suppression of hepatic glucose production, augmented decrease of whole body protein breakdown (leucine flux), and of irreversible leucine catabolism but in similar antilipolytic effects. The data suggest that insulin-like effects of IGF-I in humans are mediated in part via IGF-I receptors and in part via insulin receptors.

Characterization of Angiotensin II Receptors in Cultured Adult Rat Cardiac Fibroblasts

Coupling to Signaling Systems and Gene Expression

Maryse Crabos, Michael Roth, Alfred W. A. Hahn and Paul Erne

Abstract: Cardiac hypertrophy is largely due to cardiac fibroblast growth and increased synthesis of extracellular matrix. This study has investigated the contribution of the vasoactive hormone, angiotensin II, toward this hypertrophic process. We have demonstrated that cultures of adult rat cardiac fibroblasts express AT₁ but not AT₂ receptors for angiotensin II. The ability of angiotensin II to stimulate phosphoinositide catabolism and to elevate intracellular calcium concentrations in these cells was blocked by losartan, a specific AT₁ receptor antagonist, but not by the AT₂ receptor antagonist CGP 42112. Exposure of adult cardiac fibroblasts to angiotensin II resulted in the induction of

several growth-related metabolic events including *c-fos* protooncogene expression and increased synthesis of DNA, RNA, and protein. Angiotensin II was also found to induce collagen type I, $\alpha 1$ chain transcript expression in cardiac fibroblasts as well as the synthesis and secretion of collagen by these cells. The data demonstrate that angiotensin II, via AT₁ receptors, can stimulate cardiac fibroblast growth and increase collagen synthesis in cardiac tissue. Thus, angiotensin II may contribute toward the development of cardiac hypertrophy in conditions of hypertension that are associated with elevated concentrations of angiotensin II.

Identification and Intracellular Location of MAGE-3 Gene Product

Thomas Kocher, Elke Schultz-Thater, Fred Gudat, Christoph Schaefer, Giulia Casorati, Antonio Juretic, Thomas Willmann, Felix Har-der, Michael Heberer and Giulio C. Spagnoli

Abstract: The human *MAGE-3* gene encodes a melanoma antigenic epitope recognized by specific cytotoxic T lymphocytes, but its gene product has not been identified thus far. We produced a recombinant MAGE-3 gene product by expression cloning of the entire reading frame in the context of a fusion protein characterized by a 10-histidine tail, allowing purification by metal chelation on a nickel Sepharose column. The semipurified product was used to generate MAGE-3-specific monoclonal

antibodies. One reagent could identify by immunoblotting the native MAGE-3 gene product as *M_r* 48,000 protein in lysates of cell lines showing evidence of *MAGE-3* gene expression. No apparent cross-reactivity with recombinant or native MAGE-1 gene product was observed. Immunohistochemistry shows that, closely resembling the MAGE-1 gene product, MAGE-3 is a cytoplasmic protein.

Flt3 Ligand Level Reflects Hematopoietic Progenitor Cell Function in Aplastic Anemia and Chemotherapy-Induced Bone Marrow Aplasia

Aleksandra Wodnar-Filipowicz, Stewart D. Lyman, Alois Gratwohl, André Tichelli, Bruno Speck and Catherine Nissen

Abstract: Flt3 ligand (flt3L) is a member of a small family of cytokines acting as tyrosine kinase receptor ligands that stimulate the proliferation of primitive hematopoietic progenitors in vitro. To gain insight into the physiological role of flt3L in early hematopoiesis, levels of flt3L were determined in serum of patients with multilineage bone marrow failure and related to the severity of stem cell depletion. In patients with aplastic anemia (AA) and in cancer patients with chemotherapy-induced transient suppression of hematopoiesis, flt3L fluctuated in an inverse relationship to the degree of bone marrow failure. In severe AA at diagnosis, levels of circulating soluble flt3L were highly elevated ($2,653 \pm 353$ pg/mL) as compared with normal blood serum values of 14 ± 39 pg/mL. Flt3L returned to near normal levels within the first 3 months following successful bone marrow transplantation and in autologous remission induced by immunosuppressive therapy with antilymphocyte globulin (ALG; 100 ± 31 and 183 ± 14 pg/

mL, respectively). In contrast, rejection of the graft or relapse of the disease after ALG was accompanied by an increase to high pretreatment concentrations of the circulating cytokine ($3,770 \pm 2,485$ and $1,788 \pm 233$ pg/mL, respectively). Flt3L in serum inversely correlated with the colony-forming ability of AA bone marrow precursors in vitro ($R = -.86$), indicating that the concentration of the ligand reflects hematopoiesis at the progenitor cell level. Flt3L increased to 2,500 pg/mL in the serum of leukemia patients during chemoradiotherapy-induced bone marrow suppression and returned to normal values along with hematopoietic recovery. Expression of the membrane-bound form of flt3L was significantly elevated in mononuclear bone marrow and peripheral blood cells from patients with severe pancytopenia, suggesting de novo synthesis of the factor in response to bone marrow failure. The data provide a strong argument for the involvement of flt3L in the regulation of early hematopoiesis in vivo.

