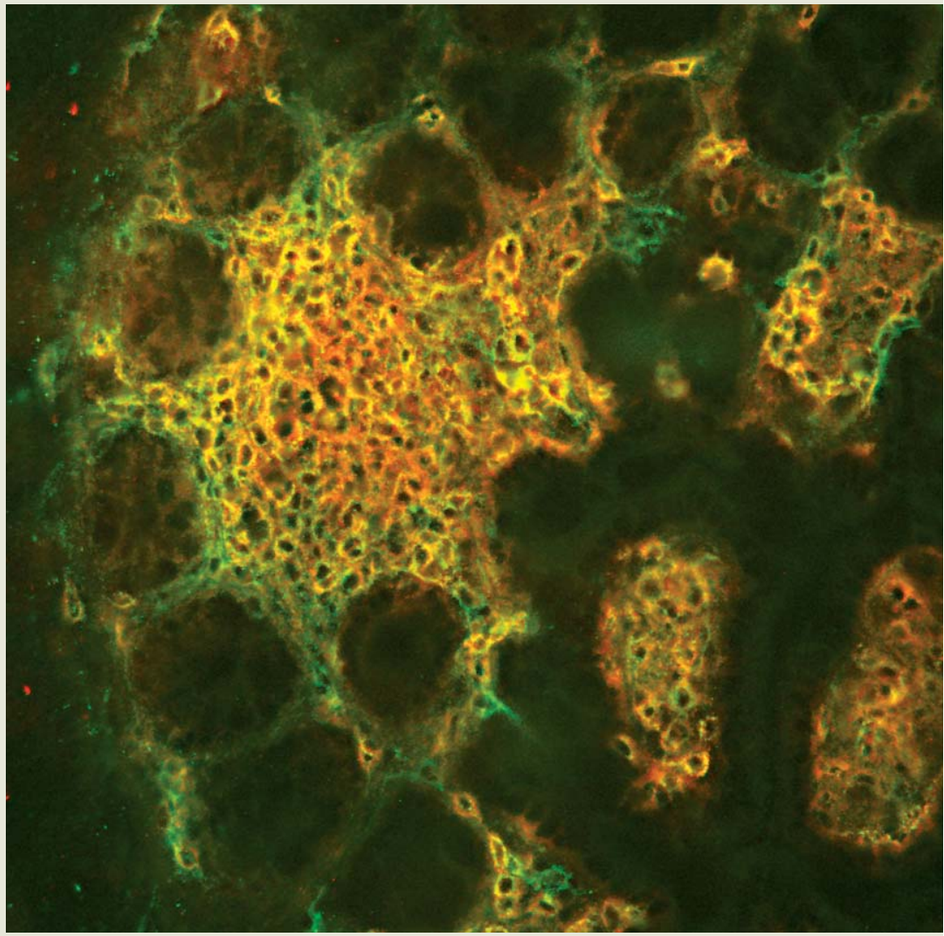
Departement
Biomedizin
Basel

DBM 2008–2010

Department of Biomedicine



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Contents

Impressum

Konzept: DBM, Advolis GmbH, Basel
Redaktion: Dr. Mark Melnyk, Manuela Bernasconi
Gestaltung: VischerVettiger, Kommunikation und Design AG, Basel
Fotos: Verena Jäggin (Gebäude, Portraits)
Druck: Isenegger AG, Möhlin

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Preface

Departement Biomedizin Basel

Ten years after its inception, the Department of Biomedicine (DBM) is well under way and flourishing. The DBM was founded in the year 2000 by the University of Basel, the University Hospital Basel, and the University Children's Hospital Basel. The idea was to create a single department that unites the entire laboratory research of the Faculty of Medicine, to abolish the barriers between the "pre-clinical" and "clinical" research units and to promote excellence in bio-medical research. To define the direction, in which future investments should be made, four key (focal) research areas have been defined: Oncology, Immunology, Neurobiology and Stem Cells/Regenerative Medicine. By providing a bridge between basic science and clinical medicine, the Department of Biomedicine is an important component in the University of Basel's strategic plan for the Life Sciences.

Key to the success of the Department of Biomedicine has been the willingness of our scientists and clinicians to communicate and to strive for excellence. Several core facilities have been established, some of them as a joint venture between our Department, the Biozentrum from the Faculty of Natural Sciences and also the D-BSSE Institute of the ETH in Basel; these provide access to key technologies, such as genomic micro-arrays, next generation sequencing and knockout mice.
The Department's research groups obtain a large proportion of their research funds from competitive grants by foundations in Switzerland, the EU and other countries. More than 60% of the members are supported by third party funds. We have a Scientific Advisory Board of eight internationally recognized experts, which visits and reviews the research activities of the DBM once a year. The recommendations of the Advisory Board provide an important basis for decisions, including promotions and changes in future directions.

This report summarizes the activities of the 57 research groups of the Department of Biomedicine during the period of 2008-2010.
The reports are grouped thematically according to the four focal areas. Each research group has selected their most relevant publications from this period and a complete list of all publication can be found in the adnex of this report (page 154).

I strongly believe that a single Department, which unites the entire laboratory research of the Faculty of Medicine provides an attractive and stimulating environment for young scientists and physicians striving for excellence in biomedical research. As this report illustrates, the DBM is well under way towards accomplishing these goals.

Prof. Dr. Radek Skoda
Head of the Department of Biomedicine

Department of Biomedicine Organization Chart 2010

HEAD OF DEPARTMENT
Prof. R. Skoda

CHIEF OPERATING OFFICER
Dr. M. Melnyk

CENTRAL SERVICES

Controlling:	G. Brunner
Human Resources:	H. Hoyermann
Departmental Assistant:	M. Bernasconi

EXECUTIVE COMMITTEE

Chair:	Prof. R. Skoda
University of Basel:	Prof. B. Bettler Prof. G. Christofori Prof. H. Hirsch Prof. R. Zeller
University Hospital:	Prof. A. Urwyler Prof. P. Itin Prof. M. Heim Prof. G. Spagnoli
Univ. Children's Hospital:	Prof. G. Holländer
Chief Operating Officer:	Dr. M. Melnyk

5 RESEARCH UNITS
Operating Managers
Organization Safety
Information Techniques
Controlling
Office
Animal Facility

RESEARCH GROUPS

FOCAL AREAS

Oncology:	Prof. G. Christofori Prof. R. Herrmann
Immunology:	Prof. A. Rolink Prof. C. Hess
Neurobiology:	Prof. B. Bettler Prof. L. Kappos
Stem Cells and Regenerative Medicine:	Prof. R. Zeller Prof. A. Gratwohl

The Department of Biomedicine is currently led by the Head of the Department Prof. Radek Skoda. The Chief Operating Officer and the staff of the Central Services support the Head of the Department in all administrative issues. Together with the Executive Committee (group of 11), the Head of the Department defines the overall strategy. The Executive Committee is composed of 4 representatives from the pre-clinical Institutes of the University, 4 representatives form the divisions of the University Hospital and one representative from the University Children's Hospital.

Key Data 2009

Research groups	57
Diagnostics services and others	4
Full professors	13
Associate professors	26
Assistant professors (Titular-, SNF-, and tenure track-assistant professors)	25
Employees total (of these 60% are paid by third-party funds)	583
Space	12'174 m²

Budget 2009

Personnel	CHF	23'573'030
Supplies		7'657'209
Income (total)		- 6'974'091
Investments (equipment)		2'317'058
Total	**CHF**	**26'573'206**
Overhead costs		11'458'311
Total	**CHF**	**38'031'517**
Third-party funds (grants etc.)	**CHF**	**21'914'584**

Department of Biomedicine
Scientific Advisory Board

Members of the Advisory Board.
From left to right: B. Löwenberg, C. Lüscher, M. Barbacid, K. Wood, G. Lemke, K.-H. Krause, D. Kioussis, P. Bianco

IMMUNOLOGY

Prof. Dimitris Kioussis
Division of Molecular Immunology,
MRC National Institute for Medical Research,
London, UK

Prof. Kathryn Wood
Nuffield Department of Surgery,
John Radcliffe Hospital, Headington,
Oxford, UK

ONCOLOGY

Prof. Mariano Barbacid
Spanish National Cancer, Research Centre Centro
Nacional de Investigaciones Oncológicas (CNIO),
Madrid, Spain.

Prof. Bob Löwenberg
Department of Hematology,
Erasmus University Medical Center,
Rotterdam, The Netherlands.

NEUROBIOLOGY

Prof. Greg Lemke
Molecular Neurobiology Laboratory,
The Salk Institute, La Jolla, USA

Prof. Christian Lüscher
Département des Neurosciences Fondamentales
& Service de Neurologie,
Centre Medical Universitaire Geneva,
Geneva, Switzerland

STEM CELLS AND REGENERATIVE MEDICINE

Prof. Paolo Bianco
Stem Cell Laboratory, Biomedical Science Park
San Raffaele and Department of Experimental Medicine
and Pathology,
La Sapienza University, Rome, Italy.

Prof. Karl-Heinz Krause
Departments of Pathology, Immunology,
and Clinical Pathology,
Faculty of Medicine and University Hospitals of Geneva,
Geneva, Switzerland.

Department of Biomedicine
Executive Committee

Prof. Dr. Radek Skoda
Head of the Department

Prof. Dr. Gerhard Christofori

Prof. Dr. Peter Itin

Prof. Dr. Bernhard Bettler

Prof. Dr. Markus Heim

Prof. Dr. Hans H. Hirsch

Prof. Dr. Giulio Spagnoli

Prof. Dr. Rolf Zeller

Prof. Dr. Georg Holländer

Prof. Dr. Albert Urwyler

Dr. Mark Melnyk

The Sites housing the Department of Biomedicine

1 **Institute of Anatomy**
Pestalozzistrasse 20, 4056 Basel

2 **Department of Biomedicine (ZLF)**
Hebelstrasse 20, 4031 Basel

3 **Pharmazentrum (7th floor)**
Klingelbergstrasse 50/70, 4056 Basel

4 **Department of Biomedicine**
Mattenstrasse 28, 4058 Basel

5 **Institute for Medical Microbiology**
Petersplatz 10, 4003 Basel

3


4

1


2


5

Research Groups of the Department of Biomedicine

grouped according to location and focal area

Department of Biomedicine
Hebelstrasse 20

- Experimental Immunology
  Prof. Gennaro De Libero
- Transplantation Immunology and Nephrology
  Prof. Ed Palmer
  Prof. Jürg Steiger
- Immunoregulation SNF-Förderprofessur
  Prof. Simona Rossi
- Immunonephrology
  Prof. Jürg A. Schifferli
- Immunobiology
  Prof. Christoph Hess
- Molecular Nephrology
  Prof. Barbara Biedermann
  Dr. Andreas Jehle
- Infection Biology
  Prof. Manuel Battegay
- Clinical Immunology
  Prof. Marten Trendelenburg
- Diabetes Research
  Prof. Marc Donath
- Immunotherapy SNF-Förderprofessur
  Prof. Martin Stern
- Psychopharmacology Research SNF SCORE
  PD Dr. Matthias Liechti
- Clinical Neuroimmunology
  Prof. Ludwig Kappos
  Prof. Raija Lindberg
- Neurobiology
  Prof. Nicole Schaeren-Wiemers
- Experimental Hematology
  Prof. Radek Skoda
- Hepatology
  Prof. Markus H. Heim
- Liver Biology SNF SCORE
  Dr. David Semela
- Pulmonary Cell Research
  Prof. Michael Roth
  Prof. Michael Tamm
- Dermatology
  Prof. Peter Itin
- Clinical Pharmacology
  Prof. Stephan Krähenbühl
- Prenatal Medicine
  Prof. Sinuhe Hahn
- Gynaecological Endocrinology
  Prof. Christian DeGeyter
- Inner Ear Research
  Prof. Daniel Bodmer
- Tissue Engineering
  Prof. Ivan Martin
  Prof. Michael Heberer
- Cell and Gene Therapy
  Dr. Andrea Banfi
  Prof. Michael Heberer
- Cardiovascular Molecular Imaging SNF SCORE
  PD Dr. Beat Kaufmannn
- Signal Transduction
  Prof. Therese J. Resink
  Prof. Paul Erne
- Ocular Pharmacology and Physiology
  Prof. Peter Meyer
- Metabolism
  Prof. Beat Müller
- Gastroenterology
  Prof. Christoph Beglinger
- Cardiobiology
  Prof. Marijke Brink
  Prof. Peter Buser
- Myocardial Research SNF SCORE
  Dr. Gabriela Kuster Pfister
- Oncology Surgery
  Prof. Giulio C. Spagnoli
  Prof. Michael Heberer
- Gynecological Oncology
  Prof. Xiao Yan Zhong
- Childhood Leukemia G. von Meissner Professur
  Prof. Jürg Schwaller
- Neuro-Oncology
  Prof. Adrian Merlo
- Medical Oncology
  Prof. Christoph Rochlitz
- Cancer Immunology SNF-Förderprofessur
  Prof. Alfred Zippelius
- Perioperative Patient Safety
  PD Dr. Susan Treves
  PD Dr. Thierry Girard

Department of Biomedicine
Mattenstrasse 28

- Tumor Biology
  Prof. Gerhard Christofori
- Molecular Genetics
  Prof. Primo Schär
- Cancer- and Immunobiology
  Prof. Matthias Wymann
- Cell migration and neuritogenesis SNF-Förderprofessur
  Prof. Olivier Pertz
- Human Genetics
  PD Dr. Karl Heinimann
- Pediatric Immunology
  Prof. Georg A. Holländer
- Developmental and Molecular Immunology
  Prof. Antonius Rolink
- Developmental Immunology DBM-Assistenzprofessur
  Prof. Daniela Finke
- Developmental Genetics
  Prof. Rolf Zeller
  Prof. Aimée Zuniga

Department of Biomedicine
Pestalozzistrasse 20

- Functional Neuroanatomy
  Prof. Cordula Nitsch
- Developmental Neurobiology and Regeneration
  Prof. Josef Kapfhammer
- Cellular Neurobiology SNF-Förderprofessur
  Prof. Suzanna Atanasoski
- Cellular Neurophysiology
  Prof. Josef Bischofberger
- Musculoskeletal Research
  Prof. Magdalena Müller-Gerbl
- Integrative Biology
  Prof. Daniel Haag

Department of Biomedicine
Klingelbergstrasse 50/70

- Molecular Neurobiology Synaptic Plasticity
  Prof. Bernhard Bettler
- Molecular Neurobiology Synapse Formation
  Prof. Hans-Rudolf Brenner
- Neuromuscular Research
  Prof. Michael Sinnreich
- Brain Tumor Biology
  Prof. Luigi Mariani

Department of Biomedicine
Petersplatz 10

- Transplantation Virology
  Prof. Hans H. Hirsch
- Molecular Diagnostics
  Prof. Thomas Klimkait

Research groups associated with DBM

- Brain Aging and Mental Health UPK Basel
  PD Dr. Anne Eckert
- Nanomedicine Research
  Prof. Patrick Hunziker
- Radiological Chemistry
  Prof. Thomas Mindt
- Rheumatology Felix Platter Spital
  Prof. Alan Tyndall

Routine Diagnostics and other Services

Institute for Medical Microbiology

- PCR/HIV Laboratory
  Prof. Hans H. Hirsch
- Serology/Virology Laboratory
  Prof. Thomas Klimkait

Institute of Anatomy

- Histology
  Prof. Konstantin Beier
- Anatomy Museum
  Prof. Magdalena Müller-Gerbl

Legend:

- Focal Area Neurobiology
- Focal Area Sem Cells and Regenerative Medicine
- Focal Area Oncology
- Focal Area Immunology
- Associated Research-Groups
- Specialities
- Services

Newly Appointed Professors 2008–2010

Prof. Dr. Josef Bischofberger, born 1965 in Saulgau, Germany, studied physics at the University of Tübingen and Göttingen. In 1995 he did his PhD at the Institute of Physiology in Göttingen working on dendritic calcium signaling in olfactory bulb mitral cells. After a short postdoctoral fellowship in Göttingen he moved to the University of Freiburg, working on synaptic transmission and neuronal calcium signaling. In 2004 he did his habilitation in physiology and started as a group leader at the University of Freiburg. In 2009 he was appointed Professor for Physiology at the Department of Biomedicine in Basel where he is working on adult neurogenesis and synaptic transmission in the hippocampus.

PD Dr. Beat Kaufmann, born 1971 in Basel, Switzerland, studied medicine at the University of Basel and the Universidad Complutense of Madrid Spain, and graduated in 1997. He completed his clinical training between 1997 and 2005 in internal medicine and cardiology. Between 2005 and 2007 he was a postdoctoral fellow at the Oregon Health and Sciences University, Portland, USA: Upon his return to the University of Basel he obtained a SCORE grant from the Swiss National Science Foundation and joined the department of biomedicine in 2009. His work focuses on ultrasound molecular imaging of early inflammatory processes in animal models of atherosclerosis.

Prof. Dr. Luigi Mariani, born 1964 in Zürich, grown up in Lugano (Ticino, Switzerland), graduated from Medical School at the University of Lausanne in 1989. He achieved the Board Certification in Neurosurgery in 1998 in Bern and was appointed as chairman of Neurosurgery in Basel in September 2008. He studied the molecular markers and genetic determinants of neoplastic invasion in patients with neuroepithelial brain tumors (gliomas) during a doctoral 1992-3 (University Hospital Zürich, Prof. Kleihues) and a postdoctoral fellowship 2001-2 (Barrow Neurological Institute, Phoenix Arizona, Prof. Berens). This is also the focus of his research group Brain Tumor Biology at the Pharmazentrum since mid 2009.

Prof. Dr. Simona Rossi Girard, born in 1976 in Lugano, Switzerland, studied biochemistry and molecular biology at the University of Basel where she also obtained her PhD in 2003. Between 2004 and 2007 she worked as postdoctoral fellow at the University of Birmingham (UK) studying the development of thymic epithelial cells. In 2007 she joined the laboratory of Transplantation Immunology at the Department Biomedicine where she started working on the role of stroma cells in establishing and maintaining tolerance after solid organ transplantation. Since 2008 she holds a Swiss National Science Foundation professorship.

Dr. David Semela, born 1972 in St. Gallen, Switzerland, studied medicine at the Universities of Fribourg and Berne, where he graduated in 1998. He completed clinical training in Internal Medicine (Berne) and in Gastroenterology (Basel) and graduated in the MD PhD program at the University of Berne and at Mayo Clinic, Rochester, USA. In 2009, he obtained a SCORE grant from the Swiss National Science Foundation and joined the Dept of Biomedicine in Basel. His work focuses on the molecular mechanisms of vascular remodeling in chronic liver disease and liver cancer, specifically the role of Notch signaling in liver sinusoidal endothelial cells.

Prof. Dr. Michael Sinnreich studied Medicine and Biology II in Basel, and did his PhD work at the Friedrich Miescher Institute. He completed his residency training in Neurology at the University Hospital of Basel and Geneva, and went subsequently for fellowships in neuromuscular diseases to the Mayo Clinic, Rochester, MN, and to the Montreal Neurological Institute, McGill University. He was on the Faculty at McGill until his move back to Basel in 2009. Michael Sinnreich is Extraordinarius for Neurology, Head of the Neuromuscular Center, Department of Neurology and Head of the Neuromuscular Research Laboratory at the Department of Biomedicine. His research interests focus on the molecular basis and the development of therapies for neuromuscular disorders.

Prof. Dr. Martin Stern, born 1972 in Zürich, Switzerland studied medicine at the University of Basel where he obtained his MD in 2001. He specialized in hematology, and from 2005 until 2007 he worked as a postdoctoral scientist in Perugia, Italy, studying the immune reconstitution after stem cell transplantation. Back to Basel, he continued his clinical work and joined the Immunobiology group at the Department of Biomedicine. In 2010 he obtained an SNSF professorship from the Swiss National Science foundation and started the Immunotherapy group. His research focuses on different functions of natural killer cells.

Prof. Dr. Alfred Zippelius, born in 1969 in Straubing, Germany, studied medicine at the University of Munich, where he graduated in 1997. After his thesis at the Institute of Immunology in Munich, he was a postdoctoral fellow at the Ludwig Institute for Cancer Research in Lausanne. He completed his clinical training in Internal Medicine and in Medical Oncology at the university hospitals Munich and Zurich. He is currently a senior leading physician in Medical Oncology. In 2010, he obtained a professorship programme from the Swiss National Science Foundation and joined the Department of Biomedicine. His work focuses on tumor antigen-specific T cell responses both in mouse models and cancer patients.

DBM Focal Area Neurobiology

Focal Area Coordinators

Prof. Dr. B. Bettler
Department of Biomedicine
Institute of Physiology
University of Basel

Prof. Dr. L. Kappos
Department of Biomedicine
University of Basel

Understanding the molecular events underlying diseases of the nervous system and exploiting this knowledge for improving treatment are among the major challenges in the life sciences. In view of the increasing social and financial burden generated by these diseases, especially in the setting of an ageing population, the Department of Biomedicine (DBM) has defined the neurosciences as one of its focal areas. The Focal Area NEUROBIOLOGY of the DBM complements parallel efforts at the Biozentrum and at the FMI. The Focal Area NEUROBIOLOGY of the DBM is part of the Neuroscience Network Basel (NNB), which was acknowledged as a center of competence by the University of Basel in fall 2008. The NNB follows a translational strategy and comprises more than 400 neuroscientists from 40 different laboratories associated with the University, the University Hospitals, the FMI and the Basel Life Science Industry. Research is conducted at all levels - from molecules to behavior – thus providing outstanding research opportunities and an excellent platform for a strong educational program. The NNB offers weekly research seminars and lecture series at the graduate and postgraduate levels, covering all aspects of basic and clinical neuroscience. The NNB is part of the trinational educational and collaborative NEUREX network with the neuroscience programs at the Universities of Freiburg (Germany) and Strasbourg (France).

A major aim of the Neuroscience groups at the DBM is to take advantage of the unique expertise in the neurosciences present in the Basel area to pursue translational research projects. As a consequence of these efforts, basic and clinical neuroscientists have successfully raised grant support for translational research projects from the Swiss National Science Foundation, the European Union, the Swiss Cancer League, the Swiss MS Society and various private foundations. The focus of these projects is on neuroinflammatory, neurodenenerative, psychiatric, neurological and neuromuscular disorders. Several members of the DBM/NNB are part of the new National Competence Center in Research (NCCR) "The Synaptic Bases of Mental Diseases". To promote the rapid translation of research results into clinical practice the DBM Focal Area NEUROBIOLOGY co-organizes the Annual Basel Neuroscience Symposium "From Bench to Bedside". The one-day event provides a platform for exchange of ideas and is regularly attended by more than 150 local neuroscientists, including basic and clinical researchers from Novartis, Roche, Actelion, Santhera Pharmaceuticals, FMI and the University.

Neurobiology
Development
Regeneration
Neural stem cells
Cell cycle
Ski

Cellular Neurobiology

Prof. Dr. Suzana Atanasoski
Department of Biomedicine
Institute of Physiology
University of Basel

Group Members
Dr. Carine Bonnon (postdoctoral fellow)
Constanze Baranek (PhD student)
Lionel Nobs (PhD student)
Manuela Dittrich (PhD student)
Nicoleta Sustreanu (PhD student)
Andrea Bieder (Master student)

Molecular Mechanisms in Neuro-development and Neurodegeneration

Neural stem cells are a focus of public and scientific interest, since with the discovery of neurogenesis in the adult brain we can think of novel strategies for the treatment of neurodegenerative diseases. The characterization of neural stem cells during brain development and repair is a prerequisite for the design of therapeutic procedures. The central nervous system (CNS) develops from self-renewing, multipotent neural stem cells present in different regions of the embryonic nervous system, where they are regionally and temporally restricted. Moreover, there is increasing evidence that mechanisms of regeneration are distinct from those of development. A central and challenging issue is to identify the extrinsic and intrinsic factors, which control the balance of self-renewal, proliferation, and cell fate decisions in a context-dependent manner. With our projects, we expect to obtain considerable insights into the expression and function of candidate genes controlling proliferation and differentiation of neural stem/progenitor cells during cortical and spinal cord development and following brain injuries.

Our group is investigating the role of the transcriptional regulator Ski and specific cell cycle proteins as part of the mechanisms by which maintenance and proliferation of progenitor cells are controlled. In the peripheral nervous system (PNS), we have identified Ski as a key player in the regulation of Schwann cell proliferation and myelination (Atanasoski et al., 2004; Jacob et al., 2008). Further, we have discovered that certain signaling pathways and distinct components of the cell cycle machinery that regulate Schwann cell proliferation during development differ fundamentally from those activated following nerve injury (Atanasoski et al., 2006, 2008).
Our recent work in the CNS shows that Ski is expressed in Sox2-positive neural stem cells throughout embryonic development (Fig. 1), and that it plays an essential role in the temporal control of progenitor cell differentiation in the dorsal forebrain (Baranek et al., 2010). Moreover, in Ski mutant mice neurons of the superficial cortical layers lose their identity and largely fail to extend across the corpus callosum. They ectopically express Ctip2, a transcription factor whose expression is normally confined to subsets of deep-layer neurons (Fig. 2). We identify the chromatin-remodeling factor Satb2 as a novel interaction partner of Ski, and show that the presence of both proteins is required for transcriptional repression of Ctip2 in upper-layer neurons. We propose a model in which Satb2 recruits Ski to the Ctip2 locus, and Ski in turn attracts histone deacetylases, thereby enabling the formation of a functional repressor complex (Fig. 3). Our data identify Ctip2 as the first in vivo target of Ski and suggest that Ski and Satb2 function in a common pathway that is necessary for specification of callosal projection neurons (Baranek et al., 2010). Our future studies are aimed at unraveling the mechanisms by which loss of Ski leads to cell cycle lengthening and precocious cell cycle exit of progenitor cells. Thus, we have established a cell culture system that allows us to elucidate the cellular function of Ski specifically in the neuronal lineage. Such cultures provide a good test system, in that the regulation of progenitor cell proliferation and differentiation can be manipulated by extracellular factors and by genetic means.

The overall goal of our projects is to improve our understanding of the pathways and molecules that regulate proliferation and differentiation in neural and glial progenitor cells from different regions in the CNS. Knowledge of how these cells can be maintained and induced to differentiate into distinct cell types, respectively, will have implications for future clinical applications, such as Parkinson's disease, multiple sclerosis, or spinal cord injuries.

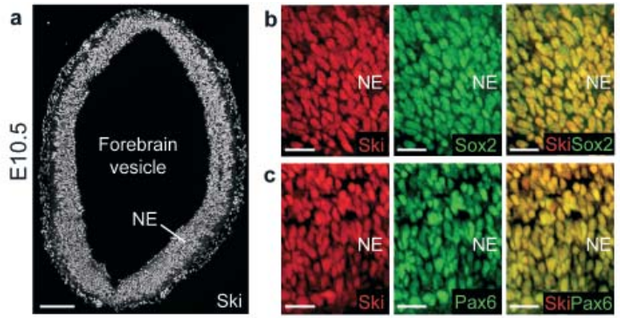

Fig. 1: Expression of Ski in neural stem cells of the forebrain
Ski immunohistochemistry on horizontal forebrain sections at E10.5 reveals prominent Ski expression throughout the neuroepithelium (NE) (a). Higher magnifications of the NE show costainings of Ski and Sox2 (b), and Ski and Pax6 (c) in nuclei of neural stem cells (yellow in the corresponding overlays). Scale bars represent 100 m (a) and 20 m (b, c).

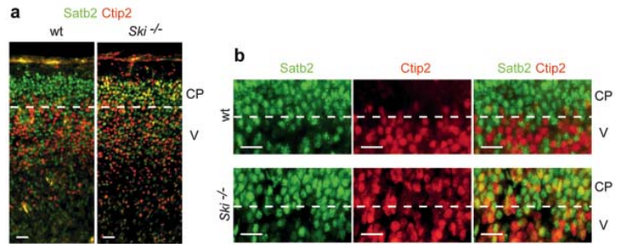

Fig. 2: Ski deletion affects Ctip2 expresion patterns in the dorsal telencephalon
Double immunostainings for Satb2 and Ctip2 on E17.5 coronal brain sections in wild type (wt) and *Ski -/-* (a). Higher-magnification images reveal ectopic expression of Ctip2 (red) in Satb2-positive cells (green) within the superficial layers of the CP in *Ski -/-* (b, lower panels), while Ctip2 expression is absent in the upper-layers of the wt CP (b, upper panels). Scale bares represent 20 m.