Functional Inactivation in the Whole Population of Human V γ 9/V δ 2 T Lymphocytes Induced By a Nonpeptidic Antagonist

Martin R. Bürk, Ilaria Carena, Alena Donda, Francesca Mariani, Lucia Mori and Gennaro De Libero

Abstract: Nonpeptidic compounds stimulate human T cells bearing the TCR- $\gamma\delta$ in the absence of major histocompatibility complex restriction. We report that one of these ligands, 2,3-diphosphoglyceric acid (DPG), which induces expansion of V γ 9/V δ T cells ex vivo, antagonizes the same cell population after repetitive activation. Stimulation with DPG results in partial early protein tyrosine phosphorylation and a prolonged, but reversi-

ble, state of unresponsiveness to agonist ligands in V γ 9/V δ 2, but not in other T cells. These findings show that TCR antagonism is a general phenomenon of T cells. However, in contrast to the clonal specificity of altered peptides antagonizing $\alpha\beta$ T cells, all the tested V γ 9/V δ 2 polyclonal cell lines and clones become unresponsive, a fact that may be relevant for the regulation of their response in vivo.

Monoallelic Expression of the Interleukin-2 Locus

Georg A. Holländer, Saulius Zuklys, Corinne Morel, Emiko Mizoguchi, Kathrine Mobisson, Stephen Simpson, Cox Terhorst, William Wishart, David E. Golan, Atul K. Bhan and Steven J. Burakoff

Abstract: The lymphokine interleukin-2 (IL-2) is responsible for autocrine cell cycle progression and regulation of immune responses. Uncontrolled secretion of IL-2 results in adverse reactions ranging from anergy, to aberrant T cell activation, to autoimmunity. With the use of fluorescent in situ hybridization and single-cell polymerase chain reaction in cells with different

IL-2 alleles, IL-2 expression in mature thymocytes and T cells was found to be tightly controlled by monoallelic expression. Because IL-2 is encoded at a nonimprinted autosomal locus, this result represents an unusual regulatory mode for controlling the precise expression of a single gene.

Ectosomes Released by Human Neutrophils Are Specialized Functional Units

Christoph Hess, Salima Sadallah, Andreas Hefti, Regine Landmann and Jürg Alfred Schifferli

Abstract: Here we show that human polymorphonuclear leukocytes (PMN) release ectosomes independently of complement attack during their activation both in vitro and at the site of inflammation in vivo. Patterns of biotinylated proteins on the surface of PMN and on PMN-derived ectosomes indicated a specific sorting of cell surface proteins into and out of ectosomes. Ectosomes expressed clusters of complement receptor 1 (CR1), which allowed them to bind efficiently to opsonized bacteria. Myeloperoxidase and human leukocyte elastase, both stored within the azurophilic granules of PMN, were found to colocalize on ectosomes with CR1. Furthermore, myeloperoxida-

se colocalized with human leukocyte elastase. In contrast, not present on CR1-expressing ectosomes were CD63, a selective marker for the azurophilic granules, and CD14, which is located within the same granules and the secretory vesicles as CR1. Of the other complement regulatory proteins expressed by PMN, only CD59 colocalized with CR1, while CD55 and CD46 were almost absent. Ectosomes released by activated PMN at the site of inflammation may function as a well organized element (ecto-organelle), designed to focus antimicrobial activity onto opsonized surfaces.