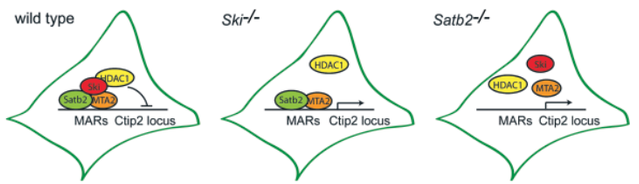

Fig. 3: Ski function at the *Ctip2* locus in callosal projection neurons
Ski is required to assemble a functional NuRD repressor complex containing Satb2, MTA2, and HDAC1 at MAR sites in the Ctip2 locus (wild type). In the absence of Ski, Satb2 still binds the regulatory DNA sequences together with MTA2, but recruitment of HDAC1 is impaired *(Ski -/-)*. In the absence of Satb2, the NuRD complex is not assembled *(Satb2 -/-)*. Thus, Satb2 and Sky play specific roles in the formation of a functional NuRD complex, and individual loss of these factors prevents transcriptional repression of *Ctip2* in callosal projection neurons.

Selected Publications

- Jacob, C., Grabner, H., Atanasoski, S., and Suter, U. (2008). Expression and localization of Ski determine cell type-specific TGFbeta signaling effects on the cell cycle. J Cell Biol 182, 519-530.
- Atanasoski, S., Boentert, M., De Ventura, L., Pohl, H., Baranek, C., Beier, K., Young, P., Barbacid, M., and Suter, U. (2008). Postnatal Schwann cell proliferation but not myelination is strictly and uniquely dependent on cyclin-dependent kinase 4 (cdk4). Mol Cell Neurosci 37, 519-527.
- Atanasoski, S., Scherer, S.S., Sirkowski, E., Leone, D., Garratt, A.N., Birchmeier, C., and Suter, U. (2006). ErbB2 signaling in Schwann cells is mostly dispensable for maintenance of myelinated peripheral nerves and proliferation of adult Schwann cells after injury. J Neurosci 26, 2124-2131.
- Atanasoski, S., Notterpek, L., Lee, H.Y., Castagner, F., Young, P., Ehrengruber, M.U., Meijer, D., Sommer, L., Stavnezer, E., Colmenares, C., and Suter, U. (2004). The protooncogene Ski controls Schwann cell proliferation and myelination. Neuron 43, 499-511.

Adult neurogenesis
Hippocampus
Synaptic transmission
Neuronal excitability
Dendritic integration
Calcium signalling

Cellular Neuro-physiology

Prof. Dr. Josef Bischofberger
Department of Biomedicine
Institute of Physiology
University of Basel

Group Members
Jörg Pohle (PhD student)
Stefanie Heigele (PhD student)
Charlotte Schmidt-Salzmann (MD student)
Michael Barz (Master student)
Selma Becherer (technician)
Martine Schwager (technician)
Heidi Ramstein (administrative assistant)

Adult neurogenesis in the the hippocampus

The hippocampal formation within the medial temporal lobe of the cerebral cortex is essential for our conscious memory for facts and events. Remarkably, the hippocampus is one of the very few regions in the central nervous system of adult mammals, including humans, where new neurons are continuously generated throughout life. This indicates that the new neurons are involved in learning and formation of new memories. In support of this hypothesis, we previously found that newly generated young neurons show enhanced excitability and synaptic plasticity as compared to the neighboring mature cells.

Within the hippocampus neurogenesis is restricted to granule cells in the dentate gyrus (Fig. 1). They receive excitatory inputs from the entorhinal cortex and project to the CA3 pyramidal cells. The dentate gyrus has some distinct structural features and is believed to serve distinct functions during memory processing. First of all, the granule cells form a so called competitive network as there is strong mutual inhibition via inhibitory GABAergic interneurons. By contrast, the CA3 pyramidal cells form an autoassociative network via mutually excitatory synaptic connections (Fig. 1). Second, the number of granule cells (~1 million in the hippocampus of young adult rats) appears to be ~5-times larger than the number of afferent entorhinal layer II principal cells and ~3-times larger than the number of CA3 pyramidal cells in the output region. This form of expansion recoding within a competitive network generates a sparse and orthogonal (non-overlapping) representation, which helps to separate similar neuronal activity patterns – a function called "pattern separation". As a consequence, each memory item can be stored within the hippocampal network in a unique fashion. Finally, new granule cells can be generated throughout life from adult neural stem cells located in the subgranular zone of the dentate gyrus (Fig. 2). Proliferation and differentiation of adult neural stem cells is tightly regulated in an activity dependent manner. Thus, the number of neurons might be adjusted to maintain sparse coding even with increasing memory load.

To understand signal processing in the dentate gyrus, we studied the functional properties of mature and newly generated granule cells (Stocca et al. 2008, Schmidt-Hieber and Bischofberger 2010) and the synaptic interaction with inhibitory GABAergic interneurons (Aponte et al. 2008, Buccurenciu et al. 2010). Using Ca^{2+} imaging in acute brain slices, we studied dendritic Ca^{2+} signals in young and mature granule cells evoked by backpropagating action potentials (Figure 3, Stocca et al. 2008). We found that the young neurons show remarkably large dendritic Ca^{2+} transients with slow decay time course. We could show that the slow decay of Ca^{2+} signals is due to low expression levels of different Ca^{2+} pumps leading to ~10-times slower Ca^{2+} extrusion rates in young cells as compared to mature granule cells. Furthermore, the young neurons show a small Ca^{2+} buffer capacity. The Ca^{2+} binding ratio (increase in buffer-bound Ca^{2+} per increase in free Ca^{2+}) in young cells was ~75 (versus ~220 in mature cells). Corresponding values published for pyramidal cells are ~100. The low Ca^{2+} buffer capacity in young cells together with the slow Ca^{2+} extrusion rate, might facilitate the generation of large Ca^{2+} signals important for dendritic growth and synaptic plasticity. By contrast, mature granule cells have a high Ca^{2+} buffer capacity more similar to GABAergic interneurons of the dentate gyrus (~200, Aponte et al. 2008). This might support stability of synaptic connections and restrict the activation of Ca^{2+} dependent processes in mature granule cells as well as in dentate gyrus interneurons to strong burst activity.

Further studies will help to understand the impact of these mechanisms on survival, differentiation and synaptic integration of the young cells into the adult neural network. This will not only be important for understanding learning and memory formation but might also help to develop future strategies for stem cell therapies after stroke and neurodegenerative diseases.

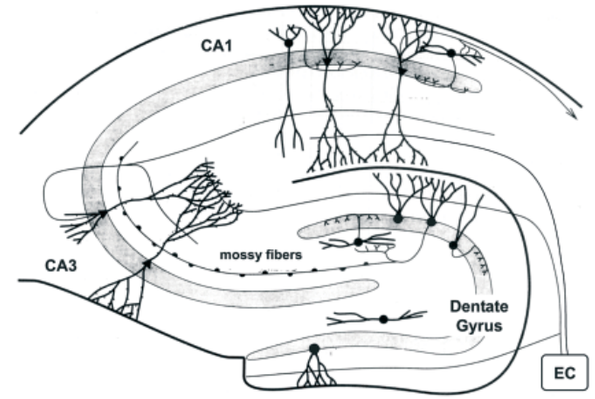

Fig. 1: Synaptic connections in the hippocampus. Granule cells in the dentate gyrus receive synaptic inputs from the entorhinal cortex (EC) and send their axons (mossy fibers) to the CA3 pyramidal cells. They project to CA1 and the CA1 pyramidal cells back to the EC via subiculum.

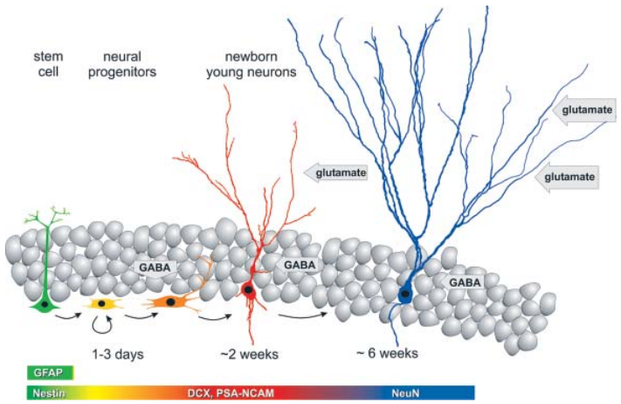

Fig. 2: Neural progenitors are generated form adult neural stem cells in the dentate gyrus. The postmitotic neurons develop a mature dendritic tree during a time period of about 6 weeks and form thousands of new inhibitory (GABA) and excitatory (glutamtate) synaptic connections. The young cells express typical embryonic proteins like DCX and PSA-NCAM and show enhanced synaptic plasticity.

Selected Publications

- Aponte Y, Bischofberger J, Jonas P (2008) Efficient Ca^{2+} buffering in fast-spiking basket cells of the rat hippocampus. J Physiol: 586: 2061-2075.
- Bucurenciu I, Bischofberger J, Jonas P (2010) A small number of open presynaptic Ca^{2+} channels triggers precisely timed transmitter release at a central GABAergic synapse. Nat Neurosci 13:19-21.
- Niehusmann P, Seifert G, Clark K, Atas HC, Herpfer I, Fiebich B, Bischofberger J, Norman C (2010) Coincidence Detection and Stress Modulation of Spike Time-Dependent Long-Term Depression in the Hippocampus. J Neurosci 30:6225-6235.
- Schmidt-Hieber C, Bischofberger J (2010) Fast sodium channel gating supports localized and efficient axonal action potential initiation. J Neurosci 30:10233-10242.
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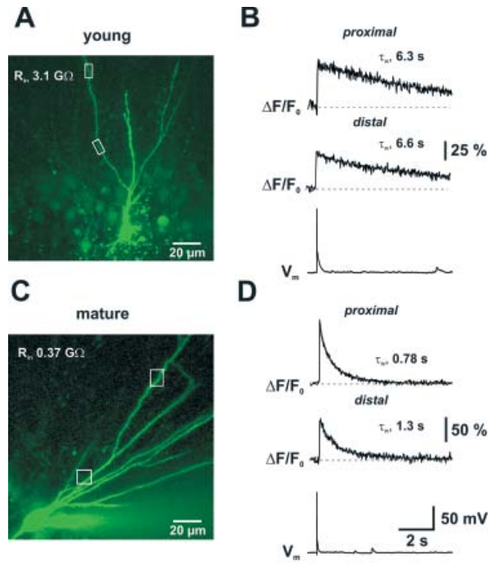

Fig. 3: Young granule cells show large and long-lasting dendritic Ca^{2+} signals. A, C A young and a mature granule cell during patch-clamp recording in acute rat hippocampal slices, filled with the Ca^{2+}-sensitive fluorescent dye OGB-1. B, D AP-evoked dendritic Ca^{2+} transients were recorded in a proximal and distal dendritic region indicated by the rectangles in A and C with a fast scanning confocal microscope.

Multiple sclerosis
Expression profiling
MicroRNA
Treatment response
Immunomodulation
Prognostic markers

Clinical Neuro-immunology

Prof. Dr.
Raija LP Lindberg

Prof. Dr.
Ludwig Kappos

Department of Biomedicine, University Hospital Basel

Group Members
Dr. Claudia Sievers
Dr. Jens Kuhle
Dr. Matthias Mehling
Francine Hoffmann (technician)
Marguerite Limberg (technician)
Nadine Daniel (technician)

Molecular and immunological analysis of Multiple Sclerosis

Our research focuses on the molecular and immunological analysis of multiple sclerosis (MS), an inflammatory, demyelinating central nervous system (CNS) disease. In earlier large-scale transcriptional analysis of brain tissue from secondary progressive multiple sclerosis (spMS) patients we provided molecular evidence of a continuum of dysfunctional homeostasis and inflammatory changes in spMS lesions and NAWM, supporting the concept of MS as generalized, as opposed to a focally restricted disease of the CNS. In extension of these studies, RNA expression profiling of peripheral blood of MS patients with different clinically defined disease courses: relapsing-remitting (rr), secondary progressive (sp) and primary progressive (pp) MS indicates that it is possible to distinguish various disease courses based on expression patterns in peripheral blood. We have also investigated the effects of natalizumab, a humanized monoclonal antibody to α4 integrins, on gene expression profiles in blood to define markers for treatment efficacy and to identify responders and non-responders. Molecular analysis demonstrates that natalizumab induces an array of changes in the regulation of almost all subtypes of blood cells including B-cells and neutrophils. These findings provide more insights into additional mechanisms of action of natalizumab and possible predictability of adverse events.

One of our main current focuses are studies on microRNAs (miRNAs), small, endogenous noncoding RNAs, which are key regulators of a wide variety of biological processes, e.g. cell proliferation and differentiation, apoptosis, signal transduction and organ development. We have analyzed the expression of 365 miRNAs in lymphocytes from RRMS patients, and provided evidence for distinct miRNA expression profiles in CD4+, CD8+ and B cells in MS as compared to those in healthy volunteers. miR-17-5p, which is known to be involved in autoimmunity, was one of the up-regulated miRNAs in CD4+ cells from MS patients. This was correlated with alterations in the expression of potential target genes of miR-17-5p, i.e. phosphatase and tensin homology (PTEN) and phosphatidyl-inositol-3-kinase regulatory subunit 1 (PI3KR1), which were down-regulated upon stimulation of CD4+ cells with antiCD3/CD28 in vitro. Functional experiments with a synthetic inhibitor of miR-17 supported the link between miRNA expression and the altered target gene expression (Fig. 1). Our findings support a role of miRNA dependent regulatory mechanisms in the immunopathogenesis of multiple sclerosis.

We are also exploring the effect of current innovative promising oral MS treatments, especially FTY720 and Fumaric acid, on peripheral T cells and antigen specific immune responses in MS patients. FTY720, an S1P receptor agonist, blocks lymphocyte egress from secondary lymphoid organs (SLO), thereby reducing peripheral lymphocyte counts to 25-40% of baseline values. This relates mainly to a reduction of CCR7-expressing naïve and central memory T cells, which re-circulate to SLO. The remaining effector T cells (TEM) rapidly produced interferon-γ upon reactivation, confirming their functional integrity and providing a partial explanation for the relatively low incidence of infections observed in clinical studies with this compound. FTY720-treatment further coincides with a major reduction of CD4+ Th17-like cells, a subpopulation of T cells which are considered to play a central role in formation and perpetuation of MS lesions.

We also aim to define biomarkers in CSF and peripheral blood for clinical practice. Previously we have investigated myelin (anti-MOG and anti-MBP) antibodies as possible prognostic markers for a conversion of patients with a first demyelinating event to clinically definite MS under interferon-β treatment in a large well-defined patient cohort (n=462). Our results showed no association between anti-myelin antibodies and progression to multiple sclerosis. Currently we are investigating neurofilament (Nf) subunits as a marker for axonal degeneration. We have developed a highly sensitive immunoassay with electrochemiluminesence detection, which facilitates determination of very low levels of Nf heavy chain (NfH) in CSF, which was not possible with the conventional ELISA techniques. Application of our method to CSF samples of various patient cohorts revealed elevated NfH levels in patients with amyotrophic lateral sclerosis, mild cognitive impairment/Alzheimer's disease, Guillain-Barre-syndrome or subarachnoid haemorrhage compared to the reference cohort (Fig. 2). We are currently studying other patient cohorts, e.g. different MS disease courses. Further object is the validation of NfH as a prognostic marker for neurodegeneration with large cohorts.

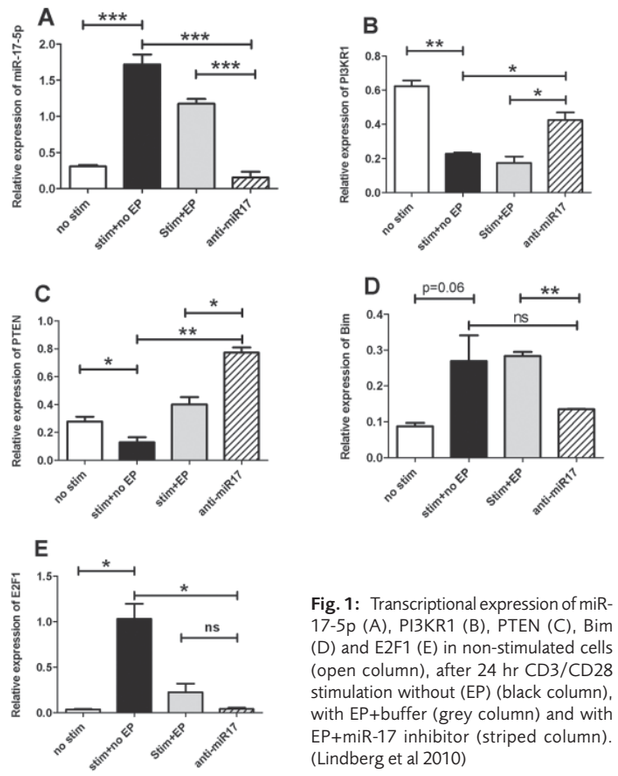

Fig. 1: Transcriptional expression of miR-17-5p (A), PI3KR1 (B), PTEN (C), Bim (D) and E2F1 (E) in non-stimulated cells (open column), after 24 hr CD3/CD28 stimulation without (EP) (black column), with EP+buffer (grey column) and with EP+miR-17 inhibitor (striped column). (Lindberg et al 2010)

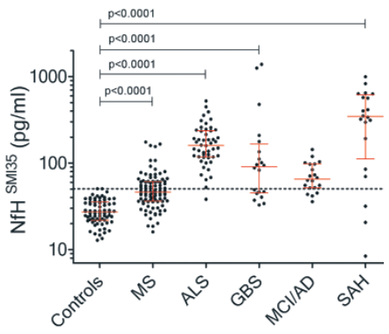

Fig. 2: NfH levels in the reference (controls) and neurological disease cohorts. ALS, GBS and SAH had higher levels of CSF NfH than controls (p<0.0001 for all) and ALS and GBS increased values compared with MCI/AD (p<0.0001 and p=0.032). SAH showed higher values than MCI/AD and GBS (p<0.0001 and p=0.001). The horizontal dotted line represents the upper reference range (cut-off value) of 50.5 pg/ml. Dots represent individual samples. (Kuhle et al 2010)

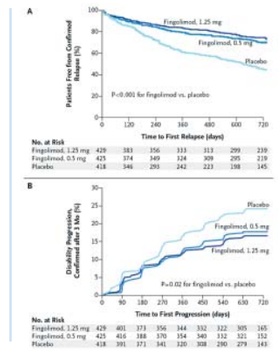

Fig. 3: Panel A shows Kaplan–Meier estimates for the time to a first relapse, and Panel B shows Kaplan–Meier estimates for the time to disability progression, confirmed after 3 months, as measured with the Expanded Disability Status Scale (EDSS).
(Kappos et al 2010)

Connection to Clinical Practice

Our Clinical Neuroimmunology Laboratory is closely connected to the Department of Neurology, University Hospital Basel, which includes an MS Clinic that sees more than 1000 MS patients per year, and therefore allows access to a unique population of MS-patients in different stages and courses/variants of the disease. There is also close collaboration with the Division of Neuroradiology and the Medical Image Analysis Centre (MIAC) that provide for qualitative and quantitative phenotypical characterization of patients with cutting edge neuroimaging. Since 2003 MS related neuroimaging research has been significantly enhanced by a research group headed by Prof. Achim Gass (2003-2010); since Oct. 2010 PD Till Sprenger, also placed in the interface of Neurology and Neuroradiology. Our Clinical MS Research Group plays a key role in organizing and conducting many of the important international innovative therapeutic studies in MS, e.g. with FTY720 (Fig 3), Fumaric acid and the humanized monoclonal antibodies Ocrelizumab (anti-CD20) and DAC HYP (anti-CD25), which are also providing unique possibilities to apply basic research approaches to understand disease mechanisms and therapeutic responses.

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– Kuhle J, Regeniter A, Leppert D, Mehling M, Kappos L, *Lindberg RLP, *Petzold A (2010). A highly sensitive electrochemiluminescence immunoassay for the neurofilament heavy chain protein. J Neuroimmunol 220(1-2):114-9. *equal contribution
– Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L, Burtin P; FREEDOMS Study Group (2010). A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 362(5):387-401.
– Lindberg RLP, Hoffmann F, Mehling M, Kuhle J, Kappos L (2010). Altered expression of miR-17-5p in CD4+ lymphocytes of relapsing-remitting Multiple Sclerosis patients. Eur J Immunol. 40(3):888-98.

Cerebellar Purkinje cells
Dendritic development
Glutamate receptors
Axonal regeneration
Spinal cord
Organotypic slice cultures

Developmental Neurobiology and Regeneration

Prof. Dr. Josef Kapfhammer
Department of Biomedicine
Institute of Anatomy
University of Basel

Group Members
Dr. Jingmin Ji (postdoctoral fellow)
Olivia Gugger (PhD student)
Raphael Streit (Master student)
Markus Saxer (technician)

The control of Purkinje cell dendritic development and axonal growth in the Central Nervous System

The shape of the dendritic tree of a neuron reflects its synaptic input because most synapses are located on the dendritic surface. Our group is interested in how functional activity does affect the growth and shape of the dendritic tree of cerebellar Purkinje cells, the principal cells of the cerebellar cortex. We take advantage of a special culture system which allows growing a thin cerebellar slice in a culture dish. In such cultured slices the dendritic development of Purkinje cells proceeds in way very similar to the in vivo situation and results in Purkinje cells with a typical dendritic tree (Fig. 1), yet the culture setup allows for simple experimental manipulation of the system. Using this culture system we have shown that the activity of the intracellular signalling molecule Protein Kinase C (PKC) is an important regulator of the dendritic growth of Purkinje cells. Stimulation of PKC activity inhibits Purkinje cell dendritic growth and branching. In contrast, inhibition of PKC activity stimulates Purkinje cell dendritic growth and branching. The PKC signalling pathway in Purkinje cells is coupled to the activity of a special class of glutamate receptors, the metabotropic glutamate receptors. When we stimulated metabotropic glutamate receptors (but not other types of glutamate receptors), the dendritic development of Purkinje cells was severely inhibited and the resulting dendritic tree was much reduced in size and complexity (see Fig. 2). This dendritic growth inhibition via activation of metabotropic glutamate receptors could be part of a negative feedback loop which protects Purkinje cells from acquiring too many excitatory synaptic connections. It is indeed well known that Purkinje cells are very sensitive to strong stimulation with the glutamate receptor agonist AMPA which can lead to excitotoxic death of Purkinje cells. We designed culture experiments involving Purkinje cells with dendritic trees of different sizes. Our results show that Purkinje cells with small dendritic trees were equally sensitive to excitotoxic death as Purkinje cells with large dendritic trees. Further studies showed that the small dendritic trees had a high density of AMPA-receptors explaining the high sensitivity to AMPA exposure (Fig. 2). Our findings suggest that rather local AMPA receptor density and not the total AMPA receptor load determines the sensitivity of Purkinje cells to AMPA-mediated excitotoxic death. In current and future projects we will further study mechanisms which link synaptic activity to dendritic growth and development in Purkinje cells and explore whether a chronic strong stimulation of such signalling pathways can result in dysfunction or even death and degeneration of Purkinje cells.

In a second line of research we are using in vitro models for research on axonal regeneration. The regeneration of axons after traumatic or vascular lesions of the nervous system is critical for functional recovery. Because axonal growth after lesions is strongly determined by the complex environment of the growing fibers, it is typically studied in animal experiments. The slice culture model, however, allows studying axonal growth in a similar microenvironment as in the intact animal. Using such in vitro models we have identified several signal transduction pathways as potential targets for pharmacological treatments aiming to improve axonal regeneration. Because the spinal cord is the CNS structure most relevant to regeneration research we have developed a slice culture model with spinal cord slices cut in the longitudinal sagittal direction. These slices can be maintained in culture and they keep their cytoarchitectonic organization similar to normal intact spinal cord (Fig. 3). Furthermore, after a few days in culture a spinal cord intrinsic longitudinal fiber tract developed within this type of spinal cord culture. This allowed us to study axonal regeneration of spinal cord axons after lesions made in vitro.

This model system has the potential to address many issues currently studied in animal experiments in this novel in vitro culture system.

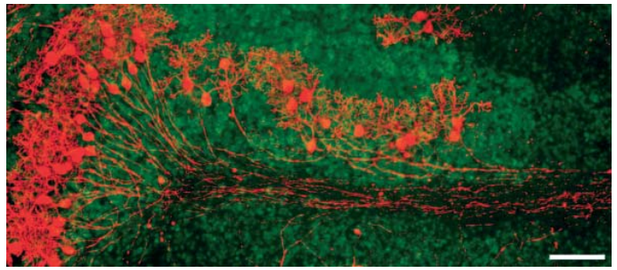

Fig. 1: View of a folium in an organotypic slice culture after 12d in vitro. Anti-calbindin staining for Purkinje cells is shown in red, anti NeuN staining for granule cells is shown in green. Due to the lower density of Purkinje cells in this area of the slice the dendritic trees of individual cells can be recognized. The Purkinje cell axons assemble to form a fiber bundle in the cerebellar white matter. (From Kapfhammer, J.P. (2010) Chapter "Cerebellar slice cultures" in "Protocols for Neural cell culture", 4th edition, 2010, Springer Protocols Handbooks, pp. 285-298.)

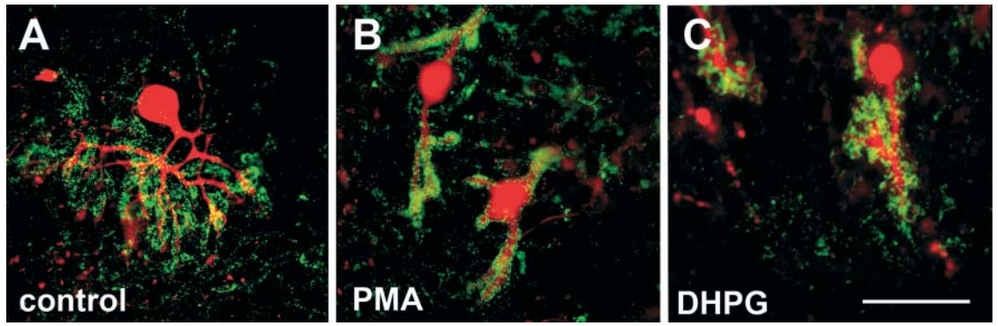

Fig. 2: Immunostaining against vGlut1 (green) reveals the presence of tight clusters of excitatory synapses on the dendrites of Purkinje cells in organotypic slice cultures.Treatment with the PKC activator PMA (B) or the mGluR agonist DHPG (C) results in dendritic trees of reduced size and complexity. The small dendritic trees of Purkinje cells in pharmacologically treated cultures show equally dense staining as control cultures. (From Gugger and Kapfhammer 2010)

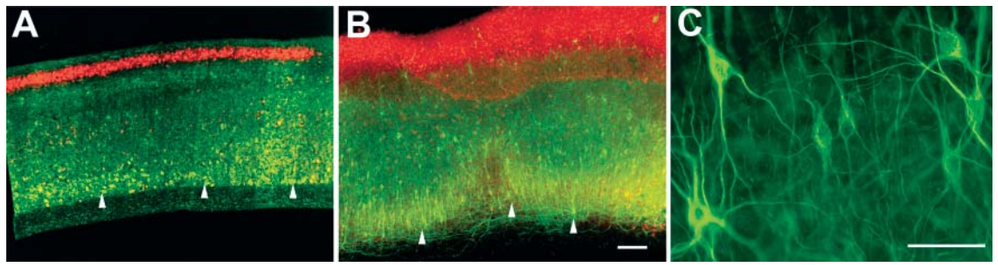

Fig. 3: A, B Spinal cord slice cultures maintain many aspects of intact spinal cord. The dorsal domains (red staning, top) and ventral domains (arrowheads, bottom) of the spinal cord are present in spinal cord slice cultures (B) similar as in intact spinal cord (A). High magnification shows the presence of motoneuron like cells in the cultured spinal cord (C). From Bonnici and Kapfhammer 2008.