Immunity

13, 255–264, 2000

The $\alpha\beta$ T Cell Response to Self-Glycolipids Shows a Novel Mechanism of CD1b Loading and a Requirement for Complex Oligosaccharides

Abdijapar Shamshiev, Alena Donda, Theodore I. Prigozy, Lucia Mori, Vanna Chigorno, Chris A. Benedict, Ludwig Kappos, Sandro Sonnino, Mitchell Kronenberg and Gennaro de Libero

Abstract: The structural basis for the T cell recognition of lipoglycans remains to be elucidated. We have described autoreactive T cells responsive to GM1 ganglioside presented by CD1b. We show that glycosphingolipids bind to CD1b on the cell surface at neutral pH and are recognized without internalization or processing. Furthermore, soluble GM1–CD1b complexes stimulate specific T cells. Oligosaccharide groups containing five or

more sugars are required to build a minimal epitope for TCR recognition. This suggests a mechanism for T cell recognition of glycosphingolipids in which much of the CD1b-bound ligand is exposed. Binding to CD1b is a highly reversible process and other ceramide-containing glycosphingolipids displace GM1. These nonantigenic compounds act as blockers and may prevent harmful autoreactivity in vivo.

Gastroenterology

120, 361–368, 2001

Blockade of GRP Receptors Inhibits Gastric Emptying and Gallbladder Contraction but Accelerates Small Intestinal Transit

Lukas P. Degen, Fuping Peng, Annette Collet, Livio Rossi, Silvia Ketterer, Yolanda Serrano, Finn Larsen, Christoph Beglinger and Pius Hildebrand

Abstract: *Background & Aims:* This study was designed to characterize [D-F₅Phe⁶, D-Ala¹¹]Bn(6-13)OMe (BIM26226) as a gastrin-releasing peptide (GRP)-preferring bombesin receptor antagonist and to determine whether GRP physiologically regulates gastrointestinal motility. Intravenous BIM26226 (5–500 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) inhibits GRP-induced gallbladder contraction and plasma cholecystokinin (CCK) release in a dose-dependent fashion. *Methods:* Gastric emptying and small bowel transit of a solid meal were quantified using scintigraphy. Meal-stimulated gallbladder contraction was measured by sonography in a 2-period crossover design. *Results:* Intravenous BIM26226 potently inhibited gastric lag time (114 ± 7 vs. 41 ± 6 minutes [control])

and gastric emptying rate ($0.11 \pm 0.02\%/ \text{min}$ vs. $0.26 \pm 0.04\%/ \text{min}$ [control]), whereas concomitant infusion of BIM26226 accelerated small bowel transit time (153 ± 41 vs. 262 ± 20 minutes [control]). A continuous liquid meal perfusion into the duodenum induced complete gallbladder contraction ($t_{50\%}$, 35 ± 4 minutes), which BIM26226 inhibited significantly ($t_{50\%}$, 64 ± 8 minutes). BIM26226 did not alter plasma CCK response, indicating that circulating CCK did not mediate these effects. *Conclusions:* These data show that BIM26226 is a potent antagonist of exogenous and endogenous GRP and suggest that GRP is a major physiologic regulator of gastric emptying, small bowel transit, and gallbladder contraction.

Nature Immunology

3, 1102–1108, 2002

Wnt Glycoproteins Regulate the Expression of FoxN1, the Gene Defective in Nude Mice

Gina Balciunaite, Marcel P. Keller, Egle Balciunaite, Luca Piali, Saulius Zuklys, Yves D. Mathieu, Jason Gill, Richard Boyd, Daniel J. Sussman and Georg A. Holländer

Abstract: T cell development and selection require the fully mature and diverse epithelial microenvironment of the thymus. Acquisition of these characteristics is dependent on expression of the forkhead (also known as winged-helix) transcription factor FoxN1, as a lack of functional FoxN1 results in aberrant epithelial morphogenesis and an inability to attract lymphoid precursors

to the thymus primordium. However, the transcriptional control of Foxn1 expression has not been elucidated. Here we report that secreted Wnt glycoproteins, expressed by thymic epithelial cells and thymocytes, regulate epithelial Foxn1 expression in both autocrine and paracrine fashions. Wnt molecules therefore provide regulatory signals critical for thymic function.

The Journal of Experimental Medicine

197, 163–168, 2003

Human T Cell Receptor $\gamma\delta$ Cells Recognize Endogenous Mevalonate Metabolites in Tumor Cells

Hans-Jürgen Gober, Magdalena Kistowska, Lena Angmann, Paul Jenö, Lucia Mori and Gennaro De Libero

Abstract: T lymphocytes expressing the T cell receptor (TCR)- $\gamma\delta$ recognize unknown antigens on tumor cells. Here we identify metabolites of the mevalonate pathway as the tumor ligands that activate TCR- $\gamma\delta$ cells. In tumor cells, blockade of hydroxymethylglutaryl-CoA reductase (HMGR), the rate limiting enzyme of the mevalonate pathway, prevents both accumulation of mevalonate metabolites and recognition by TCR- $\gamma\delta$ cells. When

metabolite accumulation is induced by overexpressing HMGR or by treatment with nitrogen-containing bisphosphonate drugs, tumor cells derived from many tissues acquire the capacity to stimulate the same TCR- $\gamma\delta$ population. Accumulation of mevalonate metabolites in tumor cells is a powerful danger signal that activates the immune response and may represent a novel target of tumor immunotherapy.

T Cell Division and Death Are Segregated by Mutation of TCR β Chain Constant Domains

Emma Teixeira, Mark A. Daniels, Barbara Hausmann, Adam G. Schrum, Dieter Naeher, Immanuel Luescher, Margot Thome, Rafael Bragado and Ed Palmer

Abstract: We have studied the role of the T cell receptor (TCR) β chain transmembrane and cytoplasmic domains (BTM/Cyto) in T cell signaling. Upon antigen stimulation, T lymphocytes expressing a TCR with mutant BTM and Cyto domains accumulate in large numbers and are specifically defective in undergoing activation-induced cell death (AICD). The mutant TCR poorly

recruits the protein adaptor Carma-1 and is subsequently impaired in activating NF- κ B. This signaling defect leads to a reduced expression of Fas ligand (FasL) and to a reduction in AICD. These β chain domains are involved in discriminating cell division and apoptosis.

A Gain-of-Function Mutation of JAK2 in Myeloproliferative Disorders

Robert Kralovics, Francesco Passamonti, Andreas S. Buser, Teo Soon-Siong, Ralph Thiedt, Jakob R. Passweg, André Tichelli, Mario Cazzola and Radek C. Skoda

Abstract: *Background:* Polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis are clonal myeloproliferative disorders arising from a multipotent progenitor. The loss of heterozygosity (LOH) on the short arm of chromosome 9 (9pLOH) in myeloproliferative disorders suggests that 9p harbors a mutation that contributes to the cause of clonal expansion of hematopoietic cells in these diseases. *Methods:* We performed microsatellite mapping of the 9pLOH region and DNA sequencing in 244 patients with myeloproliferative disorders (128 with polycythemia vera, 93 with essential thrombocythemia, and 23 with idiopathic myelofibrosis). *Results:* Microsatellite mapping identified a 9pLOH region that included the Janus kinase 2 (JAK2) gene. In patients with 9pLOH, JAK2 had a homozygous G \rightarrow T transversion, causing phenylalanine to be substituted for valine at position 617 of JAK2 (V617F). All 51 patients with 9pLOH had the V617F mutation. Of 193 patients

without 9pLOH, 66 were heterozygous for V617F and 127 did not have the mutation. The frequency of V617F was 65 percent among patients with polycythemia vera (83 of 128), 57 percent among patients with idiopathic myelofibrosis (13 of 23), and 23 percent among patients with essential thrombocythemia (21 of 93). V617F is a somatic mutation present in hematopoietic cells. Mitotic recombination probably causes both 9pLOH and the transition from heterozygosity to homozygosity for V617F. Genetic evidence and in vitro functional studies indicate that V617F gives hematopoietic precursors proliferative and survival advantages. Patients with the V617F mutation had a significantly longer duration of disease and a higher rate of complications (fibrosis, hemorrhage, and thrombosis) and treatment with cytoreductive therapy than patients with wild-type JAK2. *Conclusions:* A high proportion of patients with myeloproliferative disorders carry a dominant gain-of-function mutation of JAK2.



Epilogue

This portrait has introduced the reader to the current structure and the activities of the DF and aspects of its 27-year history. We have selected some of the highlights that symbolize the many years of dedication of a very motivated crew of physician scientists and their collaborators. We therefore wish to express our sincere thanks to our colleagues and collaborators – group leaders, postdocs, PhD students, technical assistants and staff members – who over the years have spent countless working hours experimenting and reflecting to generate an impressive collection of novel data and publications. We would like to extend our thanks to our former chair persons, the hospital directors, the deans of our faculty, the rectors of our university and members of the government who developed this excellent infrastructure; without financial and political support, modern biomedical research is simply not possible. Last but not least, our thanks go to the many foundations and private companies that have supported the DF with dozens of millions of Swiss francs during the last 27 years. We do hope that these pillars of the DF's success will continue to be at least as strong in the future as they have been in the past: Biomedical research is entering a new era of progress in terms of understanding the complexity of the functions and dysfunctions of the human body, and hence biomedical research will require full dedication and support for another 27 years to combat known and newly developing diseases.

The Editors