Selected Publications

- Camenzind, R.S., Chip, S., Gutmann, H., Kapfhammer, J.P., Nitsch, C., Bendfeldt, K. (2010) Preservation of transendothelial glucose transporter 1 and P-glycoprotein transporters in a cortical slice culture model of the blood-brain barrier. Neuroscience 170, 361-371.
- Gugger, O.S., Kapfhammer, J.P. (2010) Reduced size of the dendritic tree does not protect Purkinje cells from excitotoxic death. J Neurosci Res 88:774-783.
- Kapfhammer, J.P. (2010) Chapter "Cerebellar slice cultures" in "Protocols for Neural cell culture", 4th edition, 2010, Springer Protocols Handbooks, pp. 285-298.
- Gajendran, N., Kapfhammer, J.P., Lain, E., Canepari, M., Vogt, K., Wisden, W., Brenner, H.R. (2009) Neuregulin signaling is dispensable for NMDA- and GABA(A)-receptor expression in the cerebellum in vivo. J Neurosci. 29, 2404-2413.
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Blood-brain barrier
Neurodegeneration
Stroke
fMRI
Bilingualism
Sex-gender differences

Functional Neuroanatomy

Prof. Dr. Cordula Nitsch*
Department of Biomedicine
Institute of Anatomy
University of Basel

Group Members
Dr. I.-Piotr Maly
Dr. Anelis Kaiser**
Sophorn Chip (PhD student/technician)
Roland Camenzind (MD student)
Alexandra Inauen (MD student)
Leila Eppenberger (Master student)
Olga Bollag (technician)
Isabel Galm (technician)

* retired July 2010

** left during report period

The regional microenvironment in the brain and its role in neurodegeneration and neuroprotection.

The regional microenvironment in the brain is to a large extent controlled by the blood-brain barrier (BBB). Disturbances of the integrity and transport function of the BBB are typical for neuropathologies such as stroke, Alzheimer's disease and multiple sclerosis. The BBB separates the nervous tissue from the general circulation, thereby ensuring an optimal environment for cerebral functions. The unique BBB phenotype characterized by the tightest endothelium is the result of the continuous influence from the surrounding nervous tissue, including pericytes embedded in the basement membrane, perivascular microglia, astrocytes that surround the basement membrane with their processes, and the basal lamina. To date, useful in vitro BBB models which take the structural connectivity of the different BBB elements into account are rare. We recently introduced fibroblast growth factor (FGF-2) treated cortical organotypic slice cultures (COSCs) of newborn mice as a new model for in vitro studies of the BBB (Bendfeldt et al., 2007). In the proposed model both the viability and the structural connectivity of the different brain tissue elements are maintained for several days in vitro.

Transport characteristics of blood vessels in the organotypic slice culture

We have now further characterized this BBB model by studying maintenance and function of transport proteins typically expressed in the endothelium of cerebral blood vessels. The glucose transporter (GLUT-1) is present in blood vessels of slice cultures derived from postnatal day 4 to 21 mice. The endothelial multidrug resistance P-glycoprotein (P-gp) which is involved in the control of pharmacological substance transport across the BBB is also maintained in blood vessels, most prominently in slice cultures derived from postnatal day 14 and 21 mice. To assess P-gp function, we tested rhodamine 123 transport in presence or absence of the P-gp inhibitor verapamil. Rhodamine 123-fluorescence accumulated rapidly in the vascular lumen both in acute slices and in slices cultured for 3 days in vitro. Thus, endothelial transporters and their functional properties can be maintained in organotypic cortical slices cultures (Fig. 1).

Expression of BBB markers under hypoxic challenge

Structural and functional maintenance of blood vessels in organotypic slice cultures can be used as a testable model to evaluate the integrity and maintenance of the BBB under pathological conditions. In ischemia, BBB breakdown is an important aspect and is likely to contribute to secondary damage. The hippocampus in humans and in experimental animals is the brain region most vulnerable to hypoxia/ischemia. Therefore, we adapted our cortical BBB model to the hippocampal organotypic slice and successfully carried out ischemia experiments. Short term (15 min) oxygen or oxygen-.glucose deprivation induces regional specific neuronal cell death, and this is accompanied by a 50 % reduction in vessel counts in the affected areas but not in other regions (Fig. 2).

Selective expression of claudin-3 in the choroid plexus

The tight junction protein claudin-3 has been claimed to be a constituent of the BBB. It is, however, notoriously difficult to demonstrate at the morphological level with immunohistochemical techniques its expression in endothelial cells of brain vessels. Using an improved fixation strategy we can show that claudin-3 is detectable in epithelia from E16 onwards. In brain, it is restricted to the choroid plexus in the ventricles, together with claudin-1 and -2, while in cerebral blood vessels claudin-3 as well as claudin-1 and -2 are absent during all developmental stages up to adulthood. Rather, the BBB is characterized by the presence of claudin-5. Thus, we propose that biochemical detection of claudin-3 in brain samples is probably due to contamination with choroid plexus (Fig. 3)

Fig. 1

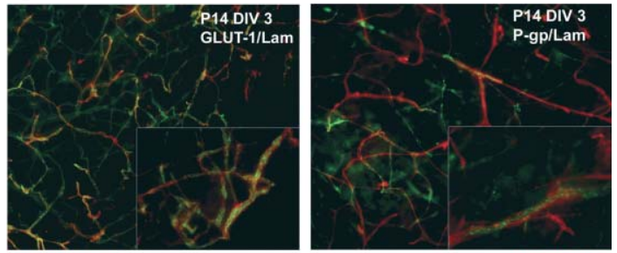


Fig. 2

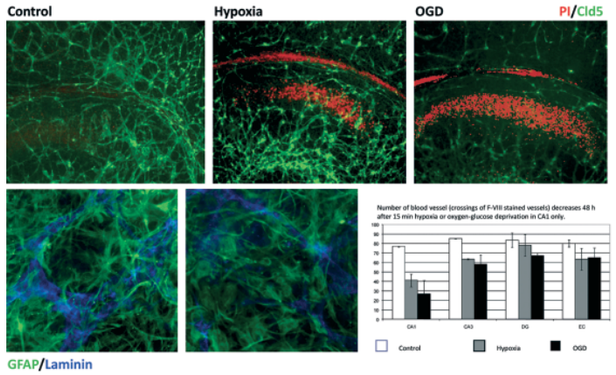
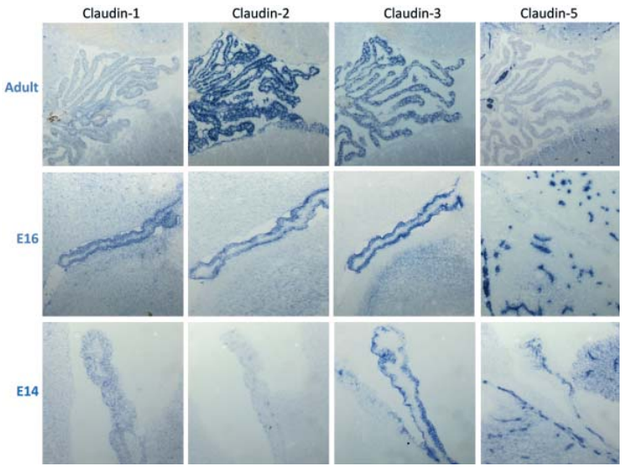


Fig. 3



From Functional Neuroanatomy to the critical reflection of sex/gender differences

Again and again, attempts have been made to find correlates of sex/gender differences in the human brain. Despite the insistence with which differences have been stated, empirical results have not been unequivocal: Evidences for and against the influence of sex in the makeup of men's and women's brains have been presented. Reanalysing our own functional data on how the brain deals with multiple languages we have studied sex/gender differences in the pattern of regional activation induced by language production. We observed that depending on the mode and thresholds of statistical analyses employed (approaches which are fully accepted by the scientific community) differences in the second level analysis of the same original data set can be present or absent and favour or refute sex/gender differences. A thorough critical analysis of the literature concerning sex/gender differences in fMRI language research, lead us to the following conclusions: there exist paradigmatic, methodological and statistical defaults that interfere with assessing the presence or absence of sex/gender differences. These criteria are, among others, the use of contrast analyses, the function of the variable sex/gender as a co-item and the "publication bias" which favours the search for the difference and not for the likeness. It is argued that dealing with the sex/gender variable will, at least to some degree, inevitably lead to the detection of differences rather than to the detection of similarities.

Selected Publications

- Maetzler W, Stünitz H, Bendfeldt K, Vollenweider F, Schwaller B, Nitsch C (2009) Microcalcification after excitotoxicity is enhanced in transgenic mice expressing parvalbumin in all neurons, may commence in neuronal mitochondria and undergoes structural modifications over time. Neuropathol. Appl. Neurobiol. 35:165-177.
- Bloch C, Kaiser A, Kuenzli E, Zappatore D, Haller S, Franceschini R, Luedi G, Radue E-W, Nitsch C. (2009) The age of second language acquisition determines the variability in activation elicited by narration in three languages in Broca's and Wernicke's area. Neuropsychologia 47: 625-633.
- Kaiser A, Haller S, Schmitz S, Nitsch C (2009) On sex/gender related similarities and differences in fMRI language research. Brain Res. Rev. 61: 49-59.
- Maetzler W, Berg D, Funke C, Sandmann F, Stünitz H, Maetzler C, Nitsch C. (2010) Progressive secondary neurodegeneration and microcalcification co-occur in osteopontin-deficient mice. Am J Pathol. 177: 829-839.
- Camenzind RS, Chip S, Gutmann H, Kapfhammer J, Nitsch C, Bendfeldt K. (2010) Preservation of transendothelial glucose transporter-1 and P-glycoprotein transporters in a cortical slice culture model of the blood-brain barrier. Neuroscience 170: 361-371.

Synapse Formation

Neuromuscular Junction

Developmental Neurobiology

Muscle

Agrin

Molecular Neurobiology Synapse Formation

Prof. Dr. Hans Rudolf Brenner
Department of Biomedicine
Institute of Physiology
University of Basel

Group Members
Dr. Gajendran Nadesan (postdoctoral fellow)
Dr. Nadine Hardel (postdoctoral fellow)
Dr. Sarah Wakefield (postdoctoral fellow)
Stefan Sladecek (PhD student)
Michèle Courtet (technician)

Signaling Mechanisms Regulating the Formation of the Neuromuscular Junction

Skeletal muscles contract in response to electrical impulses in motor nerves. Impulse transmission from motor nerve axons to muscle fibers takes place at specialized types of synaptic contact, the neuromuscular junctions (NMJ). Detailed investigation of NMJ formation at the molecular level can contribute to understanding basic mechanisms of synapse formation in general, and of the etiology of neuromuscular diseases in particular.

The formation of the NMJ involves the differentiation of the motor nerve process into a nerve terminal secreting acetylcholine (ACh) and the expression of acetylcholine receptor (AChR) genes and the anchoring of the AChR proteins at high density at the site of the neuromuscular contact. Aim of our research project is to understand the reciprocal molecular interactions between nerve and muscle involved.

Two key signaling systems generally thought to be required for NMJ formation are a.) Agrin, a heparansulfate proteoglycan secreted selectively from motor nerve terminals, activating the RTK MuSK expressed by muscle, as well as b.) neuregulins activating ErbB RTKs. Neuregulins are a family of growth and differentiation factors affecting many developmental processes both within and outside the nervous system. Their best-documented role in the nervous system is in the formation of myelin sheaths, but they have also been implicated in the regulation of neurotransmitter expression and the stabilization of glutamate receptors at central excitatory synapses. At the NMJ Neuregulin has been considered the prime factor from the motor neuron to mediate the presynaptic control of synapse-specifc transcription of AChR genes in the muscle fiber. Recently, we have found, however, that the NRG/ErbB signalling path is dispensable for synapse-specific gene transcription both at the NMJ and at CNS synapses.

Investigating the function of Agrin in vivo, we have found, that Agrin/MuSK are sufficient for the induction of a postsynaptic muscle membrane, including the accumulation of a small number of muscle nuclei at the synapse to selectively express musk and achr genes, and the transport and anchoring of their products in the postsynaptic muscle membrane (see below).

We have also uncovered a new role for NRG/ErbB at the NMJ at the post-transcriptional level. Upon abolishment of neuro-muscular neuregulin/ErbB signaling AChR anchoring in the postsynaptic membrane is impaired and components of the subsynaptic apparatus are lost. The latter serves to anchor AChRs in the subsynaptic membrane in ways that are poorly understood. On a mechanistic level, we identified α-dystrobrevin1, a component of the subsynaptic apparatus, as a target for ErbB receptor tyrosine kinases. Specifically, by phosphorylating α-dystrobrevin1, NRG/ErbB signaling appears to control the stability of the postsynaptic apparatus. In this way NRG/ErbB signalling can modulate components of the subsynaptic apparatus to affect the dynamics and stability of AChRs in the subsynaptic membrane; as a consequence the efficiency of neuromuscular transmission is impaired. Modulation of receptor anchoring is essential for plasticity at central synapses, a function affected by NRG/ErbB; moreover, α-dystrobrevin1 has been implicated in synaptic function in the CNS.

As outlined above, Agrin is sufficient to induce the formation of a postsynaptic membrane. This includes the induction of a dense microtubule network under the synaptic membrane that may be involved in the transport and/or in the translocation of muscle nuclei to the synapse. We are currently investigating the molecular pathways capturing the microtubules at the synapse and the function of the MTs for the formation and maintenance of the NMJ. Experiments so far suggest that induction is via a signaling cascade involving PI3kinase, AKT and GSK3β, a molecule involved in microtubule capturing at the cell cortex in other cell systems.

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Anxiety

Depression

Neurotransmitter

G-protein coupled receptor

Trace amines

GABA-B

Molecular Neurobiology Synaptic Plasticity

Prof. Dr. Bernhard Bettler
Department of Biomedicine
Institute of Physiology
University of Basel

Group Members
Dr. Martin Gassmann, Dr. Thorsten Fritzius,
Dr. Nicole Guetg, Dr. Klara Ivankova,
Dr. Michaela Metz, Dr. Valérie Jacquier,
Dr. Stefan Jungblut, Dr. Mercedes Tome,
Dr. Jan Tchorz, Dr. Dimitri Cloetta, Dr. Riad Seddik,
Dr. Mathieu Rajalu, Dr. Audrée Pinard,
Dr. Rostislav Turecek, Dr. Nidhi Gakhar-Koppole,
Dr. Barbara Biermann, Dr. Amyaouch Bradaia,
Dr. Nancy Gerits, Dr. Jim Tiao (postdoctoral fellows)

Valérie Besseyrias, Markus Wymann (technicians)

G-protein coupled receptors as Drug Targets for the Treatment of Mental Health Disorders

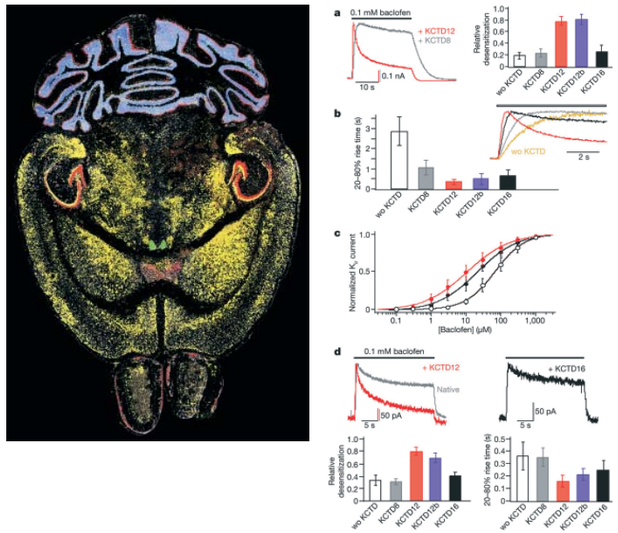
We are interested in the mechanisms that control neuronal excitability, and to exploit these mechanisms for the treatment of neurological and psychiatric diseases. We are giving emphasis to the control of neuronal excitability by G-protein coupled receptors (GPCRs), in particular $GABA_B$ receptors and Trace Amine-Associated Receptor 1 (TAAR1).

GABAB receptors

$GABA_B$ receptors are the GPCRs for the main inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain. They modulate the excitability of neurons throughout the brain and are widely considered promising therapeutic targets for a variety of disorders, including cognitive impairments, addiction, anxiety, depression and epilepsy. Before cloning, it was generally assumed that $GABA_B$ receptors would include several pharmacologically and functionally distinct receptor subtypes. It therefore came as a big surprise to many in the field that cloning efforts only identified two receptors. Even more puzzling was the finding that the two receptors, when expressed in vitro, did not exhibit pharmacological or functional differences. The two receptors are based on the subunit isoforms $GABA_{B1a}$ and $GABA_{B1b}$, both of which combine with $GABA_{B2}$ subunits to form heteromeric $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors. We showed that the two receptors target to distinct subcellular sites and mediate distinct physiological functions (Biermann et al., 2010; Guetg et al., 2009; Guetg et al., 2010). However, it remained unclear why native $GABA_B$ receptors differ in their electrophysiological and pharmacological characteristics whereas the cloned receptors do not. To address this issue we collaborated with B. Fakler (University Freiburg iBr) and affinity purified $GABA_B$ receptor complexes from brains. This comprehensive analysis identified four new auxiliary receptor subunits: the so-called KCTD proteins (Schwenk et al. 2010). The KCTD proteins have independently been identified as susceptibility genes for bipolar disorder. The KCTD proteins determine both the pharmacological and the biophysical characteristics of the $GABA_B$ receptors and explain why the previously known core $GABA_B$ receptor subunits did not reproduce the characteristics of the brain receptors. These findings could be of great therapeutic use. With the identification of the KCTD proteins it may now be possible to develop drugs that selectively influence a particular subtype of $GABA_B$ receptors. The advantages of such drugs could include a reduction in side effects as well as entirely new therapeutic applications.
We have been awarded research funding for five years under the European Commission's Framework Programme 7 (FP7) Health initiative (http://devanx.vitamib.com/). The funding will go towards the study of the molecular basis of anxiety disorders and how perturbations in early life prime the brain for altered emotionality in adulthood. The project, titled DEVANX (Serotonin and GABAB receptors in anxiety: from developmental risk factors to treatment), is undertaken by a pan-European consortium of seven laboratories. One of our main tasks will be to generate the genetic tools to inactivate and restore GABAB receptor functions in defined neural circuits.

Trace Amine-Associated Receptor 1

In collaboration with M. Hoener (Roche) we have studied TAAR1, a member of a family of nine GPCRs expressed in monoaminergic systems. TAAR1 not only responds to trace amines, which are endogenous amine compounds present at low levels in the brain, but also to classical biogenic amines and amphetamine-related psychostimulants. Our electrophysiological analysis using TAAR1 knock-out mice and a new TAAR1 antagonist revealed that TAAR1 regulates dopamine receptors in the ventral tegmental area, a brain region that is part of the reward circuit, one of the major sources of incentive and behavioral motivation (Bradaia et al., 2009). Our data support that TAAR1 antagonists potentially provide an approach to enhance the action of L-dopa in Parkinson's disease. Activating TAAR1, on the other hand, may be of therapeutic benefit in the treatment of schizophrenia, addiction, or attention deficit hyperactivity disorder.



▲ **Fig. 1:** Color-coded transcript distribution of KCTD8, 12, 12b and 16, the newly identified auxiliary subunits of $GABA_B$ receptors.

▶▲ **Fig. 2:** Functional and pharmacological effects of the KCTD proteins on $GABA_B$ responses.
a) Left: K^+ currents through $K_{ir}3.1/3.2$ channels recorded at -50 mV in response to baclofen applications (0.1 mM) from whole CHO cells co-expressing $GABA_B$, $K_{ir}3.1/3.2$ channels and the indicated KCTD proteins; wo KCTD, without KCTD. The extracellular K^+ concentration was 2.5 mM. Right: Bar graph summarizing the relative desensitization for the indicated subunit combinations; data are means and s.d. for 6–31 experiments.
b) The 20–80% rise time of $K_{ir}3.1/3.2$ currents activated by $GABA_B$ without or together with KCTD proteins. Data points are means and s.d. for 6–17 experiments. Inset: representative current onsets. c, Apparent dose–response relations obtained with $GABA_B$ (open circles) or with $GABA_B$ and KCTD proteins 12 (filled red circles) and 16 (filled black circles). Data points are means and s.d. for 7–13 experiments; lines are fits of a logistic function with values for EC_{50} values and Hill coefficients of 68.7 M and 1.02 ($GABA_B$), 21.0 M and 0.75 ($GABA_B$ + KCTD16), 9.9 M and 0.63 ($GABA_B$ + KCTD12), respectively.
d) Top: currents through $K_{ir}3$ channels recorded in experiments as in **a** from cultured hippocampal neurons without (native) or after transfection with KCTD12 (red trace) or KCTD16. Bottom: bar graphs summarizing relative desensitization (left) and onset (right) of the $K_{ir}3$ currents as in **a** and **b**; data points are means and s.d. for 7–38 experiments (Adapted from Schwenk et al., 2010).

Connection to Clinical Practice

From left to right:
Prof. Dr. Adrian Merlo, Prof. Dr. Markus Heim
Neurosurgery, Gastroenterology and Hepatology

Notch2 as a Drug Target for the Treatment of Brain Tumors and as cause of Alagille Syndrome

In collaboration with B. Hemmings (FMI) and A. Merlo (Neurosurgery) we aim at developing strategies for therapeutic interference with brain tumors (funded by Oncosuisse). Because Notch2 is lost in oligodendrogliomas and amplified in glioblastoma, we generated mouse models to test whether Notch2 can either act as a tumor suppressor gene or as an oncogene. Analysis of Notch2 transgenic mice supports that both the lack and the ectopic expression of Notch2 increases cell proliferation in the brain.
Alagille syndrome is a rare hereditary disorder that can be caused by Notch2 mutations. Patients display overt developmental abnormalities in the liver. This and additional lines of evidence supported that Notch2 plays a role in liver development, which however remained controversial. In collaboration with M. Heim (Gastroenterology and Hepatology) we therefore analyzed mice that ectopically express activated Notch2 in the liver. Our data clearly establish that Notch2 signaling regulates biliary epithelial cell differentiation, the induction of tubulogenesis during intrahepatic bile duct development and biliary epithelial cell survival (Tchorz et al., 2009).

Selected Publications

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- Guetg, N., Abdel Aziz, S., Holbro, N., Turecek R., Rose, T., Seddik, R., Gassmann, M., Moes, S., Jenoe, P, Oertner, T.G., Casanova, E. and Bettler, B. (2010). NMDA receptor-dependent GABAB receptor internalization via CaMKII phosphorylation of serine 867 in GABAB1. Proc. Natl. Acad. Sci. USA 107(31), 13924-13929.
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Myelin Biology

Axon-Glia Interaction

Membrane Domains and Trafficking

Multiple Sclerosis

Peripheral Neuropathy

Neuroprotection

Neurobiology

Prof. Dr. Nicole Schaeren-Wiemers
Departments of Biomedicine and Neurology
University Hospital Basel

Group Members
Dr. Jochen Kinter*
Dr. Thomas Zeis
Dr. Eva Herrero-Herranz*
Dr. Marie-Françoise Ritz
Andres Buser (PhD student)*
Thomas Lazzati (PhD student)
Daniela Schmid (Master and PhD student)
Svenja Zietzling (Master student)*
Fabienne Harrisberger (Master student)
Sarah Brunner (Master student)
Beat Erne (technician)*
Frances Kern (technician)*

* left during report period

Molecular Mechanisms of Myelin Formation and Maintenance in Health and Disease

The myelin sheath is a multilamellar plasma membrane structure that enwraps axons in the central (CNS) and the peripheral nervous system (PNS) of vertebrates. The insulating properties of this specialized membrane enable fast propagation of electrical signals. Two specialized cell types – the oligodendrocytes in the CNS and the Schwann cells in the PNS – generate their spiral sheaths in a structurally similar but biochemical distinct way. Recent studies indicate that the functional role of oligodendrocytes as well as Schwann cells is not only to myelinate axons but also to maintain the functional integrity of the nerve fiber throughout live. We are using basic as well as clinical approaches for investigating the complex nature of the myelin membrane. Our current projects in the lab involve the characterization of the functional role of the lipid-raft protein MAL in axon-glia interaction, and the endogenous neuroprotective mechanisms in Multiple sclerosis (MS). The knowledge of the selective function of the different components of the complex myelin structure is a prerequisite to understand the different mechanisms, which may damage myelin in MS and in primary demyelinating neuropathies leading to axonal degeneration.
The Myelin and Lymphocyte protein MAL is a four transmembrane protein expressed in CNS and PNS myelin. Its functional role in the apical sorting and transport mechanisms of polarized epithelial cells and its association with glycosphingolipids localized mainly in myelin membranes suggest that MAL is involved in the formation, transport and/or maintenance of particular glycosphingolipid microdomains, the so-called "lipid-rafts", in specialized plasma membranes. In the CNS, we have identified that MAL plays an important role in axon-glia interaction in adult mice (Schaeren-Wiemers et al., JCB 2004). Lack of MAL resulted in structural as well as in molecular alterations resulting in disruption of axon-glia interaction at the node of Ranvier. These results demonstrated a critical role for MAL in the maintenance of CNS paranodes. In the PNS, it seems that MAL does have a major influence on the onset of myelination and Remak bundle formation. Our detailed study on peripheral nerve development shows that MAL dosage influences p75 neurotrophin receptor (p75NTR) levels and by that most probably the progress of myelination (Buser et al., EJN 2009). This is unexpected since MAL is considered to be a regulator of lipid raft-dependent protein transport processes but not a regulator of gene expression. However, our data point to a cascade of events which ultimately leads to reduced levels of p75NTR receptor and delayed myelination in MAL-overexpressing mice influencing the first step of wrapping (Fig. 1).

Fig. 1

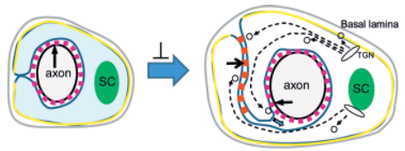

Fig. 1: First step of myelination: the Schwann cell segregates one single axon and establishes a 1 to 1 relationship. This process is mediated by direct axon-glia interaction. For the first, wrap the Schwann cell process has to elongate between the axon and its future outer tongue. This process is mediated by adhesion and elongation of the periaxonal membrane leading to wrapping of up to several hundred plasma membrane sheaths around the axon. This step needs a specialized sorting and trafficking of components synthesized in the trans-Golgi network (TGN) to the different compartments within this cell. Particular components are specific for axon-glia interaction (filled arrow), others for glia-glia interaction (open arrow) allowing wrapping and compaction of the developing myelin sheath.

Since polarized sorting and trafficking mechanisms require cytoskeletal components, a Yeast-two-Hybrid system analysis with the cytosolic N-terminal sequence of MAL was performed. Septin 6 was identified as an intracellular binding partner of MAL. Consequently, a comprehensive study of all Septins in CNS and PNS myelin was performed, elucidating which septin complexes are expressed by the myelinating cells (Buser et al., MCN 2009). Our data demonstrate that the septin cytoskeleton is an integral component of the myelin sheath, interacting with distinct myelin constituents, and therefore, septins represent intriguing candidates for membrane compartmentalization in myelin internodes (Fig. 2).

Fig. 2

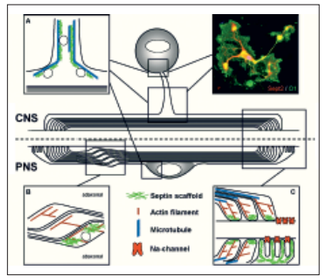

Fig. 2: A schematic drawing that illustrates septin scaffolds identified in distinct subdomains of the myelin sheath. (A) The pool of septins in the perikaryon of Schwann cells as well as in the Cajal bands (not specially indicated) and the cytoplasm channels of the oligodendrocytes might have a role in sorting and targeting of myelin components to the emerging and adult myelin sheath. Furthermore, septin scaffolds are detected in the outer rim of the Schmidt-Lanterman incisures (B) as well as in the paranodal loops and the microvilli at the nodes of Ranvier (C) where they might contribute to subdomain formation and protein turnover (Buser et al., MCN 2009).

MS is a chronic demyelinating disease of the CNS. The molecular mechanism of lesion formation is still unknown. We performed a microarray study in which we compared the expression pattern of normal appearing subcortical white and grey matter from MS and control patients. The genes that were differentially expressed in MS patients indicate the occurrence of many endogenous neuroprotective mechanisms (Graumann et al., 2003), but also of oxidative stress and activation of the innate immunity (Zeis et al., Brain 2008). Our data introduce novel concepts of the molecular pathogenesis of MS in which a subtle balance between inflammation and neuroprotection is taken place in MS brain (Zeis and Schaeren-Wiemers, 2009). Consequently, we examined these molecular changes in an animal model of MS, namely experimental autoimmune mediated encephalomyelitis (EAE). Whereas examination of the cortical white matter revealed only minor changes, we identified a number of gene expression alterations in the cerebral cortex even though morphological and cellular alterations were not evident (Zeis et al., JNI 2008). One of the most striking observations was the downregulation of genes involved in mitochondrial function as well as a whole set of genes coding for different glutamate receptors. Our data demonstrate that although the MOG-induced EAE in DA rats is not appropriate to investigate alterations observed in NAWM in MS, it is a valuable model for MS to analyze alterations in long projecting neurons due to inflammatory-induced axonal injury. In parallel, we had the opportunity to study the altered expression pattern in a biopsy with subcortical white matter tissue of a patient suffering from the first disease exacerbation (Zeis et al., Brain Pathol 2009). This single case study suggests that many observed alterations in chronic MS may already taken place during the early phase of the disease.

Connection to Clinical Practice

Prof. Andreas J. Steck
Department of Neurology
University Hospital Basel

Group Members
Prof. Dr. Philipp Lyrer,
PD Dr. Susanne Renaud,
Dr. Anna Stalder

Investigations of inflammatory neuropathies

Our focus is the investigation of mechanisms of inflammatory neuropathies and novel treatment approach. Anti-myelin-associated glycoprotein (MAG) neuropathy is an antibody-mediated polyneuropathy. By confocal microscopy, IgM deposits were found within perineurium-enclosed nerves. There was a linear correlation between IgM accumulations in nerve fascicles with IgM blood levels. Axons with specific IgM deposits had signs of axonal damage, including neurofilament disintegration (Stalder et al., 2009). Ultrastructural analysis revealed degeneration of myelinating Schwann cells. Taken together, these findings suggest that in anti-MAG neuropathy patients, IgM deposits are entrapped within cutaneous perineurium-ensheathed nerve bundles where they accumulate in the endoneurial space. High local IgM levels in the endoneurium may be required for IgM deposition on myelin and subsequent axonal injury and degeneration.
Autologous peripheral blood stem cell transplantation (PBSCT) is increasingly used for auto-immune disorders which are refractory to conventional immunosuppression. Six patients with chronic acquired demyelinating neuropathy (CADP) were treated with PBSCT. Two with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome improved. Two of the three with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and one with an IgM paraprotein and antibodies to nerve improved. The role of PBSCT in CADP refractory to other treatment deserves further investigation (Mahdi-Rogers et al., 2009).

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Muscle Disorders
Muscular Dystrophies
Dysferlinopathies
Myotonic Dystrophy
Genetic Analysis of Neuromuscular Disorders

Neuromuscular Research

Prof. Dr. Michael Sinnreich
Departments of Biomedicine and Neurology
University Hospital Basel

Group Members
Dr. Bilal Azakir (postdoctoral fellow)
Dr. Perrine Castets (postdoctoral fellow)
Sabrina Di Fulvio, M.Sc. (PhD student)
Beat Erne (technician)
Frances Kern (technician)
Dr. Jochen Kinter (postdoctoral fellow)
Dr. Maddalena Lino (postdoctoral fellow)
Dr. San Pun (postdoctoral fellow)

The dysferlin interactome: Implication for therapeutic strategies

We are interested in the cell biology of human diseases affecting skeletal muscle. Skeletal muscle presents several advantages for biomedical research: the tissue is abundant, readily accessible in humans and in experimental rodents, well characterized, and is amenable to cell culture studies. Certain features of skeletal muscle fibers, including their large size, make them suitable for investigations of particular aspects of cellular biology such as surface membrane production, maintenance and repair. An important protein implicated in muscle surface membrane repair is dysferlin.
Mutations in dysferlin are a frequent cause of the recessively inherited limb girdle muscular dystrophies (LGMD), defining the common subtype of LGMD2B. In addition to LGMD2B, dysferlin mutations also cause Miyoshi Myopathy (MM) and distal anterior compartment myopathy, which are both distal forms of muscular dystrophy.
No treatment is currently available for these disabling diseases. Finding treatment for muscular dystrophies is imperative, as these diseases have a high personal and socioeconomic impact. As skeletal muscle become weak, patients become dependent on their family members, partners and friends for displacements, personal hygiene and feeding. The design of treatment strategies for dysferlin deficiency requires knowledge about the cellular function of the dysferlin protein and about its interacting partners. This knowledge is currently scarse.
Dysferlin is a large transmembrane protein containing seven C2 domains, which are lipid and protein binding modules. We characterized the lipid binding selectivity for all dysferlin C2 domains using recombinantly generated dysferlin GST-C2 domain fusion proteins, protein-lipid overlay assays, and liposome centrifugation assays. We observed that all of dysferlin's C2 domains bound to phosphatidylserine (PS). However, only dysferlin's C2A domain showed calcium-dependent PS binding, whereas the other dysferlin C2 domains demonstrated calcium-independent PS binding. It appears that the C2A domain of dysferlin is the only calcium-dependent lipid binding C2 domain that might be important for calcium-dependent membrane interactions in muscle. The role of the other calcium-independent phospholipid binding C2 domains of dysferlin is less clear at this time, but they may modulate the membrane binding activity of the C2A domain in a similar fashion to the tandem C2 domains of synaptotagmin I.
We next set out to identify protein interactors of dysferlin. Using affinity purification followed by liquid chromatography/mass spectrometry, we identified a number of proteins in skeletal muscle that showed association with dysferlin. Importantly, we were able to identify the few proteins previously shown to interact with dysferlin, thus indicating the validity of our approach. The newly identified proteins fall into categories of surface membrane proteins, proteins involved in cellular trafficking, signal transduction proteins, proteins involved in degradation and quality control.
Currently, we are studying the interaction between dysferlin and newly identified binding partners in order to gain insights into dysferlin biology: its trafficking, internalization and degradation pathways. Those insights will help in the design of therapies for patients affected by these disabling diseases.

Establishing a pathophysiologically based, high throughput assay to identify small molecular weight compounds for the treatment of Myotonic Dystophy type I

Myotonic Dystrophy type I (DM1) is a disabling, genetic disease affecting multiple organ systems, including skeletal and cardiac muscle, central nervous system, gastrointestinal tract, endocrine glands and lense, with no causal treatment available. This disease is caused by expanded CTG triplet repeats in the 3'UTR of the Myotonic Dystrophy Protein Kinase (DMPK) gene. Disease severity is correlated to the repeat expansion size: normal subjects harbor less than 37 CTG repeats, whereas in subjects with congenital forms the repeat length can exceed 2000 triplets. On the RNA level such expanded CUG repeats (CUGexp) form hairpin structures, which lead to ribonuclear inclusions. More specifically, the RNA with expanded CUG repeats sequester the splice-factor muscleblind-like 1 (MBNL1), which is necessary to regulate alternative splicing. Lack of available MBNL1 leads to mis-regulated alternative splicing of many different genes explaining thus the multisystem involvement in DM1.
We wish to identify small molecular weight compounds that liberate sequestered MBNL1 from CUGexp-RNAs in affected organs. In order to identify such small molecular weight compounds for the treatment of Myotonic Dystrophy type I, we are developing a novel pathophysiologically based biochemical assay, compatible with high throughput screening. Our method is based on Differential Scanning Fluorometry, and enables us to characterize the interactions between recombinantly generated splice factor MBNL1 and *in-vitro* transcribed CUGexp-RNA. Our assay should allow the identification of molecular therapeutics for patients with Myotonic Dystrophy type I. Once established, this novel assay could be applied for the screening of therapeutics for other rare RNA-mediated diseases like Myotonic Dystrophy type II, Fragile-X Tremor Ataxia Syndrome and different types of Spinocerebellar Ataxias.

Connection to Clinical Practice

Molecular diagnostics of genetically determined neuromuscular diseases

Our clinical expertise and research interests are in the field of neuromuscular diseases, where there is currently an unmet clinical need to rapidly and affordably provide molecular diagnosis for patients with genetically determined diseases. Novel treatment strategies, which are being introduced into clinical practice, such as exon-skipping and stop codon read-through, are mutation-specific and require therefore precise knowledge of the underlying molecular defect.
Obtaining a molecular diagnosis in neuromuscular diseases can be challenging. A given neuromuscular disease can present with a wide phenotypic variability. Conversely, a similar neuromuscular phenotype can be caused by mutations in different genes. The large number of exons encoding individual proteins implicated in neuromuscular disorders, make a diagnostic approach, in which candidate genes from a long list of differential diagnoses are individually sequenced, time consuming and costly. Moreover, a conventional sequencing approach alone may fail to identify exonic deletions, so that such mutations may remain undetected. We are currently developing novel diagnostic methods for the rapid and inexpensive resequencing of the coding regions of genes implicated in neuromuscular disorders, which should significantly facilitate and shorten the diagnostic workup currently available for patients affected by these disorders.

Selected Publications

- Azakir, B.A., Di Fulvio, S., Therrien, C., and Sinnreich, M. Dysferlin interacts with tubulin and microtubules in mouse skeletal muscle. PLoS One 5, 2010 Apr 12;5(4):e10122.
- Therrien, C., Di Fulvio, S., Pickles, S., and Sinnreich, M. (2009). Characterization of Lipid Binding Specificities of Dysferlin C2 Domains Reveals Novel Interactions with Phosphoinositides. Biochemistry 48, 2377-2384.
- Sinnreich, M., Therrien, C., and Karpati, G. (2006). Lariat branch point mutation in the dysferlin gene with mild limb-girdle muscular dystrophy. Neurology 66, 1114-1116.
- Therrien, C., Dodig, D., Karpati, G., and Sinnreich, M. (2006). Mutation impact on dysferlin inferred from database analysis and computer-based structural predictions. J Neurol Sci 250, 71-78.

Psychostimulants
MDMA
Ecstasy
Addiction
Psychopharmacology

Psycho-pharmacology

New group since January 2010

PD Dr. med. Matthias E. Liechti, MAS
Department of Biomedicine and
Division of Clinical Pharmacology and Toxicology
University of Basel

Group Members
Cédric Hysek (PhD student)
Linda Simmler (PhD student)
Valentina Nicola (MD student)
Martina Ineichen (MD student)
Valérie Arnold (Master student)

Mechanism of action of MDMA (Ecstasy)

Our primary research focus is on the mechanism of action of psychostimulants such as 3,4-methylenedioxymethamphetamine (MDMA), well-know as the recreational drug Ecstasy. MDMA produces a state of well-being, extroversion, and relaxation in humans. Due to its unique psychotropic effects, MDMA is not only consumed as a drug of abuse by many young people, but also investigated clinically for its potential use in patients in psychiatric disorders. In addition, MDMA is used experimentally to study the pharmacological regulation of mood and its disorders. We are interested in how MDMA effects are mediated within the human brain and in particular to what extent the psychotropic effects of MDMA depend on release of serotonin and norepinephrine. We are using both preclinical and clinical research methods. At the Department of Biomedicine, we investigate how MDMA interacts with the serotonin and norepinephrine uptake site to release these neurotransmitters. For example we assess MDMA-induced serotonin and norepinephrine release from transmitter-preloaded transporter-transfected HEK cells and modulate the releasing effect with compounds that selectively bind to the serotonin or norepinephrine transporters. Compounds that block MDMA-induced release of serotonin or norepinephrine are then investigated clinically in humans to assess whether they also inhibit psychological and physiological effects of MDMA.

Role of serotonin and norepinephrine in the pharmacology and toxicology of MDMA

In clinical proof-of-mechanism studies we are administering a moderate dose of pure MDMA to healthy subjects in the Phase 1 Research Unit of the University Hospital. Clinical outcome measures include a range of pharmacodynamic measures such as psychometric tests (mood rating scales, cognitive performance tasks), physiological measures (blood pressure, heart rate, and dynamic pupillometry), neuroendocrine measures (plasma prolactine, cortisol, and catecholamines), pharmacokinetics, and pharmacogenetic measures. For example we showed that a serotonin transporter inhibitor, that prevented binding of MDMA to the transporter and blocked MDMA-induced serotonin release, also attenuated the psychological and physiological effects of MDMA in humans. These findings indicate that the psychotropic effects of MDMA may primarily be mediated by an interaction of MDMA with the serotonin transporter. The clinical studies inform us on the neurochemical basis of mood states such as euphoria/hedonia and mania-like disorders mimicked by MDMA. Finally, the findings may provide clinicians with guidance for the treatment of intoxications with MDMA and other stimulants.

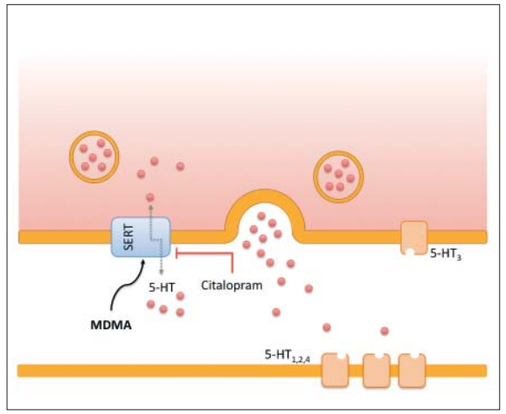

Fig. 1: 3,4-methlyenedioxymethamphetamine (MDMA, ecstasy) releases serotonin (5-HT) via the 5-HT transporter (SERT). In vitro, SERT blockers prevent MDMA-induced release of 5-HT. In humans, the SERT blocker citalopram attenuates MDMA-induced positive and negative mood changes, perceptual effects, and increases in blood pressure and heart rate. These finding indicate that MDMA's psychotropic and cardiovascular effects mainly depend on release of 5-HT.

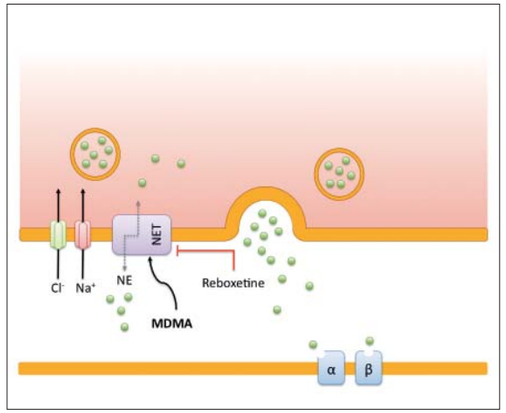

Fig. 2: MDMA also binds to the norepinephrine transporter (NET) to release norepinephrine (NE). In humans, the NET blocker reboxetine reduced MDMA-induced emotional excitation and the blood pressure response to MDMA indicating that these effects of MDMA are mediated via release of NE. In contrast, a β-blocker, that prevents NE from stimulating postsynaptic adrenergic β-receptors does not affect the pressure response to MDMA due to unopposed stimulation of α-adrenergic receptors.

Selected Publications

- Liechti, M.E., Vollenweider, F.X. (2001). Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Hum Psychopharmacol Clin & Exp 16, 589-598
- Liechti, M.E., Lhuillier, L., Kaupmann, K., Markou, A. (2007). Metabotropic glutamate 2/3 receptors in the ventral tegmental area and the nucleus accumbens shell are involved in behaviors relating to nicotine dependence. J Neuroscience 27, 9077-9085
- Liechti, M.E., Markou, A. (2008). Role of the glutamatergic system in nicotine dependence: Implications for the discovery and development of new pharmacological smoking cessation therapies. CNS Drugs 22, 705-24
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DBM Focal Area
Stem Cells and Regenerative Medicine

Focal Area Coordinators

Prof. Dr. R. Zeller
Department of Biomedicine
Institute of Anatomy
University of Basel

Prof. Dr. A. Gratwohl
Division of Hematology
University Hospital Basel

Stem cell research and tissue engineering constitutes one of the four main focuses within the Department of Biomedicine and the life science strategy of the University of Basel. The last decade has seen major effects to establish stem cells of both adult and embryonic origin, which can be induced to differentiate into the various cell-types that form many of the tissues and organs in the human body. The department is active in various aspects of this fascinating research field with relevance to both basic, mechanistic and clinically applied, translational research.

An large number of research groups in the Department of Biomedicine are devoted to studying specific aspects of stem cell biology. Groups active in basic research try to identify and isolate stem cells and to understand how stem cells are maintained in their normal niches within the embryo and/or body. For example, several groups are studying how stem cells of the blood are maintained in the bone marrow, differentiate into the various different cell-types of the haematopoietic system and how their differentiation potential is altered in malignant states that result in stem cell-based cancers (e.g. leukaemia or lymphomas). Due to the close interactions of clinical with basic researchers, this research aims to bridge the gap between fundamental and translational research. For example, attempts to grow and differentiate mesenchymal stem cells, which are isolated from human bone marrow, into different cell- and tissue-types in vitro are rather advanced and may e.g. lead to clinically relevant cartilage and bone replacement therapies in the not too distant future. Donor derived haematopoietic stem cells are followed after clinical stem cell transplantation in their new host with respect to their potential to differentiate into haematopoietic cells and their potential to trans-differentiate into cells of other embryonic tissue types. Information gained from these experiments is essential for future, clinically applied tissue engineering and efforts in regenerative medicine, which aims to reactivate/support the regenerative potential of the body in a controlled manner.

In spite of these impressive advances, it is important to gain a much better understanding of how stem cells interact with their niche to either maintain their multi-potency or give rise to daughter cells that upon leaving the niche undergo controlled transient amplification in concert with cell-type specification and differentiation. The challenge is to define culture conditions that allow one to maintain stem cells in culture and induce their specification and differentiation into functional tissues in an efficient and controlled manner. As organs and tissues are composed of different, well organised and functionally interacting cell-types, it is important to understand the functions of embryonic signalling centres in the process of tissue patterning und cell-type specification by combining tissue engineering attempts with knowledge gained from analysing cell-type, tissue specification and organogenesis during normal embryonic development. Recent studies by others have begun to reveal the mechanism by which adult cells (e.g. skin cells) can be re-programmed to revert to stem cells, thereby providing an novel source of defined multi-potent progenitor cells for cell-differentiation and tissue engineering studies. The research groups in the department will also have to incorporate the use of such cells, which can be easily obtained from patients, into their experimental strategy. This fits with the strategy of the department to promote collaborative efforts between basic research groups and clinicians to close the gap between the lab bench and patient's bed as much and as fast as possible.

Moreover, the department has realised the need to broaden its collaborative network. Groups at the Biozentrum, the FMI, the University Hospital and research institutions in the industry have come together and founded the Basel Stem Cell Network, which is one of the Competence Centres within Life Sciences at the University of Basel. In the frame work of this Competence centre, stem cell researchers have the opportunity to closely interact and collaborate with developmental biologists, geneticists and even mathematicians, which helps to promote innovative research. Last but not least, several currently ongoing appointments will strengthen both basic and translational research efforts in this rapidly emerging and highly competitive research field.

Cardiac remodeling
Myocytes
Cytokines
Growth
Signal transduction

CardioBiology

Prof. Dr. Marijke Brink
Department of Biomedicine
Institute of Physiology
University of Basel
and University Hospital Basel

Group Members
Dr. Michaela Brosig (postdoctoral fellow)
Dr. Katrin Bühler-Popowski*
Dr. Isabelle Plaisance*
Dr. Frédérique Dubouloz (postdoctoral fellow)
Dr. Silvia Meili-Butz (postdoctoral fellow)
PD Dr. Dagmar I. Keller
PD Dr. Thomas Dieterle
Pankaj Shende (PhD student)
Ludwig Villiger (Master student)
Michaela Ramser (Master student)
Christian Morandi (technician)
Dietlinde John*

* left during report period

Cardiac pathways of protein and energy metabolism in health and disease

The heart is a plastic organ, which gradually changes its geometry, cellular composition and function during cardiovascular disease, especially hypertension and ischemic heart disease, but also independently during obesity and diabetes. This "cardiac remodeling" is the consequence of changed neurohormonal balances and inflammatory responses, and if pathological triggers are not controlled in a timely manner heart failure may develop. Heart failure is a most pressing health problem and economic burden because it affects high numbers of elderly individuals in our Western society.

TNF- enhances protein translation in cardiomyocytes via a rapamycin-resistant mechanism

Tumor necrosis factor- (TNF) is involved in the hypertrophic response to cardiac stress. We established that it promotes growth in C2C12 and primary rat myotubes by enhancing protein translation via the TNF-R1 (Plaisance, 2008). Recent data support that mammalian target of rapamycin (mTOR) adapts cellular growth and metabolism to hormone and nutrient availability, energy status and stress. The question if and how mTOR regulates hypertrophic responses of cardiomyocytes to stress-induced cytokines has been central in our recent studies. In neonatal rat cardiomyocytes, we found that rapamycin blocks IGF-induced phosphorylation of S6K1 and 4E-BP1 as well as TNF-induced phosphorylation of S6K1, but not the ability of TNF to phosphorylate 4E-BP1. Consistently, protein synthesis was abolished after IGF, but still significantly increased after TNF treatment, suggesting that TNF causes cardiomyocyte hypertrophy in a rapamycin-resistant manner. Currently we are identifying the involved pathways.

Consequences of raptor deficiency in the adult mouse heart

Relevant to all potential clinical applications of mTOR inhibition, we are investigating the role of mTORC1 and mTORC2 in heart-specific growth regulatory pathways. To this end we have, in collaboration with M. Rüegg and M. Hall at the Biozentrum, generated genetic mouse models in which raptor and rictor are ablated from cardiomyocytes during adulthood. Cardiac function deteriorated rapidly in the raptor knockout mice, resulting in high mortality within six weeks. Voluntary exercise increased mortality and aortic banding-induced pathological overload resulted in severe dilated cardiomyopathy within one week without a prior phase of adaptive hypertrophy. The mechanism involved a lack of adaptive cardiomyocyte growth via blunted protein synthesis capacity as well as a reduced mitochondrial content, a shift in metabolic substrate use, and apoptosis. These results demonstrate that mTORC1 is essential in the heart under physiological as well as pathological conditions.

CRF-related peptides in heart disease

The objective of this project was to analyze the effects of a new class of molecules, the CRF-associated peptides, on the structure and function of the heart during the development of hypertension-induced left ventricular hypertrophy and dysfunction, up to the stage of heart failure. Using salt-sensitive Dahl rats as a model of arterial hypertension, we established that urocortin 2 (Ucn2), the cardiac-specific member of this group of peptides, has long-term blood-pressure lowering effects (Dieterle 2009). In further experiments we showed that chronic Ucn2 treatment prevented the progression from hypertrophy to left ventricular dysfunction. Moreover, chronic application of Ucn2 to rats with overt heart failure reduced mortality. Finally, Ucn2 rapidly improved left ventricular function and increased the ventricular fibrillation threshold in failing, isolated rat hearts with increased propensity for ventricular arrhythmias, suggesting a potential use of Ucn2 as a safe and novel agent for the treatment of acute heart failure (Meili-Butz, 2010). As coronary artery disease is a leading cause of mortality and morbidity, we also analyzed the molecular regulation and potentially cardioprotective effects of Ucn2 under hypoxic conditions. This project resulted in a better understanding of the molecular mechanisms by which Ucn2 exerts its beneficial effects (Bühler 2009).

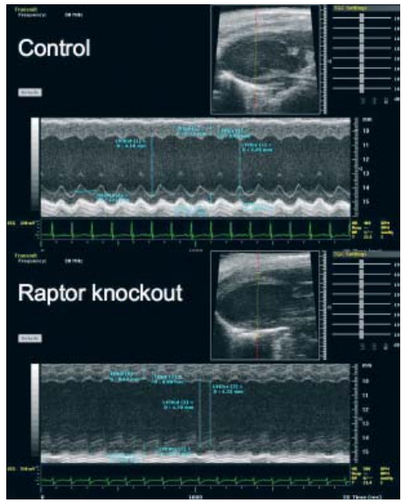


Fig. 1: Ultrasound analysis of a raptor knockout mouse, illustrating that the mouse develop a dilated heart.

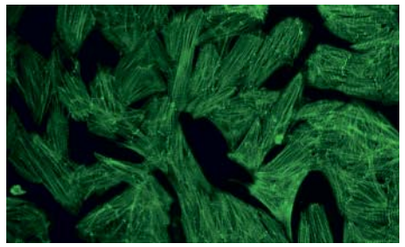


Fig. 2: Cardiomyocytes are isolated form neonatal rat hearts to analyze molecular mechanisms of hypertrophy in vitro. Cells were stained with an antibody to alpha-actinin to visualize the sarcomeric structure.

Connection to Clinical Practice

Genetic background of familial sudden cardiac death in cardiomyopathies and arrhythmic syndromes

The most common genetic cardiac disorders are familial hypertrophic cardiomyopathy and dilated cardiomyopathy, which are structural heart diseases, and the long QT syndrome, the Brugada syndrome, the congenital conduction defect and the congenital sick sinus syndrome, which are diseases of the cardiac ion channels. In the CardioGenetics program headed by PD Dr. Dagmar I. Keller, patients are based on the clinical diagnosis selected for genetic testing, subsequently performed using PCR with primers to cover all exons and important intronic sites of known disease-causing genes, followed by DHPLC analysis, and confirmation of the genetic variants by sequencing. The genetic test will confirm a clinically determined diagnosis, predict risk and prognosis in a clinically affected patient, and it provides options for therapy not only in the patient, but also in clinically unaffected relatives who carry the disease-causing mutation. Index patients and their families are followed-up in the outpatient clinics. Whenever novel mutations are discovered in ion channel genes, these are assessed for their biophysical characteristics (Keller 2009).

Selected Publications

– Buhler, K., Plaisance, I., Dieterle, T., and Brink, M. (2009). The human urocortin 2 gene is regulated by hypoxia: identification of a hypoxia-responsive element in the 3'-flanking region. The Biochemical journal 424, 119-127.
– Dieterle, T., Meili-Butz, S., Buhler, K., Morandi, C., John, D., Buser, P.T., Rivier, J., Vale, W.W., Peterson, K.L., and Brink, M. (2009). Immediate and sustained blood pressure lowering by urocortin 2: a novel approach to antihypertensive therapy? Hypertension 53, 739-744.
– Keller, D.I., Grenier, J., Christe, G., Dubouloz, F., Osswald, S., Brink, M., Ficker, E., and Chahine, M. (2009). Characterization of novel KCNH2 mutations in type 2 long QT syndrome manifesting as seizures. The Canadian journal of cardiology 25, 455-462.
– Meili-Butz, S., Bühler, K., John, D., Buser, P., Vale, W.W., Peterson, K.L., Brink, M., and Dieterle, T. (2010). Acute effects of urocortin 2 on cardiac function and propensity for arrhythmias in an animal model of hypertension-induced left ventricular hypertrophy and heart failure. Eur J Heart Fail 12, 797-804.
– Plaisance, I., Morandi, C., Murigande, C., and Brink, M. (2008). TNF-alpha increases protein content in C2C12 and primary myotubes by enhancing protein translation via the TNF-R1, PI3K, and MEK. Am J Physiol Endocrinol Metab 294, E241-250.

Molecular Imaging
Ultrasound
Microbubbles
Atherosclerosis
Vascular Inflammation
Cell Adhesion Molecules

Cardiovascular Molecular Imaging

PD Dr. Beat Kaufmann
Department of Biomedicine and
Division of Cardiology
University Hospital Basel

Group Members
Elham Khanicheh (PhD student)
Martina Mitterhuber (technician)

Ultrasound Molecular Imaging in Atherosclerosis

Cardiovascular diseases are the most important reason of death in western countries. Using established risk stratification algorithms, it is estimated that currently up to 40% of the adult population in western countries fall into an intermediate risk category with a 6% to 20% risk of developing symptomatic coronary heart disease within 10 years. Therefore, methods for further risk stratification of individuals at intermediate risk are needed. Noninvasive imaging has developed rapidly in the last years, and for all major imaging techniques (CT, SPECT, PET, MR, Ultrasound), recent advances have been used to better evaluate cardiovascular disease. Given the fact that atherosclerosis is a complex, chronic disorder involving inflammatory and proliferative signaling pathways, it is generally thought that imaging of molecular events during the pathogenesis of atherosclerosis could contribute to better and earlier diagnostic assessment, risk estimation and measurement of treatment effects. Molecular imaging with ultrasound contrast agents relies on the detection of microbubbles within diseased tissue. Microbubbles produce an acoustic signal owing to their resonant properties in an ultrasound field. Microbubble targeting is accomplished by either manipulating the microbubble shell for attachment of microbubbles to activated leukocytes, or by conjugation of disease specific ligands to the microbubble surface (Fig. 1).

Ultrasound molecular imaging of vascular inflammation in atherosclerosis

Up-regulation and surface expression of vascular endothelial cell adhesion molecules are early events in atherogenesis. Interactions between P-selectin on the endothelial cell surface and modified glycoprotein counterligands on leukocytes mediates rolling and activation of leukocytes. These events are requisite for firm arrest and transmigration. Slow rolling and firm adhesion are mediated by interaction between leukocyte $\alpha 4\beta 1$ and Vascular Cell Adhesion Molecule-1 (VCAM-1) on the endothelial surface. Together, these molecules play a critical role in leukocyte arrest in blood vessels, and participate in the early stages of atherogenesis.

We previously could show in a mouse model of atherosclerosis that ultrasound molecular imaging of the expression of VCAM-1 can be used for imaging of vascular inflammation (Kaufmann et al, Circulation 116, 276-284, 2007) in advanced atherosclerosis. In a reproducible age-dependent murine model of aortic atherosclerosis we were now able to show that molecular imaging of pathogenic endothelial cell adhesion molecules such as VCAM-1 and P-selectin can detect atherosclerotic vascular phenotype before the development of advanced lesions (Fig. 2). We believe that the detection of very early immune responses is an ideal application for molecular imaging with a contrast enhanced ultrasound approach. Since early identification of proatherogenic vascular phenotype is likely to be used as a screening tool, the brevity of contrast enhanced ultrasound molecular imaging protocols and the availability of ultrasound in the outpatient setting are practical advantages. Currently we are focusing on contrast enhanced ultrasound molecular imaging as a tool for the assessment of treatment effects that are thought to influence vascular inflammatory processes in atherosclerosis. Therapies aimed at interrupting inflammatory signalling mechanisms or the inciting deposition of oxidized LDL in the vessel wall are being used therapeutically or being investigated (antibodies to oxidized LDL). HMG-CoA reductase inhibitors have been shown to reduce VCAM-1 expression in experimental atherosclerosis independent of the effect on cholesterol. A method to noninvasively assess the reduction of VCAM-1 and other markers of inflammation in response to HMG-CoA might potentially be of use in assessing the adequacy of HMG-CoA dosing regimens. More importantly, non-invasive molecular imaging of the expression of VCAM-1 or P-Selectin may be useful for selecting patients for emerging anti-inflammatory therapies and assessing the response to these agents.

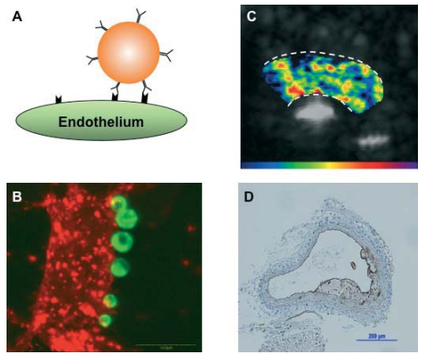


Fig. 1: Principles of ultrasound molecular imaging. Antibodies or other ligands for disease specific antigens are attached to the surface of microbubbles (A). Attachment of microbubbles to VCAM-1 on an endothelial cell *in vitro* (B). Colour coded ultrasound image of VCAM-1 targeted microbubble attachment to the aorta of an ApoE-/- mouse (C) with established atherosclerosis (D).

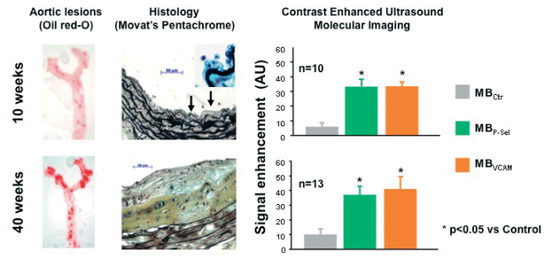


Fig. 2: Early detection of vascular inflammation in atherosclerosis. In LDLR-/-ApoBec-/- mice, minimal aortic lesions on Oil red-O stains and minimal intimal thickening are seen at 10 weeks (top row). Established atherosclerosis with aortic lesions and complicated lesions are seen at 40 weeks (bottom row). On ultrasound molecular imaging increased signal for microbubbles targeted to P-Selectin (MB_{PSel}) and to VCAM-1 (MB_{VCAM}) compared to control microbubbles (MB_{Ctr}) are seen *both* at 10 weeks (top row) and at 40 weeks (bottom row).

Selected Publications

- Behm,C.Z., Kaufmann,B.A., Carr,C., Lankford,M., Sanders,J.M., Rose,C.E., Kaul,S., and Lindner,J.R. (2008). Molecular imaging of endothelial vascular cell adhesion molecule-1 expression and inflammatory cell recruitment during vasculogenesis and ischemia-mediated arteriogenesis. Circulation 117, 2902-2911.
- Kaufmann,B.A. (2009). Ultrasound molecular imaging of atherosclerosis. Cardiovasc. Res. 83, 617-625.
- Kaufmann,B.A., Carr,C.L., Belcik,J.T., Xie,A., Yue,Q., Chadderdon,S., Caplan,E.S., Khangura,J., Bullens,S., Bunting,S., and Lindner,J.R. (2010). Molecular imaging of the initial inflammatory response in atherosclerosis: implications for early detection of disease. Arterioscler. Thromb. Vasc. Biol. 30, 54-59.
- Kaufmann,B.A., Carr,C.L., Belcik,T., Xie,A., Kron,B., Yue,Q., and Lindner,J.R. (2010). Effect of acoustic power on in vivo molecular imaging with targeted microbubbles: implications for low-mechanical index real-time imaging. J Am. Soc. Echocardiogr. 23, 79-85.

Angiogenesis
Myoblasts
Mesenchymal stem cells
Cell therapy
Gene therapy
Ischemia

Cell and Gene Therapy

Dr. Andrea Banfi
Department of Biomedicine
Institute for Surgical Research
and Hospital Management (ICFS)
Basel University Hospital

Group Members:
Dr. Roberto Gianni' Barrera (postdoctoral fellow)
Dr. Jeroen Geurts (postdoctoral fellow)
Dr. Nunzia Di Maggio (postdoctoral fellow)
Silvia Reginato (PhD student)
Uta Helmrich (PhD student)
Marianna Trani (PhD student)
Elena Groppa (PhD student)
Veronica Sacchi (PhD student)
Dr. med. Edin Mujagic*
Dr. med. René Largo*
Dr. med. Ludovic Melly

* left during report period

Cell and gene therapy for controlled angiogenesis in regenerative medicine

Therapeutic angiogenesis aims at restoring blood flow to ischemic tissues by the generation of new vessels. Our research focuses on the basic principles governing the growth of blood vessels and their translation into therapies for ischemic diseases and for improving the vascularization of tissue engineered grafts. We use precursor cells genetically engineered to express controlled levels and combinations of angiogenic factors, in order to provide both vascular growth and tissue regeneration, combining the specific advantages of cell and gene therapy.
Vascular endothelial growth factor (VEGF) is the most potent and specific angiogenic factor. However, uncontrolled expression leads to the growth of vascular tumors (angiomas). We are developing novel methods to deliver the VEGF gene alone or in combination with maturation factors, in order to increase both its safety and efficacy in vivo. Research is funded by national (SNF and Swiss Heart Foundation), European (FP7) and US agencies (NIH).

1) Controlled microenvironmental expression of VEGF

We have previously shown that the therapeutic window of VEGF delivery does not depend on the total dose administered, but rather on the microenvironmental levels of expression (Ozawa et al. J Clin Invest 2004). In fact, since VEGF remains tightly localized in tissue around the cells producing it, different growth factor concentrations do not average each other, even between neighboring muscle fibers. Therefore, a few "hotspots" of high expression are sufficient to cause hemangioma growth even if the total VEGF dose is rather low. This finding helps to explain the apparent difficulty to achieve a manageable therapeutic window in clinical trials of VEGF gene therapy. In fact, currently employed gene therapy methods, such as direct injection of constitutive adenoviral and plasmid vectors, only allow control on the total dose (titer) of gene delivered, but not the distribution of microenvironmental levels in vivo. Therefore, in order to avoid even rare "hotspots" of expression, the total dose must be kept low and efficacy is wasted (Banfi et al. Curr Atheroscl Rep 2005).
In order to translate this biological concept into a clinically applicable approach, we have recently developed a high-throughput FACS-based technology to rapidly purify progenitors expressing specific VEGF levels after in vitro transduction (Fig. 1), leading to safe and efficient angiogenesis in normal and ischemic muscle, while completely avoiding angioma growth (Misteli et al. Stem Cells 2010; Wolff et al. submitted). In preparation for a clinical application, the system is currently being applied to human myoblasts lentivirally transduced to express human VEGF.
We are currently extending this approach to transduced multipotent mesenchymal progenitors to induce controlled angiogenesis in a model of myocardial infarction, as well as to improve in vivo vascularization and bone formation in clinical-size osteogenic constructs.

2) Co-delivery of VEGF and PDGF-BB

VEGF can induce normal capillaries at low levels and angiomas at high levels and the transition between normal and aberrant angiogenesis does not occur gradually, bur rather as an all-or-none response across a threshold VEGF dose. However, we found that such threshold is not an intrinsic property of VEGF dose, but depends on the balance between VEGF-induced endothelial stimulation and vascular maturation mediated by pericyte recruitment by PDGF-BB (Fig. 2, Banfi et al, manuscript submitted).
Current projects are aimed at understanding the mechanism by which PDGF-BB modulates VEGF-induced angiogenesis and determine the dose-dependent effects of their co-expression. Furthermore, VEGF and PDGF-BB co-expression leads to homogeneous normal angiogenesis despite heterogeneous expression levels. Therefore, we are testing the hypothesis that PDGF-BB co-expression can overcome the requirement for control on the microenvironmental level distribution of VEGF and make direct gene therapy approaches, which are unsuitable to VEGF alone, safe and efficacious.

Fig. 1

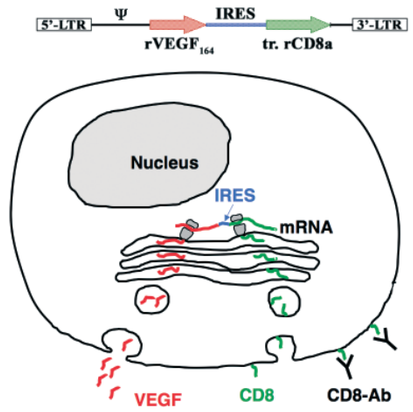
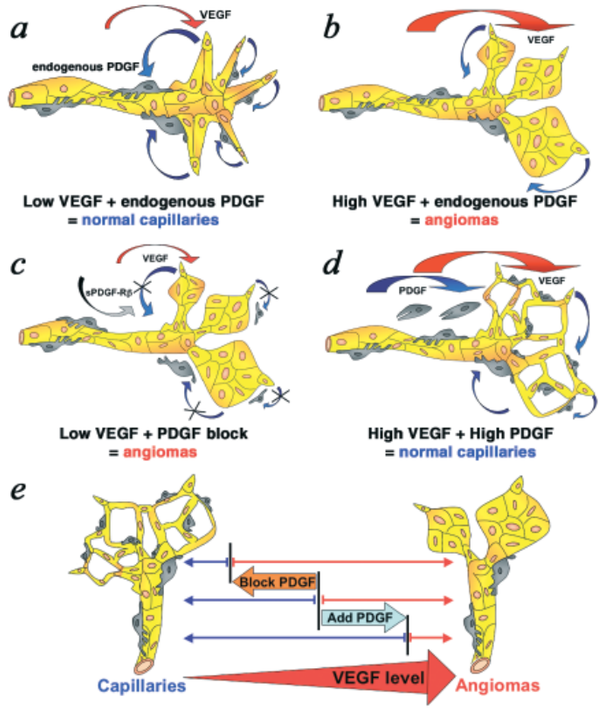


Fig. 2



Connection to Clinical Practice

From left to right:

Prof. Dr. Lorenz Gürke, Vascular and Transplantation Surgery, University Hospital Basel
Prof. Dr. Dirk Schäfer, Plastic and Reconstructive Surgery, University Hospital Basel
Prof. Dr. Friedrich Eckstein
Cardiac Surgery, University Hospital Basel

The goal of the group is to translate the basic biological principles controlling the physiological generation of normal and functional vascular networks into the design of rational strategies to induce therapeutic growth of new blood vessels. We are currently pursuing this concept in three main areas of clinical interest:

1) **Vascular and Transplantation Surgery** To achieve controlled angiogenesis in chronically ischemic muscle tissue for the treatment of peripheral artery disease patients, by using primary human myoblasts transduced with a lentiviral vector and FACS-purified to deliver controlled levels of human VEGF (Dr. T. Wolff, Dr. H. Misteli, Dr. E. Mujagic and Prof. Dr. L. Gürke, Vascular Surgery USB).
2) **Plastic and Reconstructive Surgery** To achieve rapid vascularization of the inner core of clinical-size osteogenic grafts in order to favor progenitor survival and differentiation, leading to improved bone formation, by using VEGF-expressing transduced bone marrow-derived osteoprogenitors (Dr. R. Largo and Prof. Dr. D. Schäfer, Plastic and Reconstructive Surgery USB).
3) **Cardiac Surgery** To induce controlled angiogenesis and improve cardiac function in a model of myocardial infarction by transduced and FACS-purified adipose tissue-derived mesenchymal progenitors (Dr. L. Melly and Prof. F. Eckstein, Cardiac Surgery USB).

Selected Publications

- Sanchez de Miguel, L., Neysari, S., Jakob, S., Petrimpol, M., Butz, N., Banfi, A., Zaugg, C.E., Humar, R. and Battegay, E.J. (2008). B2-kinin receptor plays a key role in B1-, angiotensin converting enzyme inhibitor-, and vascular endothelial growth factor-stimulated in vitro angiogenesis in the hypoxic mouse heart. Cardiovasc Res *80*, 106-113.
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- Kupatt, C., Hinkel, R., Pfosser, A., El-Aouni, C., Wuchrer, A., Fritz, A., Globisch, F., Thormann, M., Horstkotte, J., Lebherz, C., et al. (2010). rAAV-cotransfection of VEGF-A and PDGF-B resolves chronic ischemic malperfusion: Role of vessel maturation. J Am Coll Cardiol *56*, 414-422.
- Scherberich, A., Müller, A.M., Banfi, A. and Martin, I. (2010) Adipose tissue-derived progenitors for engineering osteogenic and vasculogenic grafts. J Cell Physiol *225*, 348-353.

Angiogenesis
Myoblasts
Mesenchymal stem cells
Cell therapy
Gene therapy
Ischemia

Clinical Pharmacology

Prof. Dr. Stephan Krähenbühl
Department of Biomedicine and
Division of Clinical Pharmacology and Toxicology
University Hospital Basel

Group Members:
Dr. Peter Lindinger (postdoctoral fellow)
Dr. Karin Brecht (postdoctoral fellow)
Réjane Morand, MSc (PhD student)
Swarna Mensani, MSc (PhD student)
Andrea Felser, MSc (PhD student)
Peter Mullen, MSc (PhD student)
Estelle Hirzel, MSc (PhD student)
Patricia Hägler (Master student)

Cellular and *in vivo* models for idiosyncratic toxicity of drugs

Most drug toxicities are related to a too high exposure of the patients to a certain drug. This toxicity is named type A toxicity, is related to the pharmacological action of drugs and is mostly detected already during the development phase. Another type of toxicity is named type B or idiosyncratic toxicity. Idiosyncratic toxicity is rare, mainly not related to the pharmacological action of a drug and usually not detected during drug development. Target organs are mostly the liver and/or skin, but may also be skeletal muscle, nervous system, bone marrow or any other organ. Mechanisms are immunological (mostly T-cell driven) or non-immunological (so called metabolic) toxicity.
Regarding the non-immunological type of idiosyncratic toxicity, many features can be reproduced *in vitro* using isolated cells, cell cultures and/or isolated cell organelles exposed to high concentrations of a drug or drug metabolites. This observation has led to the concept that patients showing this type of toxicity have risk factors rendering them more sensitive to drug effects than the average patient.
Our research in this field has two aims: 1. to explore mechanisms of idiosyncratic toxicity *in vitro* (cell cultures, isolated cell or cell organelles) and *in vivo* in animals, and 2. to find out possible risk factors and predictive cell or animal models.
One example is the toxicity of benzbromarone and amiodarone, two benzofurane derivatives. Amiodarone, an antiarrhythmic drug, has different types of toxicity, one of them is liver toxicity. The histological picture of affected livers shows fat accumulation, possibly explained by impaired β-oxidation of fatty acids. We could demonstrate inhibition of β-oxidation and of other mitochondrial functions, which was associated with hepatocyte apoptosis and/or necrosis, for both amiodarone and benzbromarone. Further studies showed that this type of toxicity is associated with a certain structure of the side chain of amiodarone. Assuming that the desethylated metabolites of amiodarone are more toxic than amiodarone itself, we currently investigate the toxicity of amiodarone in HepG2 cells expressing CYP3A4 and the effects of benzbromarone and amiodarone on the mitochondrial proteome.
A second example is the hepatic toxicity of valproate. Valproate is very rarely associated with acute liver failure; mainly early in therapy and more often in children than in adults. Also in this case, the important histological feature of the affected livers is fat accumulation. We tested the hypothesis whether a mitochondrial damage is a risk factor for increased hepatotoxicity using $jvs^{+/-}$ mice. $Jvs^{+/-}$ mice are heterozygous for a mutation in the gene encoding octn2, the renal carnitine carrier. $Jvs^{+/-}$ mice have decreased carnitine body pools by approximately 50%, but can oxidize fatty acids efficiently. We could demonstrate that valproate was associated with a larger decrease in hepatic β-oxidation and with more accentuated hepatotoxicity in $jvs^{+/-}$ than in wild type mice. Further studies in this field are focused on the mitochondrial effects associated with valproate. We are currently investigating the effect of valproate on the mitochondrial proteome in different cell types.
Statin-associated rhabdomyolysis is a third area of interest. In a first study, we could show that lipophilic statins are mitochondrial toxins and can induce apoptosis and/or necrosis in cultured skeletal muscle cells. More recently we demonstrated that statins inhibit cholesterol biosynthesis also in skeletal muscle cells and that this inhibition is associated with impaired O- and N-glycosylation of proteins. Future studies include the effect of statins on cardiomyocytes, the effect of statins on the mitochondrial proteome and on the IGF-1 signalling pathway as well as on the function of skeletal muscle, liver and heart of mice with impaired mitochondrial β-oxidation.

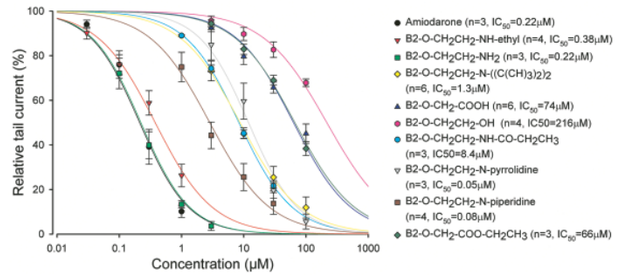

Fig. 1: Inhibition of the hERG channel by amiodarone and amiodarone derivatives (Br J Pharmacol 2008;155:585-95).

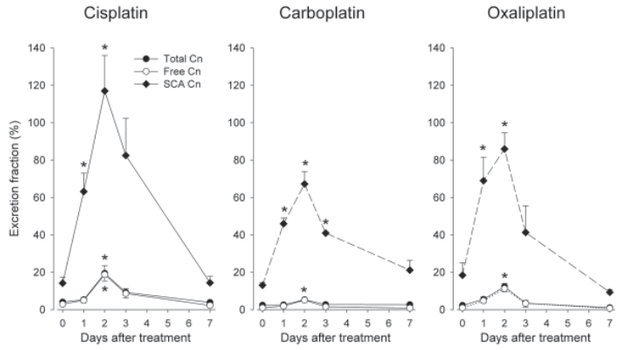

Fig. 2: Urinary excretion of carnitine by patients treated with a single dose of different platin derivatives (Nephrol Dial Transplant 2010;25:426-33).

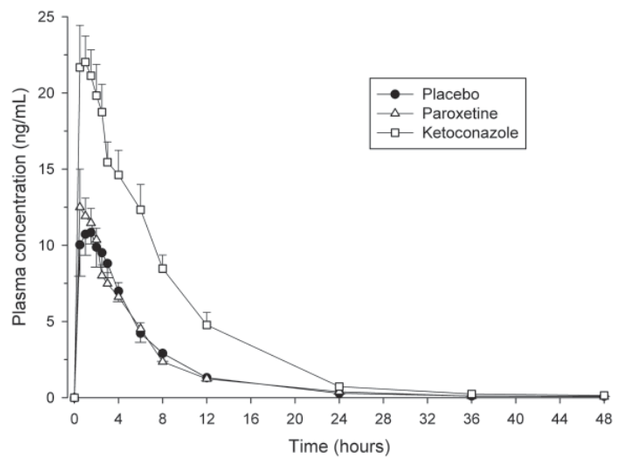

Fig. 3: Plasma concentration-time profile of oxycodone in subjects treated with CYP inhibitors (Eur J Clin Pharmacol 2010;in press).

Connection to Clinical Practice

Translational medicine in clinical pharmacology and toxicology

Clinical Pharmacology is well suited to connect clinical and basic research.

1. Impact of basic research in toxicology on clinical problems: Amiodarone, valproate and statins are drugs used frequently in the clinical setting. The toxicity of these drugs is therefore and important clinical problem. Solutions to this problem can directly help patients treated with such drugs and the knowledge gained may help to develop predictive models improving drug safety.
2. Finding answers to clinical questions with specific research projects: Drug interactions and toxicity of thienopyridines are clinically important. We recently studied drug interactions with the activation of clopidogrel *in vitro* using different models. The results of these investigations can be directly linked to the clinical management of patients treated with clopidogrel. Another example is the *in vitro* investigation of the clinical observation that patients treated with platin derivatives excrete high amount of carnitine. Recent investigations with cell models in our laboratory provide possible mechanisms for this finding. Currently, we are investigating the interaction of valproate with the carnitine pool in humans *in vivo* and in cell cultures *in vitro*.
3. Specific clinical projects: Our division heads a phase I clinical trial unit, enabling us to perform clinical research projects. We are particularly interested in studies concerning bioequivalence of drugs, food effects on drugs, drug-drug interactions and dosage adaptation in specific patient populations. Beside such trials, we are currently developing tools for better kinetic characterization of probands and patients engaged in clinical studies.

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- Knapp, A.C., Todesco, L., Beier, K., Terracciano, L., Sagesser, H., Reichen, J., and Krahenbuhl, S. (2008). Toxicity of valproic acid in mice with decreased plasma and tissue carnitine stores. J Pharmacol Exp Ther 324, 568-575.
- Mullen, P.J., Luscher, B., Scharnagl, H., Krahenbuhl, S., and Brecht, K. (2010). Effect of simvastatin on cholesterol metabolism in C2C12 myotubes and HepG2 cells, and consequences for statin-induced myopathy. Biochem Pharmacol 79, 1200-1209.
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- Zahno, A., Brecht, K., Bodmer, M., Bur, D., Tsakiris, D.A., and Krahenbuhl, S. (2010). Effects of drug interactions on biotransformation and antiplatelet effect of clopidogrel in vitro. Br J Pharmacol 161, 393-404.

Genodermatosis
Skin lesions
Gardner syndrome
Skin cancer
Hereditary cancer
Genetics

Dermatology

Prof. Dr. Peter H. Itin
Department of Biomedicine
and Department of Dermatology
University Hospital Basel

Group Members
Dr. Bettina Burger (project leader)
Dr. Iris Spoerri (postdoctoral fellow)
Rosaria De Lorenzo (Study nurse)
Danielle Stegmann (PhD student)
Nadja Cattani (MD student)*
Nicole Getzmann (Master student)*

*left during report period

Skin lesions in connection with hereditary diseases and their value as a predictive marker

Skin is the largest human organ and important in many different functions. It is not only to protect its host from environment, but also to allow interaction with the environment at the same time. Skin is not only a physical permeability barrier but also responsible for physical appearance. It protects the person from infectious agents and UV-light; beneath wound repair and regeneration also thermoregulation and sensation are part of its function. As in other organs malignant neoplasms as well as benign lesions occur and affect quality of life and life itself. Types of malignant tumors are melanoma, squamous cell cancer (SCC), and basal cell cancer (BCC) amongst others, arising from different cell types in the skin. Benign tumors like fibromas and lipomas are common in the general population without pathogenicity, but sometimes they occur as a sign of a severe disease.

One of our research topic focuses on diagnostic potential of such benign lesions as a non-invasive predictive marker for an inherited colorectal cancer disease named Gardner syndrome. Gardner syndrome has been described as the triad of colonic polyposis, osteomas and soft tissue tumors in 1950. Characteristic benign skin alterations are epidermal cysts (elastic node in the skin), fibroma (benign neoplasm of connective tissue), and lipoma (benign neoplasm of adipose tissue) amongst others. These skin lesions arise also in the common population, but more often in patients with Gardner syndrome.
In 1987 results of linkage analysis suggested that Gardner syndrome and familial colorectal cancer (FAP) are allelic disorders. In 1991, the adenomatous polyposis coli gene (APC) on chromosome 5q21-22 was identified, whose product is expressed in many tissues. It was recognized that mutations in the APC gene were the cause for both Gardner syndrome and FAP. FAP is an autosomal dominant disorder with a complete penetrance characterized by inheritance of colorectal cancer and specific extracolonic features. Typical manifestation is the development of hundreds to thousands of colorectal polyps which have a nearly 100% progression rate to colorectal cancer, when left untreated. The prevalence of FAP is estimated at 1 in 5000 – 10'000 and accounts for nearly 1% of all colorectal cancers. More than 90% of families affected by FAP have a mutation in the APC gene and up to 25% are de novo mutation. Because of the complete penetrance of the disease a livelong monitoring of the colorectum by sigmoidoscopy is recommended for patients with an identified mutation, starting at the age of 10 to 12 years.
In addition to gastro-duodenal polyps, which are the only main feature with 100% penetrance, different skin lesions may arise. In addition to already mentioned manifestations which are on our focus (epidermal cysts, fibromas, and lipomas), desmoids (a low malignant type of fibrosarcoma with very high relapse potential), osteomas (benign bone tumor), congenital hypertrophy of the retinal pigment epithelium (CHRPE), and dental abnormalities occur in some of the affected patients. Recent analyses reveal that many patients with APC mutation show some of Gardner typical skin lesions, but exact data are still unknown.
Reasons for skin lesions as well as connections between these skin lesion and mutation site in the APC are scarcely investigated and poorly understood. Occurrence and expression of skin lesions in FAP patients vary between individuals even in families with the same APC mutation. Currently it is impossible to use skin lesions as a predicting factor because no data are available, even though some people are supposed to develop skin lesions like fibromas or lipomas before colorectal adenomas or carcinomas arise.

We are interested in value of the mentioned specific skin lesions for early recognition of patients, mainly patients with de novo mutations. Furthermore the difference of appearance of these benign skin lesions in patients with Gardner syndrome and sporadic cases without underlying disease will be investigated. In the last years our research has focussed on clinical description and characterisation of skin lesions in FAP patients. Since two years we have contacted and investigated patients with genetically confirmed FAP in collaboration with the Department of Medical Genetics of the University Hospital Basel. Until now more than 40 patients are examined, 85% of whom have shown extracolonic manifestations, including about 57% skin specific lesions. Analysis of clinical data reveals that presymptomatic identification of de novo FAP patients could be possible by an attentive medical doctor before colorectal adenomas or carcinomas arise. In our study the positive predictive value of cutaneous lesions as a marker of FAP was about 75%. By these specific skin manifestations some presymptomatic patients could be identified and be carried to further examinations, e.g. an indirect ophthalmoscopic examination for CHRPE and/or a coloscopy.
A brand-new topic of our research is the development of squamous cell cancer (SCC) relating to hereditary diseases. SCCs arise in the epidermis as precancerous and develop to metastatic cancer over several weeks or years. Amongst others UV-light is conducive to formation of SCC, but genetic predisposition and influences of viruses are also known in some cases. Known genetic factors are mutations in two genes, TMC6 and TMC8, causing the genodermatosis epidermodysplasia verruciformis (EV). EV is a rare autosomal recessive dermatosis characterized by susceptibility to infection by specific human papilloma viruses (HPV), which contributes to the development of flat wart like and pityriasis versicolor like lesions, Bowen type squamous cell carcinoma in situ and ultimately invasive SCC (see figure 1 and 2). In 2002 it was discovered that patients with EV carry mutations in the mentioned genes TMC6 and TMC8 (both on chromosome 17q25.3). Mutations in these genes could be found in only 75% of all patients with EV. TMC6 and TMC8 are members of the transmembrane channel-like proteins which are localized in the endoplasmic reticulum. The function of TMCs is widely unknown and the linkage to development of EV is not well understood. Both genes contain a numerous SNPs with unknown influence to EV. Our project aims on characterization of their influence to development of EV particularly in clinical diagnosed patients without identified mutation.

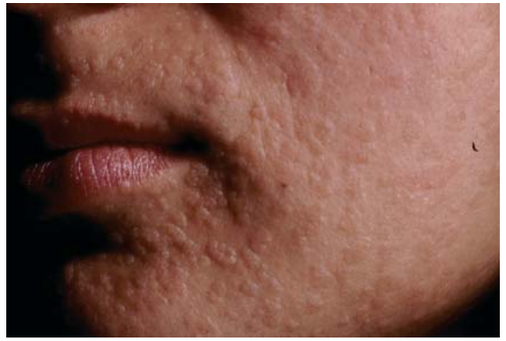

Fig. 1: Flat wart like lesions in a patient with EV.

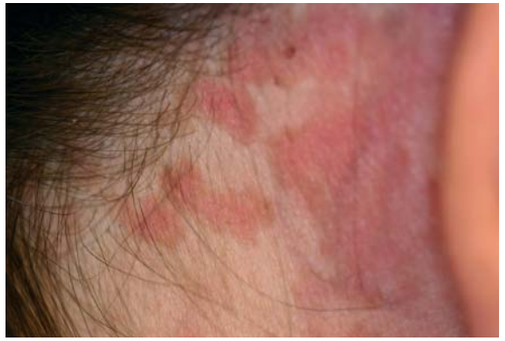

Fig. 2: Pityriasis versicolor like lesions in an EV patient.

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Limb development
Mouse genetics
Organogenesis
Signalling networks
Systems biology

Developmental Genetics

Prof. Dr. Rolf Zeller
Dr. Aimée Zuniga
Department of Biomedicine
University of Basel

Group Members
Christine Müller-Thompson (personal assistant 50%)
Alexandre Schauerte (research assistant)*
Dario Speziale (research assistent)
Dimitri Robay (research assistant)*
Dr. Javier Lopez-Rios (postdoctoral fellow)
Dr. Catherine Vaillant (postdoctoral fellow)
Dr. Jean-Denis Benazet (postdoctoral fellow)
Dr. Alexandre Gonçalves (postdoctoral fellow)
Dr. Amandine Duchesne (postdoctoral fellow)
Simone Probst (PhD student)
Marco Osterwalder (PhD student)
Emanuele Pignatti (PhD student)
Frederic Laurent (PhD student)
Adrian Hermann (Master student)
Sandro Nuciforo (Master student)
Patric Schlenker (Master student)

*left during report period

The mouse limb bud: a paradigm to study the signalling networks orchestrating organogenesis

We use a systems biology approach that combines mouse molecular genetics, transcriptome analysis, biochemistry with mathematical simulations of the relevant interactions (in collaboration with D. Iber from D-BSSE) to gain insight into signalling interactions that control vertebrate limb bud organogenesis. One of the fascinating problems that we study is how progenitor cells are selected as embryonic organizers. These organizing centres orchestrate the signalling networks that pattern the limb bud along its three axes and determine the identities of the chondrocyte progenitors that form the limb skeleton (Fig. 1). Together with many other groups, we have established that cells responding to signals activate specific antagonists, which either inhibit signalling or interfere with signal transduction. In fact, it has become clear that embryonic cells produce many antagonists to tune-down signals upon receiving them. Therefore, a significant part of our research focuses on understanding how such signalling systems are established. We showed that activation of the BMP antagonist Gremlin1 in the limb bud mesenchyme is key to initiating the signalling interactions between the main signalling centres (Fig. 1). We have uncovered a robust signalling system that regulates limb bud development from initiation to termination in a largely self-regulatory manner (Fig. 2). One of the most surprising aspects we uncovered is that high BMP activity is required to initiate the signalling system, but that it drops rapidly as a consequence of BMP4-mediated activation of Grem1 expression (Fig. 2). Genetic inactivation of BMP4 during initiation disrupts limb development, while slightly later inactivation causes digit polydactyly – i.e. the opposite phenotype. These results would have been impossible to explain without the mathematical simulations and illustrate the importance of tight regulation of signalling for normal development. The resulting feedback signalling system interlinks the BMP, SHH and FGF pathways and compensates signalling variations by inter-pathway connectivity and self-terminates signalling at the right moment (Fig. 2). Our publication has allowed us to formulate a first integrative model, which provides the conceptual framework for our systems biology approach to limb bud organogenesis. Using genome-wide, integrative approaches, we have been able to gain first insights into how SHH coordinates development of the two main limb bud axes (Probst et al., submitted).

Our findings are also relevant to tissue engineering and regenerative medicine and we have initiated a collaboration with I. Martin to analyse the expression and functional relevance of the endogenous signals during cartilage and bone development of human mesenchymal stem cells. Furthermore, aberrant signalling feedback loops and modulation of their activities may underlie tumourigenesis. Therefore, we have initiated a study of the most common and deadly juvenile brain tumours in humans – medullablastomas. We have previously shown that PN1 is an extra-cellular modulator of SHH signalling during normal cerebellar development. However, PN1 is also highly expressed in the majority of human medullablastoma biopsies and medullablastomas arising in Ptch1 heterozygous mice. Genetic reduction of PN1 drastically reduces the tumour frequency in Ptch1 mice. Our studies reveal that elevation of PN1 is a key event during medullablastoma progression. In the long run, we hope to test novel therapeutic strategies in the Ptch1 mouse model.

One of the major challenges is the systems biology-type analysis of complex signalling networks. We need to quantitate pathway activities using the appropriate real-time sensors. For this purpose, we have developed a novel genetic tool – dRMCE – that allows rapid and highly efficient retargeting of a vast number of genomic loci in mouse ES-cells. Using dRMCE, we can easily introduce epitope tags into the endogenous key regulator genes for specific detection in vivo and functional identification of interacting proteins and target genes. Another truly challenging task is the mathematical simulation of the relevant signalling interactions using quantitative data. The combination of systematic genetic and cell-biochemical analysis with such simulations should enable us to gain insights into the complexity of the signalling networks that orchestrate organ and tissue development.

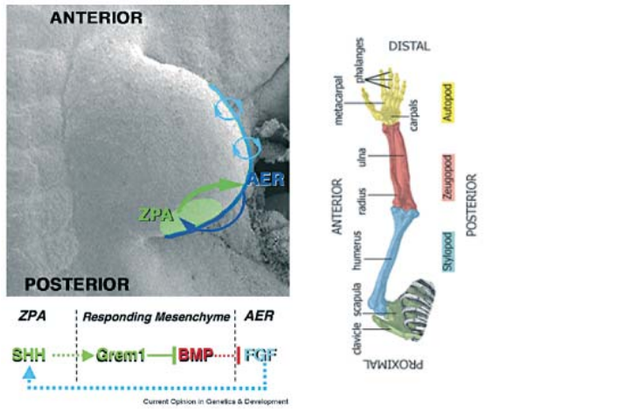

Fig. 1: Left Panel: The development of vertebrate limb buds is orchestrated by feedback signalling between two main organizing centers: the SHH expressing ZPA in the posterior mesenchyme and the FGF expressing apical ectodermal ridge (AER). The BMP antagonist Gremlin1 is essential to establish the epithelial-mesenchymal feedback signalling interactions (taken from Zeller and Zuniga). Right panel: The skeletal elements of a human arm skeleton (adapted from Vesalius, 1543). The stylopod (S; in blue) gives rise to the most proximal limb bud skeletal element, the humerus. The zeugopod (Z, in red) forms the radius (anterior) and ulna (posterior) and the distal autopod (A, in yellow) the wrist (carpals), palm (metacarpals) and digit (phalanges) bones

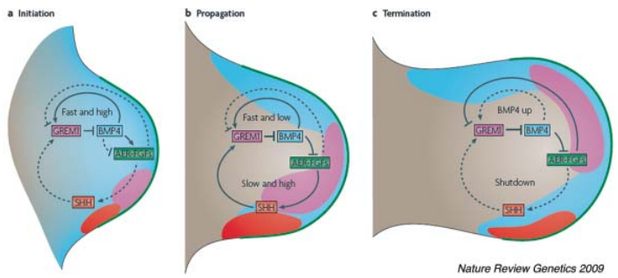

Fig. 2: A self-regulatory system of signalling feedback loops controls the orderly progression of limb bud organogenesis from initiation to termination of its initial patterning and outgrowth (taken from Zeller et al., 2009).

Selected Publications

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- Galli A., Robay D., Osterwalder M., Bao X., Bénazet J.D., Tariq M., Paro R., Mackem S. and Zeller R. (2010). Distinct Roles of Hand2 in Initiating Polarity and Posterior Shh Expression during the Onset of Mouse Limb Bud Development. PLoS Genet. 2010 Apr 8;6(4):e1000901.
- Osterwalder M., Galli A., Rosen B., Skarnes W.C., Zeller R.* and Lopez-Rios R.* (*joint senior authors). (2010). Dual RMCE permits high-throughput re-engineering of mutant alleles in mouse ES cells. Nat Methods. 2010 Nov;7(11):893-5.
- Scotti C., Tonnarelli B., Papadimitropoulos A., Scherberich A., Schaeren S., Schauerte A., Lopez-Rios J., Zeller R., Barbero A. and Martin I. (2010) Recapitulation of endochondral bone formation using human adult mesenchymal stem cells as a paradigm for developmental engineering Proc. Natl. Acad. Sci. USA 107, 7251–7256.

Hematopoiesis
Myeloproliferative disorders
Kinase inhibitors
Transgenic mice
Familial predisposition
Genomic rearrangements

Experimental Hematology

Prof. Dr. Radek Skoda
Department of Biomedicine
University Hospital Basel

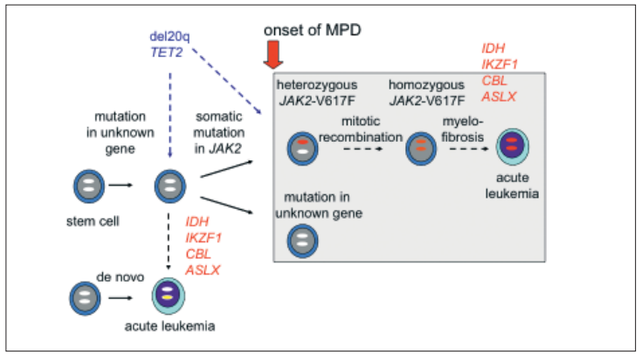
Group Members (R. Skoda)
Dr. Sophie Candfield (postdoctoral fellow)
Dr. Adrian Duek (postdoctoral fellow)
Dr. Lucia Kubovcakova (postdoctoral fellow)
Dr. Sai Li (postdoctoral fellow)
Dr. Pontus Lundberg (postdoctoral fellow)
Dr. Franz Schaub (postdoctoral fellow)*
Dr. Alexey Veligodskiy (postdoctoral fellow)
Dr. Anita Hochuli Daglio (personal assistant)
Annalisa Pianta (PhD student)
Sabine Tresch (Master student)
Renate Looser (technician)
Hui Hao-Shen (technician)
Soon-Siong Teo (technician)*
Dr. Dejing Pan (postdoctoral fellow)*
Dr. Kun Liu (postdoctoral fellow)*

* left during report period

Molecular pathogenesis of myeloproliferative neoplasms

Myeloproliferative neoplasms (MPN) are a group of blood diseases characterized by aberrant proliferation of precursors of the myeloid, erythroid and megakaryocytic lineages. They represent clonal stem cell disorders with a tendency towards leukemic transformation. Currently, no curative therapy is available. MPNs comprise 3 entities: polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). The goal of our studies is to advance the understanding of the molecular events that cause MPN and influence its progression to leukemia. A recurrent mutation in exon 14 of the Janus kinase 2 (JAK2) gene that substitutes a valine to phenylalanine at position 617 (JAK2-V617F) is present in a majority of patients with MPN, in particular PV. This mutation leads to constitutive activation of the Jak2 kinase and represents a driver for the proliferation of hematopoietic cells. Activating mutations in exon 12 of JAK2 have been described in patients with PV that are negative for JAK2-V617F. Despite this progress, several questions remain unsolved including how a single JAK2 mutation causes three different MPN phenotypes, what other genes might be involved and what determines the progression to acute leukemia. We are examining these questions by combining three approaches: molecular studies in patients with sporadic MPN, genetic analysis of familial MPN and transgenic mouse models that mimic the human disease.

Analysis of clonal progression in MPN
In a subset of patients with sporadic MPN we found evidence for mutations in as yet unknown genes, some of which may precede the acquisition of JAK2-V617F. In some MPN patients only a small percentage of blood cells carries the JAK2-V617F mutation, while surprisingly, the remaining cells are clonal. By examining individual colonies grown from patient's peripheral blood we were able to determine the order of events in MPN patients that carry more than one mutation. We found that deletions on chromosome 20q (del20q) or mutations in the TET2 gene in some patients occur before JAK2-V617F, whereas in other patients the inverse order of events occurred. In addition, a substantial proportion of patients displayed two independent clones, i.e. biclonal disease. These results are compatible with the hypothesis that a clonal pre-JAK2 event is present in a subset of stem cells in these patients. This pre-JAK2 mutation predisposes these stem cells to acquire JAK2-V617F and in rare cases also to acquire other mutations and progress to acute leukemia (Fig. 1). Using the single colony approach, the clonal anatomy of disease progression can be studied in serial samples from the same patients.



Familial predisposition for MPN
Familial syndromes resembling MPN can be grouped into two classes:
1. Inherited disorders with high penetrance and polyclonal hematopoiesis.
2. Hereditary predisposition to true MPN, with low penetrance, clonal hematopoiesis and occurrence of somatic mutations, e.g. in JAK2-V617F. We identified mutations in the thrombopoietin (THPO) gene as the cause for an inherited form of thrombocythemia in several families with a "class 1" phenotype. In another family we found a previously described mutation in the gene for the thrombopoietin receptor (MPL). However, in the majority of families neither THPO nor MPL is mutated. The search for these disease genes is ongoing. Families with "class 2" phenotype are more common than generally assumed. These germ line mutations increase the likelihood of acquiring a somatic JAK2-V617F mutation. We are using genetic methods to map the locus for these pre-disposing mutations.

Mouse models for MPN
We generated JAK2-V617F transgenic mice that express a human JAK2-V617F gene. This conditional construct can be activated by Cre-recombinase. Depending on the mode of Cre-mediated activation, these mice developed a phenotype resembling ET with strongly elevated platelet counts or a PV-like phenotype with increased hemoglobin, thrombocytosis and neutrophilia. We found that the ratio of mutant to wild type JAK2 correlated with the phenotypic manifestation. These results suggest that the relative activity of the mutant JAK2 may be a major determinant of the ET versus PV phenotype. We currently use this model to assess possible synergy between JAK2-V617 and inactivating TET2 mutations in vivo. We have now developed a similar model for a JAK2 exon 12 mutation. These mouse models can be used for pre-clinical screening of Jak2 inhibitors and also allow us to address questions related to the nature of the MPD initiating stem cells.

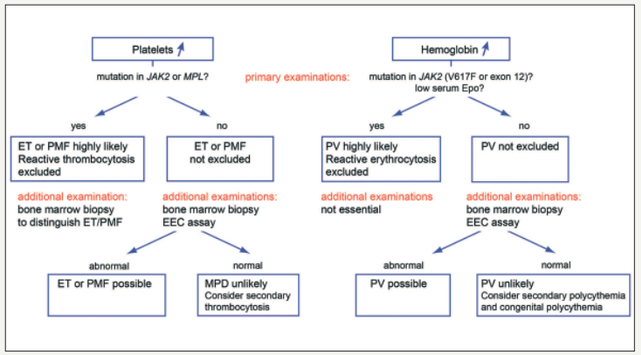
Selected Publications

- Schaub, F.X., Looser, R., Li, S., Hao-Shen, H., Lehmann, T., Tichelli A, Skoda, R.C., Clonal analysis of TET2 and JAK2 Mutations suggests that TET2 can be a late event in the progression of myeloproliferative neoplasms (2010) Blood 115: 2003-7
- Schaub, F.X., Jäger, R., Looser, R., Hao-Shen, H., Hermouet, S., Girodon, F., Tichelli, A., Gisslinger, H., Kralovics, R., Skoda, R.C., Clonal analysis of deletions on chromosome 20q and JAK2-V617F in MPD suggests that del20q acts independently and is not one of the pre-disposing mutations for JAK2-V617F (2009) Blood 113: 2022-7
- Tiedt, R., Coers, J., Ziegler, S., Wiestner, A., Hao-Shen, H., Bornmann, C., Schenkel, J., Karakhanova, S., de Sauvage, F.J., Jackson, C.W., Skoda, R.C., Pronounced thrombocytosis in transgenic mice expressing reduced levels of Mpl in platelets and terminally differentiated megakaryocytes (2009) Blood 113: 1768-77
- Li, S., Kralovics, R., De Libero, G., Theocharides, A., Gisslinger, H., Skoda, R.C. Clonal heterogeneity in polycythemia vera patients with JAK2 exon12 and JAK2-V617F mutations (2008) Blood, 111:3863-6
- Tiedt, R., Hao-Shen, H., A. Sobas, M.A., Looser, R., Dirnhofer, S., Schwaller, J., and Skoda R.C. Ratio of mutant JAK2-V617F to wild type Jak2 determines the MPD phenotypes in transgenic mice (2008) Blood, 111:3931-40

Connection to Clinical Practice

Improved diagnostics of MPN and new therapeutic approaches: From bench to bedside (Prof. A. Tichelli)

The first challenge in the diagnostic approach to MPN is to distinguish between reactive changes (i.e. elevated blood counts secondary to other diseases) and true MPN (i.e. primary disease of the bone marrow cells). In a second step, the definitive category of the MPN, i.e. polycythemia vera (PV), essential thrombocythemia (ET) or primary myelofibrosis (PMF), has to be established. Until recently, MPN was a diagnosis of exclusion and sometimes long-term follow-up was needed to definitively distinguish MPN from reactive alterations. The discovery of the JAK2-V617F mutation has completely changed the diagnostic approach to patients with a suspected MPN. Since JAK2-V617F is absent in reactive thrombocytosis, erythrocytosis or leukocytosis, the presence of a JAK2 mutation can be used to exclude such reactive changes. JAK2-V617F can be found in about 95% of patients with PV and in approximately 50-60% of PMF and ET and also in other chronic myeloid neoplasms, such as refractory anemia with ringed sideroblasts and thrombocytosis (RARS-T). Therefore, mutation screening for JAK2-V617F cannot distinguish between different forms of MPN and blood counts, erythropoietin levels and additional parameters (bone marrow trephine and cytology, cytogenetic analysis) and search for less frequent mutations (JAK2 exon 12, MPL, thrombopoietin, Epo-receptor and others) have to be taken into consideration. In the near future, classification and diagnosis of myeloid neoplasm will be mainly based on disease-specific genetic markers. Furthermore, inhibitors of JAK2 are being developed and some of them are already undergoing clinical trials. There is hope that these JAK2-inhibitors will prove to be effective for treating patients with MPN.



Hematopoietic stem cells
Bone marrow
Leukemia
Transplantation
Flt3 ligand
Natural killer cells

Experimental Hematology

Prof. Dr. Aleksandra Wodnar-Filipowicz*
Department of Biomedicine
University Hospital Basel

Group Members
PD Dr. Christian Kalberer (postdoctoral fellow)
Dr. Gabriela Oser (postdoctoral fellow)
Dr. Linda Kenins (postdoctoral fellow)
Dr. Uwe Siegler (postdoctoral fellow)
Heike Himmelreich (PhD student)
Ulrich Langenkamp (MD/PhD student)
Simon Jörger (MD Dissertant)
Silvia Sendelov-Plattner (technician)
Iryna Perahud (technician)

* retired December 2010

The control of blood cell development after stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is the front-line therapy for acute leukemias and other rapidly progressing blood cell disorders with poor prognosis. High doses of cytostatic agents, total-body irradiation, and transplantation of allogeneic stem cells offer the best chance of cure, but relapses are frequent and often fatal. Therefore, understanding the microenvironmental interactions and requirements of normal and leukemic hematopoietic cells in the bone marrow niches after HSCT has important therapeutic implications.

Role of flt3 ligand in recovery of normal hematopoiesis
Based upon our previous findings, flt3 ligand (FL), a hematopoietic cytokine interacting with tyrosine kinase flt3 receptor on stem and early progenitor cells, is expressed in the bone marrow, promoting a recovery of transplanted healthy stem cells. Recently, we unraveled a role of FL in the development of T cells in the thymus. As the thymus does not contain hematopoietic stem cells with a self-renewing potential, T cell production throughout life depends on constant immigration of bone marrow-derived T cell progenitors from the blood into the thymus. We identified perivascular fibroblasts as the localized source of FL at the entry site of flt3 receptor-positive thymocyte precursors (Fig.1). Using the wild-type, FL-knockout and flt3 receptor-knockout animals in bone marrow transplantation, fetal thymic organ cultures, and renal grafting experiments, we demonstrated an intra-thymic requirement for FL in steady-state thymopoiesis. Expression of FL around the thymic blood vessels is upregulated following total-body irradiation, and results in an accelerated immunoreconstitution of the thymus following HSCT. Since the thymic activity is severely affected by myeloablative conditioning, and since delayed recovery of T cell immunity is a major complication of HSCT, the identification of FL as a rescue cytokine in the repair process of the thymus is important from the clinical perspective.

Role of flt3 ligand in malignant hematopoiesis
The microenvironmental requirements of leukemias and its self-renewing component, leukemic stem cells (LSCs), are largely unknown, however important for understanding the pathophysiology of the disease. Using a serial transplantation mouse model of acute myeloid leukemia driven by the human MLL-ENL translocation transgene, we studied leukemia growth in an FL-deficient background. We found that leukemia growth is favored in a FL proficient microenvironment, indicating that FL plays a role in supporting the maintenance of flt3 receptor-positive LSCs in their niche. Analysis of the bone marrow stroma, using flow cytometry and immunohistochemistry, revealed expression of FL by cell populations belonging to the endothelial compartment. It is intriguing to speculate that the FL-expressing stromal cells represent the vascular niche that supports the leukemia-initiating LSCs.

Role of NK cells in control of leukemia
NK cells are the innate immunity lymphocytes designated to recognize and kill malignant cells. Our studies exploit the alloreactivity of NK cells for recognition of human acute myeloid leukemia (AML). We generated human NK cell lines with single inhibitory killer immunoglobulin receptor (KIR) specificities for the major HLA-class I allotypes and demonstrated an efficient cytolysis of KIR-HLA-class I-mismatched patient-derived AML blasts. The anti-leukemic effect was augmented pharmacologically with the histone deacetylase (HDAC) inhibitor, valproic acid, which increased the recognition of AML blasts through NKG2D receptor-ligand interactions. Extending these findings to LSCs, the self-renewable component of leukemia, we showed that NK effectors with single KIR specificity can effectively recognize HLA-mismatched AML-$CD34^+CD38^-$ LSCs, while healthy bone marrow $CD34^+CD38^-$ hematopoietic stem cells are spared. Using a murine NOD/SCID xenotransplantation model, we demonstrated an effective cytolysis of human leukemia by adoptive transfer of alloreactive NK in vivo. This served as a basis for development of a clinical immunotherapy project with NK cells to prevent leukemia relapse after HSCT (see "Connection to Clinical Practice").

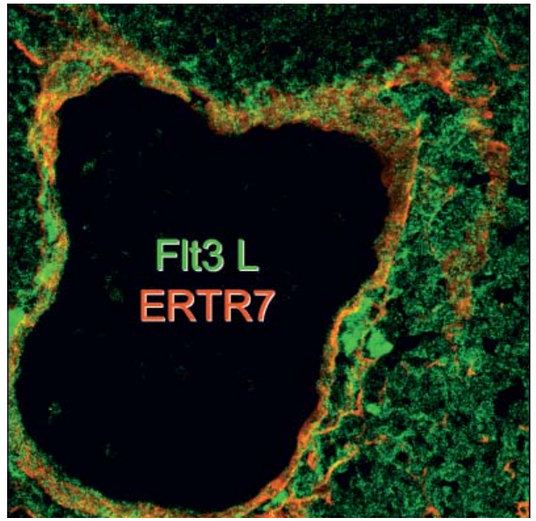


Fig. 1: Expression of Flt3 ligand (FL) in the thymus localizes to the perivascular fibroblasts. FL, green signals; ERTR7, red signals indicating the perivascular zone.

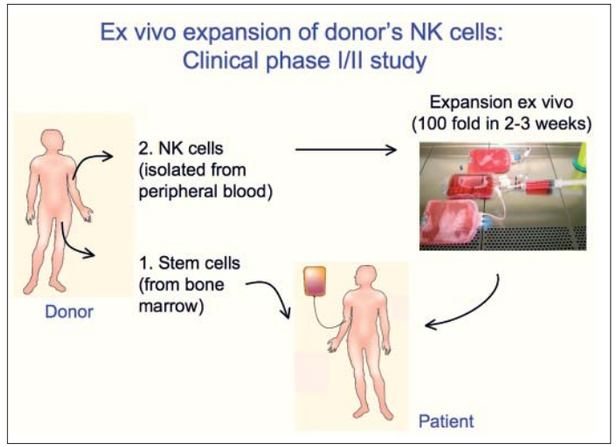


Fig. 2: Phase I/II study with ex vivo-expanded donor NK cells in AML patients treated by haploidentical HSCT.

Connection to Clinical Practice

Name of Research Group Leaders
Prof. Dr. Alois Gratwohl
Prof. Dr. André Tichelli
Prof. Dr. Aleksandra Wodnar-Filipowicz
PD Dr. Christian Kalberer

Immunotherapy of human leukemia with NK cells: From bench to bedside

This study aims at advancing the immunotherapeutic trials in hematological malignancies by developing clinically-suitable approaches to increase the recognition and elimination of human AML by NK cells. The infrastructure of good manufacturing practice (GMP) for large scale NK cell expansion was set up for most efficient and secure procedures to obtain a highly purified NK cell product for clinical use. The GMP-compliant protocol of cell sorting and large-scale expansion of single-KIR-positive alloreactive human NK cells for multiple infusions to patients was established. The feasibility, safety and efficacy of administration of expanded NK cells will be evaluated in phase I/II trials in different clinical settings: (A) in AML patients after haploidentical HSCT (Fig.2), (B) in patients with multiple myeloma after autologous HSCT, and (C) in elderly AML patients not eligible for intensive chemotherapy and HSCT.

Selected Publications

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– Diermayr, S., Himmelreich, H., Durovic, B., Schneeberger-Mathys, A., Siegler, U., Langenkamp, U., Hofstenge, J., Gratwohl, A., Tichelli, A., Paluszewska, M., Wiktor-Jedrzejczak, W., Kalberer, C.P., and Wodnar-Filipowicz, A. (2008). NKG2D ligand expression in AML increases in response to HDAC inhibitor valproic acid and contributes to allorecognition by NK cell lines with single KIR-HLA-class I specificities. Blood 111, 1428-1436.
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– Siegler, U., Meyer-Monard, S., Jörger, S., Stern, M., Tichelli, A., Gratwohl, A., Wodnar-Filipowicz, A.,* and Kalberer, C.P.* (2010). GMP-compliant cell sorting and large-scale expansion of single-KIR-positive alloreactive human NK cells for multiple infusions to leukemia patients. Cytotherapy 12, 750-763.

Taste receptors

Gastrointestinal signals

Appetite regulation

Gut-brain axis

Gastro-enterology

Prof. Dr. Christoph Beglinger
Department of Biomedicine
and Division of Gastroenterology and Hepatology
University Hospital Basel

Group Members
Prof. Dr. Jürgen Drewe
Dr. med. Bettina Woelnerhanssen (MD student)
Dr. med. Felix Schulte (MD student)
Dr. phil. Angelika Graber-Maier (postdoctoral fellow)
Dr. med. Svetlana Beglinger (MD)
Anne Christine Gerspach (PhD student)
Robert E. Steinert (PhD student)
Luzia Schönenberger (MD student)
Luisa Baselgia (academic technician)
Gerdien Gamboni (technician)

The tasting gut and appetite control

The global obesity problem supports the urgent need for research that aims to understand the basic mechanisms that regulate food intake, appetite and body weight. The varieties of nutrients in developed countries presents modern humans with a problem: what are the best combinations of macro- and micronutrients that promote health and longevity in each individual? Why and how does an individual select among foods of different compositions and amounts when they are in surplus? Is food selection only due to particular taste and odor receptors or are there connections among taste and metabolic needs for energy or regulatory processes? That is, is there a genetic basis for food intake? These basic science questions have significant implications for individuals and society since an increasing percentage of the population is obese or overweight.
The information available for the biochemical processes that control hunger and satiety is still insufficient. There is new evidence that taste receptors are important cofactors in this regulatory control system. Activation of these receptors by specific nutrients is associated with the secretion of a number of gastrointestinal hormones, including peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and cholecystokinin (CCK). These peptides interact with appetite centres in the brain and the brainstem in order to induce satiety. The administration of PYY or GLP-1 reduces energy intake in healthy subjects and in obese persons. This research has stimulated interest in these hormones as targets for the development of anti-obesity therapies. The present proposal focuses on the physiology, mechanism of action and interactions of the gut hormones GLP-1 and PYY as satiety hormones in relation to taste receptor activation to prepare the path for potential therapeutic application. Our research focuses on the following issues:

- What is the role of ingested nutrients as regulators of digestive functions?
- How are ingested nutrients sensed in the gut?
- How does this information trigger regulatory circuits?
- How does this link to feeding behaviour and energy consumption?

Maintenance of weight homeostasis is a complicated process for the body. The complex interactions of the neural and hormonal systems that regulate food intake and satiety depend on a wide range of factors; specific nutrients in the gut activate different pathways with activation of taste receptors being one potential pathway. These mechanisms are important for short-term control of appetite, but more important they help to keep body weight constant over long periods of time. The understanding of these mechanisms is essential with important implications for public health with respect to weight control and obesity-related morbidity. Our project focuses on specific aspects of this control system: gastrointestinal triggered feedback mechanisms through nutrients with activation of specific signals (taste receptors) and their potential interactions.

Fig. 1

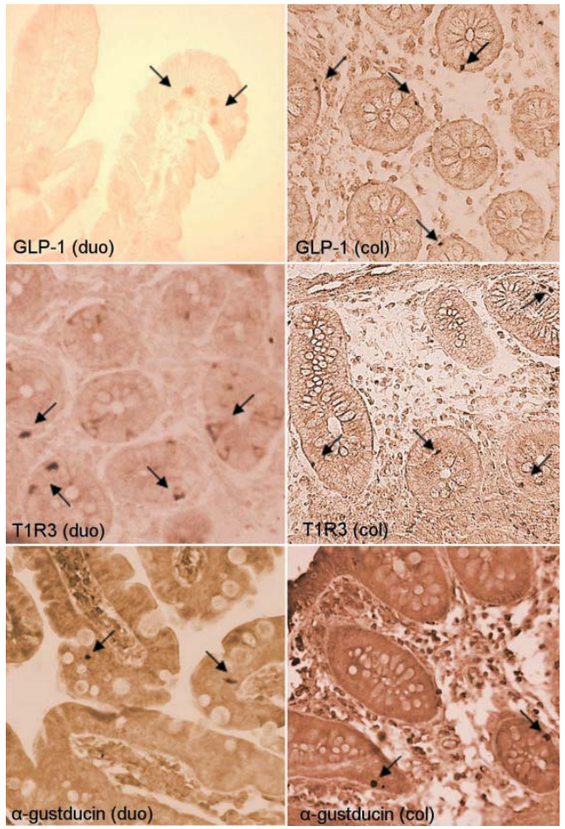

Fig. 2

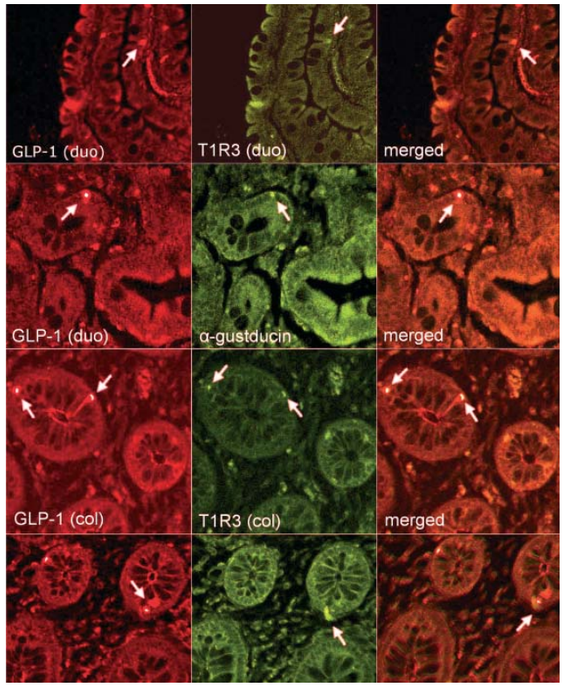

Fig. 1: Taste signaling proteins and GLP-1 are present in enteroendocrine mucosal cells of human duodenum and colon. Immunostaining of paraffin-embedded sections show the enteroendocrine cells expressing the hormone GLP-1, and the sweet receptor elements T1R3 and α-gustducin. Arrows point at some of the positively stained cells in duodenal (left panels) and colonic (right panels) sections. The cells react to glucose in the gut lumen through activation of the sweet receptor and stimulate the release of GLP-1. (R. Steinert, unpublished).

Fig. 2: Taste signaling elements are colocalized to GLP-1 in mucosal cells of human duodenum and colon. Double labeling immunofluorescence histochemistry showing GLP-1 (left panels in red), T1R3 or α-gustducin (center panels in green) and merged images (right panels in red+green) in duodenal and colonic parafine-embedded sections. Arrows point at positively stained cells that colocalize.

Connection to Clinical Practice

Clinical approaches to obesity and food intake

Scientific interest in the physiology of eating and body weight regulation has grown rapidly in recent years. There are both purely scientific and cultiral reasons for this development. The scientific interest relates the development of molecular tools, which have fundamentally changed the picture: 1) taste receptors for sweet, sour, salt and bitter have been identified in the gut, which form the basis for regulatory circuits in the control of digestive processes and food intake; 2) the adipose tissue has become an endocrine organ with close connections to metabolism, energy expenditure and food intake; 3) functional brain imaging and other new techniques can help to illuminate brain-behavior relationships during eating. The importance of these new developments for the physiology of eating and body weight regulation can hardly be overestimated.The cultural reason relates to the increasing global obesity epidemic. Obesity is associated with type 2 diabetes mellitus, coronary heart disease, gall bladder disease, increased risk in colon cancer, respiratory complications, and increased mortality. The health care costs related to the obesity epidemic have become clear in recent years, but we lack effective strategies to control eating and body weight. It is therefore in the public interest to better understand the physiology of eating and body weight and the pathogenesis of obesity. Food intake is modulated by sensation of hunger and satiation. The gastrointestinal tract is a key element in this complex system. Our group attempts to advance the knowledge in this area by focusing on specific aspects of gut controlled processes in health and disease.

Selected Publications

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Granulosa
Apoptosis
Stem cell
FSH
FSH receptor
Infertility

Gynecological Endocrinology

Prof. Dr. Christian De Geyter
Department of Biomedicine
and Division of Gynecological Endocrinology
and Reproduction Medicine
University Hospital Basel, Women's Hospital

Group Members
Hong Zhang, PhD (senior researcher)
Dr. Oliver Sterthaus (postdoctoral fellow)
Anne-Catherine Feutz (postdoctoral fellow)
Katarzyna Kossowska-Tomaszczuk (PhD student)
Nadira M'Rabet (PhD student)
Afzal Pasha Syed (Master student)
Fabienne Emch (MD student)
Donato D'Alonzo (MD student)
Brigitte Schneider (technician)

Ovarian function is regulated through endocrine signalling, apoptosis and paracrine interactions centered around the oocyte

The ovary consists of various functional compartments, all centered around the oocyte. Ovarian follicular growth is characterized by a rapid proliferation of granulosa cells, which both nurse the enclosed oocyte but also produce the bulk of the hormones preparing the female organism for reproduction. The granulosa function for its share is regulated by surrounding thecal cells, which not only produce the precursor steroids for the enzymes of the granulosa, but also the blood vessels needed for follicular growth, ovulation and subsequent formation of the luteal body. Many aspects of ovarian function still remain unknown and in order to acquire more knowledge, we stepwise developed an in-vitro model of follicular growth. For this purpose we characterized the first immortalized human granulosa cell line, which enabled us to demonstrate the signalling arising from human oocytes towards granulosa cells, separated from the co-cultured human oocytes by a semipermeable membrane. The culture method in use now consists of a three-dimensional collagen type I scaffold embedded in culture medium containing the leukaemia-inhibiting factor and activin A, which allows the growth of functional human granulosa cells over prolonged time periods. With this culture system the differential effects of the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH) on functional granulosa cells can be dissected. In addition, the causes of the often overwhelming interindividual differences in the receptivity of the granulosa cells to the action of FSH, as found in many women suffering of infertility are being examined.
Based on existing gene expression data of granulosa cells, new genes specifically involved in ovarian function were identified. One of these, EULIR, binds to the inhibing binding protein (InhBP/p120), the putative co-receptor of inhibin. We constructed a transgenic model, which has demonstrated that EULIR is essential for embryonic growth, but also for the development of the placenta.
During reproductive life, follicular atresia by far outnumbers the process of follicular development, as only a few hundreds of follicles become ovulated, whereas millions invariably undergo atresia. Atresia is induced by cellular apoptosis and various members of the Bcl-2 family serve as central checkpoints in this process. Despite its quantitative importance in ovarian physiology, little is known about the mediators of apoptosis in the ovary. Several new members of the Bcl-2 family have been identified in our laboratory, such as human Bok and Bcl2l10, and their respective functions in gonadal physiology have been elucidated. A homozygous Bcl2l13-deficient mouse line was established but proved to be phenotypically normal. Through interbreeding with other transgenic mice lacking either Bax or Bak, double and triple knockout models were produced and the observed differences in fertility rates of these animals are now providing new insights into the highly redundant processes regulating apoptosis.
Despite the recent development of induced pluripotent stem cell technology (iPS), embryonic stem cells (ESC) remain the gold standard in stem cell research. The access to supernumerary human embryos, the possibility to trace back the very origin of those supernumerary embryos and the maintenance of quality assurance throughout the entire process justify the development of specialized centres dealing both with assisted human reproduction and the derivation of human ESC lines together with iPS under good manufacturing practice (GMP) conditions. The unit of assisted reproductive medicine located in the University Hospital has instituted a GMP-grade laboratory for the isolation and characterization of new human ESC lines at the University of Basel. These activities have resulted in the derivation and characterization of four novel human ESC lines (CHES2, CHES3, CHES5 and CHES6), among them the first in Switzerland with a normal chromosome complement. In addition, novel protocols for the non-viral-mediated production of iPS are underway thereby avoiding the integration of vectors into the genome of the reprogrammed somatic cells.

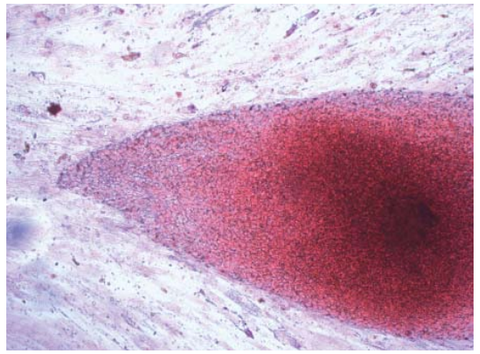

Fig. 1: Human embryonic stem cell colony (CHES-3) growing on a monolayer with feeder cells. The stem cells are stained with alkaline phosphatase (10 x magnification).

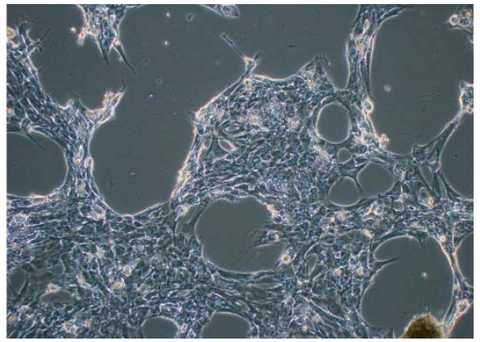

Fig. 2: Cultured granulosa cells, collected from a mature ovarian follicle. These cells can be culture over prolonged time periods in the presence of LIF and can be used to study the role of FSH in ovarian physiology.

Fig. 3: Homozygous EULIR knockout mouse embryo showing exencephaly and eye defects.

Connection to Clinical Practice

Molecular pathways causing breast cancer in postmenopausal women treated with hormonal replacement.

Hormonal replacement therapy, particularly if both oestrogens and progestagens are administered, leads to a higher breast cancer incidence. Yet, the molecular pathways involved remain elusive. The differential effects of oestradiol, oestradiol and a progestagen, tibolone and no treatment on breast cancer-related gene expression in normal postmenopausal breast tissue might help to understand the different levels of susceptibility. This research is carried out together with the Department of Medical Oncology at the Erasmus University in Rotterdam. Breast tissue samples were collected from 33 healthy postmenopausal women both before and after 6 months of one of the treatments mentioned above. Except for oestradiol alone, which was given to women after hysterectomy only, the allocation to each of the three other treatment modalities was randomized. The expression of 102 selected genes and 46 microRNAs putatively involved in breast cancer was determined in the tissue samples.
As compared to women left without treatment, the highest number of differentially regulated genes and miRNAs (17.6%) were detected after six months of administration of oestradiol and progestagen ($p<0.05$), followed by oestradiol alone (10.1%) and tibolone (4.7%). Among the genes that were most significantly down-regulated by were oestrogen-receptor-α and androgen receptor, whereas the various genes regulating oestrogen-metabolism were significantly up-regulated.
Currently, whole genome analysis is being performed on these tissue samples. We await ample information about the molecular pathways leading to higher breast cancer susceptibility among postmenopausal women

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- Zhang, H., Gao, S., De Geyter, Ch. (2009 A natural antisense transcript, NAToB, regulates the pro-apoptotic activity of hBok. International Journal of Oncology 34: 1135-1138.
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Liver

Signaling

Viral Hepatitis

Hepatocellular Carcinoma

Interferon

Hepatology

Prof. Dr. Markus H. Heim
Department of Biomedicine
and Division of Gastroenterology and Hepatology
University Hospital Basel

Group Members
Dr. Francois H.T. Duong (postdoctoral fellow)
Dr. Balasubramanian Sivasankaran (postdoctoral fellow)
Michael Dill (MD/PhD student)
Zuzanna Makowska (PhD student)
Vijay Shanker (PhD student)
Gaia Trincucci (PhD student)
Philippe Megel (Master student)
Sylvia Ketterer (technician)

Innate immunity and interferon signaling in viral hepatitis

A better understanding of interferon (IFN) signal transduction in hepatitis C virus (HCV) infected liver cells is imperative both for the understanding of the natural course of HCV infections, specifically the molecular mechansims responsible for the high persistence rate of HCV after infections, and for further improvements of the current HCV therapy with pegylated IFNα (pegIFNα) and ribavirin.

Over the last 10 years, my laboratory has systematically investigateed IFN signaling in chronic hepatitis C (CHC). In 1999, we published the original discovery that IFNα induced signal transduction through the Jak-STAT pathway is inhibited by expression of HCV proteins in cells (Heim et al., J Virol, 1999). This finding was confirmed in HCV transgenic mice (Blindenbacher et al., Gastroenterology, 2003) and liver biopsies of patients with CHC (Duong et al., Gastroenterology, 2004). In the following years, we investigated the molecular mechanisms responsible for this inhibition, and found that HCV upregulates an important cellular phosphatase, PP2A, through induction of endoplasmatic reticulum stress response pathways (Christen et al., J Virol, 2007; Christen et al., Hepatology, 2007). PP2A inhibits protein arginine methyltransferase 1 (PRMT1) with consequences for both IFNα signaling and the activity of the viral helicase (Duong et al., Gastroenterology, 2004; Duong et al., J Virol, 2005). Most importantly, the negative effects of PP2A upregulation by HCV could be corrected by treating cells with the methyl-group donor S-adenosyl-methionine (AdoMet, SAMe) (Duong et al., Hepatology, 2006). As a result of this translational research, we have performed a clinic pilot study where previous non-responders to pegIFNα/ribavirin are retreated with a combination of pegIFNα, ribavirin, AdoMet and Betaine.

To understand the molecular mechanisms responsible for non-response to pegIFNα/ribavirin, we investigated IFNα signaling in paired liver biopsies of 16 patients with CHC before and 4 hours after the first injection with pegIFNα. We discovered that non-responders to therapy had a pre-activated endogenous IFN system already before therapy, and injection of pegIFNα did not further activate Jak-STAT signaling nor did it further induce IFN target genes in liver cells (Sarasin-Filipowicz et al., PNAS, 2008). In this group of patients pegIFNα therapies have little chance for cure, because pegIFNα injections have no effect in liver cells.

More recently we investigated the role of microRNA for host-HCV interaction in the liver of patients with CHC (Sarasin-Filipowicz et al., Nature Medicine, 2009). Several miRNAs, including liver-specific miR-122, have been implicated in the control of HCV RNA replication and its response to interferon (IFN) in human hepatoma cells. Our analysis of liver biopsies from patients with chronic hepatitis C (CHC) undergoing IFN therapy revealed no correlation of miR-122 expression with viral load and markedly decreased pre-treatment miR-122 levels in patients who had no virological response during later IFN therapy; other investigated miRNAs showed only limited changes. These data have implications for the prospect of targeting miRNAs for CHC therapy.

Within hours after the first injection, IFNα signaling became refractory to further stimulation. The negative regulator SOCS1 was rapidly upregulated and likely responsible for early termination of IFNα signaling. For long-lasting refractoriness, neither SOCS1 nor SOCS3 were instrumental. Instead, we identified the inhibitor USP18/UBP43 as the key mediator. Our results indicate that the current therapeutic practice using long-lasting pegIFNα is not well adapted to the intrinsic properties of the IFN system. Targeting USP18 expression may allow to exploit the full therapeutic potential of recombinant IFNα (Sarasin-Filipowicz et al., Mol Cell Biol, 2009).

Selected Publications

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Aminoglycosides
Apoptosis
Cochlea
Hair cells
Hearing loss
Matrix metalloproteinases

Inner Ear Research

Prof. Dr. Daniel Bodmer
Department of Biomedicine
and Ear Nose and Throat Department
University Hospital Basel

Group Members
Dr. Sibylle Bertoli (postdoctoral fellow)
Dr. Yves Brand (postdoctoral fellow)
Dr. Vesna Radojevic (postdoctoral fellow)
Claudia Hanusek (MD student)
Alwin Listyo (MD student)
Cristian Setz (MD student)

Molecular mechanisms involved in hair cell survival and death

Studies conducted over the last couple of years demonstrated that signalling pathways that operate in the organ of Corti in the inner ear play a central role in survival and death of hair cells. An important goal of molecular otology is to characterize these signalling pathways in normal inner ears and inner ears exposed to a variety of different forms of stress, such as ototoxic substances and noise overexposure. In one study, we used high performance reverse protein microarray technology and phospho-specific antibodies to examine the activation status of defined molecules involved in cellular signalling (Caelers 2010). We demonstrated that reverse protein microarrays based on the highly sensitive planar-waveguide technology provide an effective and high-throughput means to assess the activation state of key molecules involved in apoptotic and pro-survival signalling in microdissected organ of Corti explants over time. In this study, we showed that gentamicin and a specific NF-kappaB inhibitor increase the ratio of phospho-c-Jun/c-Jun in organ of Corti explants of postnatal rats soon after exposure to these drugs (Fig. 1). In addition, we found a decrease in the phospho-Akt/Akt ratio in organ of Corti explants early after NF-kappaB inhibition. Finally, we observed an early and consistent decrease of the phospho-p38/p38 ratio in the explants exposed to the NF-kappaB inhibitor and only a transient decrease of this ratio after gentamicin exposure, respectively.
In an additional study, we examined the role of matrix metalloproteinases in the inner ear. The matrix metalloproteinases are a family of proteins involved in the remodelling and homeostasis of the extracellular matrix. The composition of the extracellular matrix is important for the proper functioning of the inner ear, especially the organ of Corti. In our study, we focused on the expression and function of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) in the cochlea. We examined their expression in 5-day-old Wistar rat cochleas by RT-PCR, real-time PCR and Western blot, and in C57BL/6 adult mice we localized their presence in the cochlea by immunohistochemistry. We also determined whether organ of Cortis exposed to aminoglycosides would show a change in the MMP-2 and MMP-9 expression pattern. We observed that MMP-2 and MMP-9 proteins are expressed within the cochlea at three locations: the organ of Corti, the spiral ganglion and the stria vascularis. MMP-2 had an equally distributed gene expression in the cochlea while MMP-9 mRNA expression was particularly highly concentrated in the spiral ganglion. We also observed by immunofluorescence their specific location mainly in inner and outer hair cells and in the spiral ganglion (Fig. 2). Organ of Corti explants treated with gentamicin showed an up-regulation of MMP-2 and MMP-9 proteins after 24 hours of exposure to gentamicin with no change in their relative mRNA expression after 12, 24 and 36 hours. Inhibition of the MMP activity in organ of Corti explants incubated with an MMP inhibitor in organotypic cultures resulted in hair cell death, suggesting that a basal level of MMP activity is required for hair cell survival.

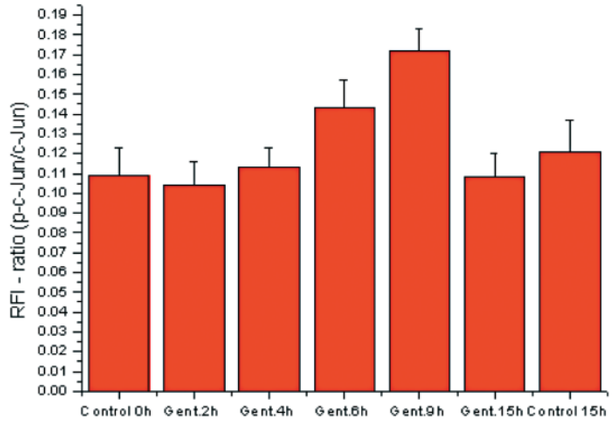

Fig. 1: Time course of the ratio phosph-c-Jun/c-Jun ratio in the organ of Corti after gentamicin exposure

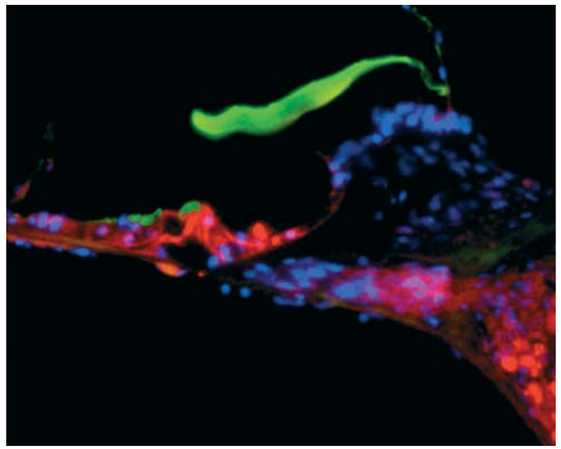

Fig. 2: Expression of matrix metalloproteinase 9 (red) in the inner ear. Cell nuclei are stained in blue and stereociliae are labelled in green with calbindin

Connection to Clinical Practice

National survey on hearing aid use and satisfaction in Switzerland and their determinants

The number of persons provided with hearing aids in Switzerland has nearly doubled from 1995 to 2005 and more than 50'000 hearing aids are dispensed per year, but little is known about the actual use and users' satisfaction with their devices.
We performed a representative national cross sectional survey using a postal questionnaire sent to 14'285 adult hearing aid owners. The overall response rate was 62% (n=8707). To correct results for a potential non-response bias, 193 randomly selected non-respondents were contacted by telephone. Questionnaire data were combined with information on hearing loss and type of hearing aid provided by the hearing aid dispensing practice. 85% used their devices regularly, 12% only occasionally and 3% never. 80% were satisfied with their aids. It was concluded that rates of regular hearing aid use and satisfaction were high in Switzerland compared to the data from other countries. Logistic regression analyses were performed to identify determinants of regular use and satisfaction. The risk of non-regular use was significantly higher in persons aged 65-74 years, men, German-speaking persons, with mild hearing loss and a total duration of hearing aid use of less than five years. There was also small but significant evidence that bilateral compared to unilateral amplification and devices with more advanced signal processing features contribute to successful hearing aid fitting, resulting in longer duration of use. The risk of not being satisfied with the aid was associated with difficulties in handling, irregular use and a total duration of use of at least two years, while French-speaking persons were more satisfied compared to the German-a.

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Angiogenesis
Notch signaling
Portal hypertension
Hepatocellular carcinoma
Nodular regenerative hyperplasia
Vascular remodeling

Liver Biology

New group since April 2009

Dr. David Semela
Department of Biomedicine
and Division of Gastroenterology and Hepatology
University Hospital Basel

Group Members
Sonja Rothweiler (PhD student)

Notch Signaling in Hepatic Microcirculation and Chronic Liver Disease

The focus of our group is angiogenesis and vascular remodeling in chronic liver disease and hepatocellular carcinoma. Chronic liver disease leads to profound changes of the sinusoidal vascular network with development of portal hypertension. The microvasculature in cirrhotic liver is remodeled and abnormal with vessels of varying diameter separated into micronodules. Several processes have been recognized to lead to vascular remodeling in the liver: On a cellular level resting stellate cells become activated and start to deposit matrix proteins, which will lead to formation of a basement membrane around the sinusoids. Liver sinusoidal endothelial cells (LSEC) become dysfunctional and deficient for production i.e. of the vasodilator nitric oxide. These changes finally will transform the low resistance vascular bed leading to portal hypertension with all its consequences such as variceal bleeding, formation of collateral vessels porto-systemic shunts and formation of ascites. Although contractility of hepatic stellate cells and matrix deposition are well established in the process of cirrhosis and portal hypertension, the role of LSEC signaling and sinusoidal vascular remodeling are less understood. Under physiological conditions, LSEC are resting and highly differentiated cells showing unique morphology with fenestrations and a lack of a basement membrane. However, in chronic liver disease, LSEC become activated, start to proliferate, upregulate various arterial surface markers and loose their fenestrations eventually leading to dedifferentiation and capillarisation of the hepatic microvascular bed. A key signaling pathway in vascular differentiation and interendothelial cell interactions is Notch signaling. Notch signaling plays a pivotal role in embryonic vascular development and vascular differentiation. Notch-1 receptor and its ligands Jagged and DLL are expressed in healthy adult liver. However, their function in liver is unknown.

We have therefore developed animal models in order to study the hepatic microcirculation in different Notch knockout mice suffering form portal hypertension and liver cancer with active tumor angiogenesis. We have found that Notch signaling is critical in the homeostasis of liver sinusoidal endothelial cells and regulates physiological functions as well as differentiation of the hepatic vascular bed. Using liver biopsies from patients suffering from portal hypertension or liver cancer we are analyzing the role of the Notch pathway in human liver disease in a translational study.

Selected Publications

- Semela D, Das A, Langer DA, Kang N, Leof E, Shah V (2008). PDGF signaling through ephrin B2 regulates pericyte function and vascular structure in liver. Gastroenterology 135, 671-679.
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Functional adaptation
Subchondral bone plate
Stress distribution
Mineralisation
Mechanical properties
Correction osteotomy

Musculo-skeletal Research Group

Prof. Dr. Magdalena Müller-Gerbl
Department of Biomedicine
Institute of Anatomy
University of Basel

Group Members
PD Dr. Luminita Göbbel (postdoctoral fellow)
Dr.A. Leumann*
Dr.M. Bilici*
Dr. A.Nowakowski (postdoctoral fellow)
Valentin Zumstein (Master student)
Marco Kraljevic (Master student)
Mireille Toranelli (technician)
Jean-Paul Böglin (technician)
Roger Kurz (technician)
Peter Zimmermann (technician)

*left during report period

CT-Osteoabsorptiometry – An in vivo technique for displaying the subchondral mineralisation patterns as a measure of long-term stress

The anatomy of the subchondral region is highly variable. These variations include the contour of the tidemark and cement line, the number and type of perforations in the subchondral bone plate and its thickness, density and biochemical composition. Differences in the trabecular structure and mechanical properties of weight-bearing and non-weight-bearing areas have also been recognized.
Several studies confirmed that every joint surface has regular reproducible patterns of density distribution, and it can be suggested that these are correlated with the mechanical situation in the joint and reflect the long-term stress acting there.
In healthy subjects the density distribution in the tibial plateau exhibits a central maximum in the medial and lateral compartment (Fig. 1a). In patients with malalignment of the knee joint the density patterns deviate from the normal: in cases of genu varum the density was considerably raised in the region of the medial tibial condyle and the maximum was displaced towards the medial edge. Laterally the density was significantly lowered (Fig. 1b). With genu valgum the situation was reversed showing that these patterns reflect the overall load distribution in the malaligned knee, too.
To test the hypothesis that these density patterns adapt sensitively to a change in the mechanical environment, we investigated in a prospective study 35 patients with genu varum preoperatively and 1 year after a correction osteotomy by means of CT-osteoabsorptiometry (CT-OAM, Müller-Gerbl, 1992, 1998).
In all patients submitted to osteotomy the patterns of subchondral mineralisation showed changes one year after operation. If displacement of the resultant towards the middle as the result of a successful operation is attained, displacement of the stress maxima due to a change in the impact point of the resultant leads to a shift of the high bone density, and thus to a new density pattern reflecting the accompanying mechanical condition. Exactly this situation we found in group 1 (Fig. 1c). The patients in group 2 showed no actual shift of the maxima, but a clear dissolution of the zones of highest density indicating that the time course of possible changes is dependent on the degree of the initial mineralisation. Group 3 and 4 showed both clinically and in the mineralisation patterns a non-satisfactory result.
Our results demonstrate that it is now possible to evaluate non-invasively and in-vivo the success of an operation by displaying the subchondral density patterns, which allow a quantitative estimation of the changes occurring. With this comparative study it has been possible for the first time to establish in human subjects that changes in the subchondral density are an adaptation to an altered mechanical situation based on a change in the local stress.
In a following study we measured in the same tibial plateaus both strength (indentation-tests) and density values of the subchondral plate (CT-OAM) at about 72 locations within the joint surfaces and found a significantly high correlation between the distribution of the strength and that of the mineralization (Fig. 2). Thus proof is obtained that the subchondral mineralization pattern – which can be evaluated in living people – reflects not only the density distribution, but also the distribution of such material properties as strength. In this way the density values can be used to provide information about the bone quality of individual joints in living patients.

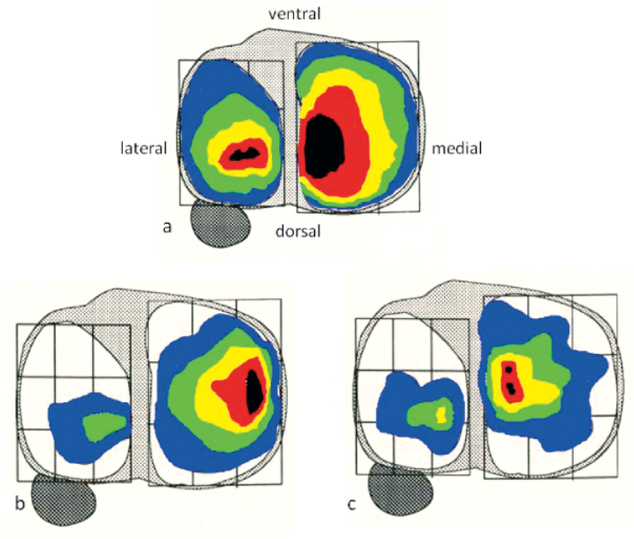

Fig. 1: Schematic drawings oft he distribution of mineralization in the subchondral bone plate of the tibial plateau (seen from above) a. Healthy person b. Patient with genu varum (preoperatively) c. same patient one year after correction osteotomy (black and red are zones of highest density, green and blue of lowest density)

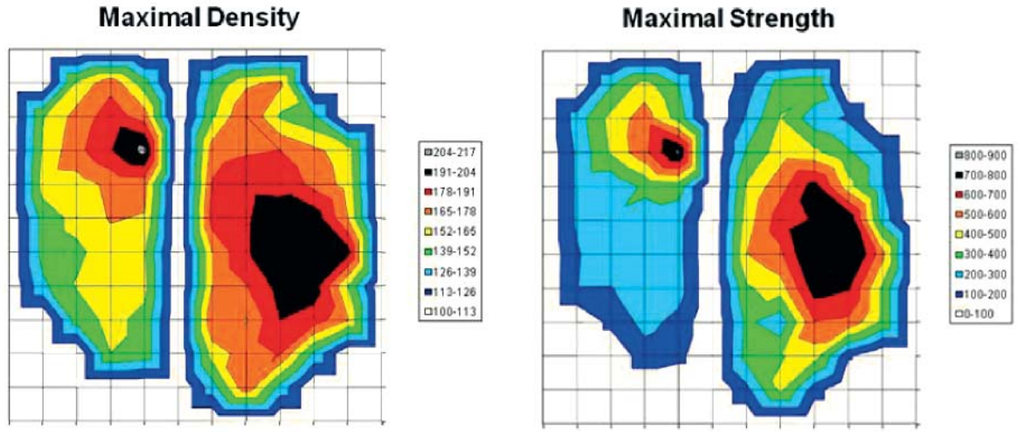

Fig. 2: Schematic drawing of density (HU-values converted in Gray-values) and strength values (N) in the same tibial plateau (seen from above).

Selected Publications

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Heart failure
Cardiac progenitor cells
Reactive oxygen species
Hematopoietic growth factors
β1-integrin

Myocardial Research

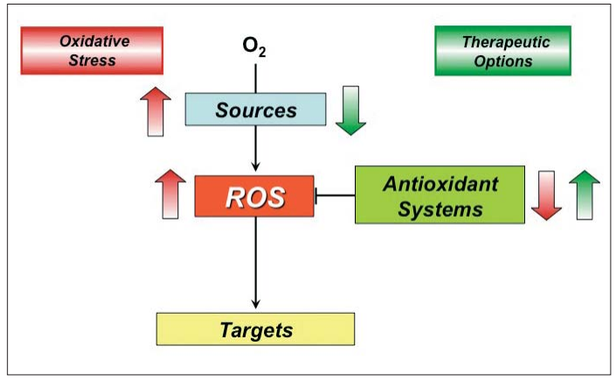
Dr. Gabriela M. Kuster Pfister
Department of Biomedicine
and Division of Cardiology
University Hospital Basel

Group Members
Dr. Otmar Pfister (project leader)
Berit Rosc-Schlüter (PhD student)
Stéphanie Häuselmann (PhD student)
Vera Lorenz (technician)

Cardioprotection and Repair

Heart failure is a major complication of cardiac diseases and a leading cause of death and hospitalization. Pathophysiologically, it is caused by the continuous structural and functional re-organization of the myocardium referred to as *myocardial remodeling*. Whereas adaptive in the early stages of the disease, this remodeling turns maladaptive as the disease progresses, thereby leading to alterations of the myocardial matrix and the perturbation of the myocardial cell homeostasis. Our research aims at defining strategies to counteract the maladaptive aspects of the remodeling process and at identifying potential novel target molecules for prevention and treatment of heart failure.

1. Sources and roles of reactive oxygen species in adaptive myocardial remodeling
Reactive oxygen species (ROS) are important mediators of myocardial remodeling. They arise from molecular oxygen (O_2) through action of intracellular enzymes including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase or the mitochondria. Various antioxidant systems protect the cell from excessive ROS (oxidative stress) (Figure). Besides their unspecific, mostly damaging effects, ROS act as signaling molecules and mediate both adaptive and maladaptive cellular events. We are currently studying the role of ROS in the regulation of cardiomyocyte-matrix interactions and adaptive remodeling focusing on β1-integrin as target molecule. β1-integrin is a cell surface receptor and adhesion molecule that, via interaction with the myocardial matrix, mediates hypertrophy and cell survival in cardiomyocytes. We found that ROS originating from a Rac1-dependent NADPH oxidase regulate the expression and function of β1-integrin, thereby promoting cardiomyocyte survival and contributing to adaptive remodeling. Based on these findings, we are currently focusing on the distinct roles of NADPH oxidases as sources of ROS in myocardial remodeling and the potential clinical implications regarding the future use of NADPH oxidase inhibitors to treat cardiovascular disease in humans.



2. Identification of novel cardioprotective factors
Recently, multipotent cardiac progenitor cells were identified that have the capacity to differentiate into all cardiac cell lineages including cardiomyocytes. A variety of cytokines and growth factors regulate survival as well as proliferation and differentiation capacities of these cardiac progenitor cells. Analogous to bone marrow derived progenitor cells, cardiac progenitor cells exhibit receptor systems that are responsive to hematopoietic growth factors and similar systems may be expressed on cardiomyocytes. The second major focus of our research includes the characterization of such receptor systems and their role in the regulation of the myocardial cell homeostasis with the ultimate goal to identify novel cardioprotective factors.
Flt3 ligand (FL) is a hematopoietic growth factor that promotes survival and proliferation of bone-marrow derived stem cells. FL is enriched in the ischemic myocardium implicating the Flt3/FL system in the regulation of cardiac cells. In our ongoing project we seek to determine how erythropoietin and flt3 ligand affect the function of cardiac myocytes and progenitor cells and regulate their survival. The results of these studies will further our understanding of how the heart maintains and restores its structural and functional integrity and will help to identify novel "cardiopoietic" factors that could be used for therapeutic intervention to prevent and treat heart failure.

Connection to Clinical Practice

Dr. Otmar Pfister
Division of Cardiology
University Hospital Basel

Clinical investigations in the setting of our oxidative stress focus aim at the identification of potential novel markers of oxidative stress and the characterization of the redox balance in heart failure patients. We could demonstrate that there are differences in the regulation of oxidative stress and the antioxidative potential between the cardiac and the peripheral circulation, indicating an enhanced level of oxidative stress locally in the heart. We further found that the cytosolic antioxidant copper-zinc superoxide dismutase (Cu/Zn-SOD), the major enzyme primarily responsible for the clearance of (NADPH oxidase-derived) cytosolic superoxide, is regulated in response to heart failure treatment targeting the renin-angiotensin-system. These findings support the hypothesis that standard drugs used for heart failure therapy exhibit important redox-modulatory properties.
Our clinical research aiming at the therapeutic exploitation of novel cardioprotective systems focuses on the effects of the long-acting erythropoietin derivative Mircera® in patients with acute myocardial infarction (BEAT-STEMI). A respective phase II pilot study is ongoing (ClinicalTrials.gov Identifier: NCT01093820).

Selected Publications

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Glaucoma
Neurodegeneration
Meningothelial cells
Mitochondria
Oxidative stress
Ubiquitination

Ocular Pharmacology and Physiology

Prof. Dr. Peter Meyer
Department of Biomedicine
Eye Clinic
University Hospital Basel

Group Members
Dr. Albert Neutzner (project leader)
Prof. Dr. Hanspeter Killer
Dr. Katarzyna Konieczka (postdoctoral fellow)
Dr. Claudia Bippes (postdoctoral fellow)
Dr. Bin Fan (postdoctoral fellow)
Dr. Xiaorong Xin*
Charles Hemion (PhD student)
Anne-Sophie Benischke (PhD student)
Tatjana Binggeli (technician)
Monique Sauter (technician)

*left during reporting period

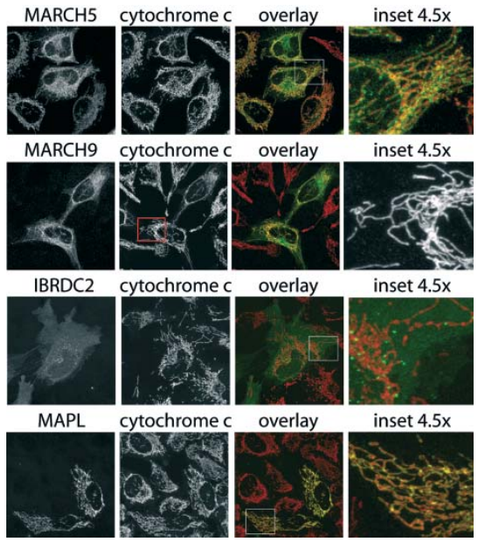
Pathways to glaucomatous neurodegeneration

Glaucoma is a common neurodegenerative disorder and a leading cause of blindness affecting more than 70 million people worldwide. Underlying the impairment and eventual loss of vision is the progressive degeneration of retinal ganglion cells which form the optic nerve and are responsible for the flow of visual information from the retina to the vision centers in the brain. There are a number of risk factors for glaucomatous damage including increased intraocular pressure, vascular dysregulation and systemic hypotension. However, despite one century of research into the causes of glaucoma, the mechanism for the observed death of retinal ganglion cells is still unclear and thus a rational based treatment of this disease is hampered.

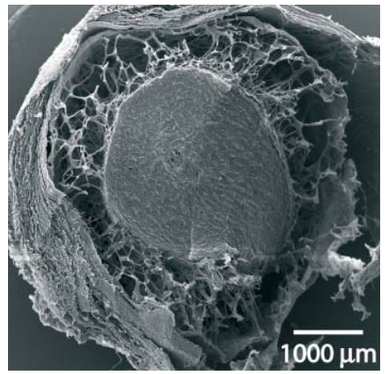
To better understand the causes for glaucoma, we follow two lines of investigation:
First, we concentrate on the role of mitochondria and mitochondrial maintenance in neurodegeneration. Amounting evidence links proper mitochondrial function to neuronal death associated with various neurodegenerative disorders ranging from Alzheimer's and Parkinson's disease to glaucoma. We and others recently described a potential new pathway for the turnover of mitochondrial proteins by ubiquitin ligases localized to the outer mitochondrial membrane. While turnover of whole damaged mitochondria through the process of mitophagy is well established as important for neuronal health e.g. in Parkinson's disease, whether and how ubiquitin-dependent protein degradation impacts mitochondrial health and thus cellular survival is unclear. We are in the process of studying these proteins and to assess their role in mitochondrial health and neuronal survival. We found that mitochondrial morphology – a process vital for mitochondrial health and cellular survival – is regulated by two of these ubiquitin ligases and that mitochondrial function in the form of the mitochondrial membrane potential is impacted. We have now started to identify potential substrates of these ubiquitin ligases which might help to further unravel their function. In addition, we are currently developing an in vitro model for retinal ganglion degeneration using retinal neuronal precursor cells incubated under elevated hydrostatic pressure and will use this system to study the connection between mitochondrial morphology and maintenance and cell death.
Mitochondria derived reactive oxygen species cause oxidative damage to cells and tissues and this damage has been implicated in a wide variety of neurodegenerative diseases and other age-related degenerative processes. Growing evidence also supports the involvement of oxidative stress as a component of glaucomatous neurodegeneration. Furthermore, different studies provide cumulating evidence that vascular dysfunction may contribute to oxidative stress in glaucoma, especially in patients without increased intraocular pressure. Hence, glaucoma patients are expected to display a higher level of systemic oxidative stress. In this study, patients already thoroughly examined with regard to their propensity for ocular vascular dysregulation in a Swiss National Funds cohort study will be compared to healthy controls for their level of systemic oxidative stress and their capacity of antioxidative defence. To this purpose, lymphocyte lysates and plasma are processed for quantitative determination of oxidized proteins using oxyblot, and antioxidant status in plasma and cell lysates from study subjects. This study is the first to assess oxidative damage on proteins in glaucoma patients.
Second, we hypothesize that the microenvironment of the optic nerve might be involved in maintaining optic nerve function and that disturbances in the space around the optic nerve might negatively impact retinal ganglion cell survival. Based on our clinical and pathological observations where we found meningothelial cell proliferation in glaucoma patients, we focus on the cells forming the barrier between the cerebrospinal fluid (CSF) and the circulatory system using immortalized human as well as primary porcine meningothelial cells (MECs). These cells react to elevated pressure and oxidative stress – two conditions associated with glaucoma. While MECs proliferate after exposure to elevated hydrostatic pressure, their barrier-associated endocytotic/transcytotic function is severely inhibited by pressure as well as oxidative stress. Furthermore, moderate oxidative stress not only impacts the endocytotic function of MECs but also the physical barrier formed by desmosomes between these cells is negatively impacted. Taking the delicate balance of the CSF and the confined space around the optic nerve into consideration, both increased proliferation and diminished CSF turnover through decreased endocytosis might well have a negative impact on axonal survival. In addition, we have preliminary results supporting a role for MECs as immune modulatory cells possibly linking these cells to astrocyte activation and potentially neuronal death. While most research into the causes of glaucoma focused so far on the eye and the retina, this project will illuminate the contribution of the optic nerve microenvironment to this blinding disease and might open up new therapeutic options for glaucoma patients.

Selected Publications

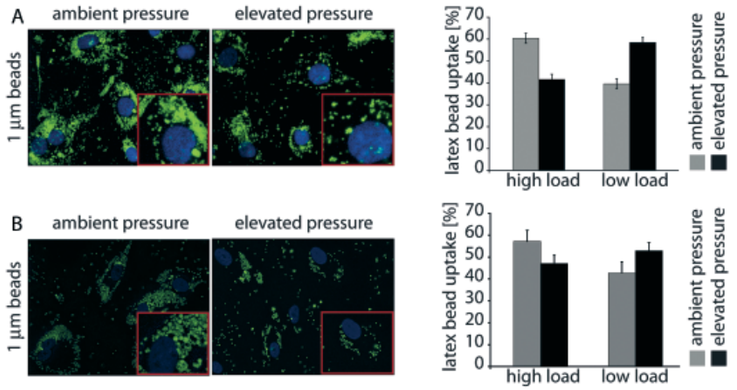
- Xin, X., Fan, B., Killer, H.E., Neutzner, A., Flammer, J., Meyer, P. (2010) Primary cell culture of meningothelial cells-a new model to study the arachnoid in glaucomatous optic neuropathy. Graefes Arch Clin Exp Ophthalmol. 2010 Sep;248(9):1273-8.
- Xin, X., Huber, A., Meyer, P., Flammer, J., Neutzner, A., Miller, N.R., Killer, H.E. (2009) L-PGDS (betatrace protein) inhibits astrocyte proliferation and mitochondrial ATP production in vitro. J Mol Neurosci. 39(3):366-71.
- Neutzner, A., Benard, G., Youle, R.J., Karbowski, M. (2008) Role of the ubiquitin conjugation system in the maintenance of mitochondrial homeostasis. Ann N Y Acad Sci. 147:242-53.
- Mozaffarieh M, Grieshaber MC, Orgül S, Flammer J. The potential value of natural antioxidative treatment in glaucoma. Surv Ophthalmol. 2008;53:479-505.
- Pache, M., Meyer P. (2006) Morphological changes of the retrobulbar optic nerve and its meningeal sheaths in glaucoma. Ophthalmologica. 220(6):393-6.



◀ **Fig. 1:** Mitochondrial ubiquitin ligases. Hela cells were transfected with constructs for the expression of MARCH5-YFP, MARCH9-YFP, IBRDC2-YFP and MAPL-YFP, fixed and stained using antibodies against the mitochondrial marker cytochrome c. Please note the colocalization of all four proteins with cytochrome c indicative for mitochondrial localization.



◀ **Fig. 2:** Coronary section of optic nerve visualized using electron microscopy. Note the delicate arrangement of arachnoid trabelulae, the meningothelial cell layer covering the inner layer of the arachnoid facing the subarachnoid space (arrow). Arachnoid trabeculae covered with meningothelial cells (arrow head).



◀ **Fig. 3:** Endocytotic function of MECs is impacted by elevated hydrostatic pressure. Ben-Men-I cells (A) or procine MECs (B) were treated with elevated pressure for two days and fluorescent latex beads were added to assess endocytotic activity by fluorescence microscopy. Ben-Men-I cells as well as PMCs showed a significant decrease in endocytotic activity after pressure treatment compared to control treated cells.

Chronic inflammatory lung disease
Epigenetics
Regulation of cell differentiation
Human diseased cell culture model
Asthma
COPD

Pulmonary Cell Research

Prof. Dr. Michael Roth
Department of Biomedicine
and Division of Pneumology
University Hospital Basel

Group Members
Dr. Pieter Borger (postdoctoral fellow)
Dr. Mesut Gencay (postdoctoral fellow)
Dr. Katrin Hostettler (postdoctoral fellow)
Dr. Nicola Miglino (postdoctoral fellow)
Dr. Jun Zhong (postdoctoral fellow)
Luigi Costa (PhD student)
Laura Keglowich (PhD student)
Heidi Bodmer (technician)

The molecular biology of chronic inflammatory lung diseases

Worldwide asthma and COPD increase, while the reason remains unknown. Chronic inflammation is regarded as the major cause for both diseases and thus little attendance was given to the role of tissue forming resident cells. Increasing evidence challenges this view and indicates that tissue forming cells are more than a reactive cell mass. There is data that suggests these cells may initiate inflammation. In our studies we included immune cells and pro-inflammatory mediators with the focus on their interaction with human diseased primary tissue forming cells.
Airway smooth muscle cells of asthma patients proliferate faster and show increased constriction and mobility than healthy controls. We linked this pathology to their contractile properties. In addition we showed that cell differentiation depends on the composition of a complex formed by the glucocorticoid receptor and C/EBP isoforms. Cell differentiation was also affected by the density of the cells.
We are currently investigating if this differentiation controlling mechanisms have any relevance to the pathologies of asthma and COPD. It might be possible that at least in asthma, the deregulation of the intracellular Erk1/2 mitogen activated protein kinase is involved in density regulated cell differentiation. In additional studies, we provided evidence that viral infection modifies intracellular signalling of airway smooth muscle cells and macrophages leading to increased virus propagation and cytokine synthesis.
Most importantly, we could identify the cause of the earlier described asthma associated lack of the transcription factor/differentiation factor C/EBP-alpha. Our data was the first to show that the lack of C/EBP-alpha in asthma is based on a faulty translation control mechanism. Currently, we are investigating the cells type specific and disease specific nature of this epigenetic control mechanism. At least two well known asthma triggers, house dust mite and cigarette smoke abolished C/EBP-alpha translation in the susceptible airway smooth muscle cells. This mechanism is significantly different from the mechanisms which have been reported in rodent models of asthma.
In regard of remodelling, we could confirm our earlier findings that epithelial cells are the major control element for the function of fibroblasts and for mesenchymal cells in general. We could also show further pathologies in airway smooth muscle cells of asthma patients which are a total lack of the tissue water content control factor hyaluronic acid and a partly down regulation of two receptors (CD44, RHAMM). Regarding the assessment of novel drugs in asthma and COPD therapy, we reported that dimethylfumarate modulates the synthesis of pro-inflammatory cytokines and therefore may be considered as a novel anti-inflammatory drug.
Currently, we are investigating the role of the redox system in asthma and COPD, with a special focus of its regulation by mitochondrial proteins and genes, the majority of the later is regulated by C/EBP dependent promoters. We hope that these studies will provide sufficient novel information to develop curative therapies for asthma and may be also for COPD.
In regard to fibrosis we showed that epithelial cells control fibroblast proliferation and differentiation. New data obtained in human primary cells strongly suggest that the process underlying fibrosis is different from animal model. The latter argues for an overshooting epithelial mesenchymal transition (EMT) to cause fibrosis. Our new data suggest that the reverse process, mesenchymal-epithelial transition (MET) is the normal end-point of lung repair, and that this is reduced in fibrotic conditions. As studied by real time microscopy over a period of 5 days epithelial like cells obtained from patients with fibrosis have a strongly reduced MET phase and stay in a "myo-fibrotic" stage. Similar studies with asthmatic cells and COPD cells are on their way.

Connection to Clinical Practice

Prof. Dr. Michael Tamm
Internal Medicine/Pneumology
University Hospital Basel

Improve long term management of patients with chronic inflammatory lung diseases

Clinical research of the clinic of pneumology focuses on COPD outcome research , randomised interventional trials and pulmonary complications in immunocompromised patients. Prof Daiana Stolz, which has recently been awarded with a swiss national Foundation professorship for clinical research, leads a European COPD cohort study analysing the predictive value of clinical and laboratory parameters including biomarkers for disease progression and late outcome. Furthermore the impact of viral infections will be analysed to optimise treatment strategies. A translational research approach allows to integrate basic research and clinical research investigating new mediators in the blood and lung of patients with COPD. Interventional placebo controlled trials focus on optimized bronchoscopic techniques. The role of different viral infections is not only investigated in COPD exacerbations but also in immuno-compromised patients with pulmonary complications. There is a experienced team of clinical researchers and study nurses integrating clinical and basic research.

Selected Publications

- Yang JQ, Rüdiger JJ, Goulet S, Gencay-Cornelsen MM; Borger P, Tamm M, Roth M: Cell differentiation modifies composition and function of the glucocorticoid receptor C/EBP complex. American Journal of Respiratory and Molecular Cell Biology 2008, 38:414-422
- Oliver BGG, Johnston SL, Wark P, Laza-Stanca V, King N, Black JL, Burgess JK, Roth M, Lim S. Rhinovirus exposure impairs immune responses to bacterial products in human alveolar macrophages. Thorax 2008, 63:519-525
- Daikeler T, Gencay MM, Roth M, Regennass S, Tyndall A, Hess C: Increased Serum Levels of Soluble Triggering Receptor Expressed on Myeloid Cells-1 in Anti Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis. Annals of the Rheumatic Diseases 2008, 67:723-724
- Borger P, Miglino N, Baraket M, Tamm M, Black JL, Roth M: Impaired translation of C/EBPa in bronchial smooth muscle cells of asthma patients. Journal of Allergy and Clinical Immunology, 2009,123:639-645
- Klagas I, Goulet S, Zhong J, Karakiulakis G, Baraket M, Black JL, Papakonstantinou E, Roth M. Decreased expression of hyaluronic acid in airway smooth muscle cells from patients with asthma and COPD. European Respiratory Journal, 2009, 34:616 - 628

Neutrophil extracellular traps (NETS)

Inflammation

Endothelial damage

Preeclampsia

Prenatal Medicine

Prof. Dr. Sinuhe Hahn
Department of Biomedicine
University Women's Hospital

Group Members
Dr. Kesava Chuddupah (postdoctoral fellow)
Dr. Anurag Gupta (postdoctoral fellow)*
Dr. Sebastien Lalevee (postdoctoral fellow)
Dr. Corinne Rusterholz (postdoctoral fellow)*
Dr. Varaprasad Kolla (postdoctoral fellow)
Chancal Sur Chowdury (PhD student)
Marianne Messerli (PhD student)*
Friederike Kettelhack (MD student)
Nicole Chiodetti (technician)

* left during report period

Preeclampsia: a severe auto-inflammatory disorder?

Preeclampsia is a severe pregnancy related disorder, involving aberrant differentiation of trophoblast tissues, leading to the release of inflammatory micro-debris by the placenta.
Members of the innate immune system, such as circulatory polymorphonuclear neutrophils (PMNs), mast cells and eosinophils have been shown to be capable of releasing their DNA into the extracellular environment to generate ETS (extracellular traps). The main purpose of these DNA containing structures appears to be to ensnare and kill micro-organisms.
In this context we made the novel observation that syncytiotrophoblast derived micro-debris can trigger isolated PMNs to generate NETs. That this in-vitro finding may have a physiological consequence was underscored by detection of vast numbers of NETs in the inter-villous space of preeclampsia, but not in pregnancies with normal healthy deliveries. Since preeclampsia is associated with hypoxia-reperfusion damage, it could be that the massive presence of NETs could lead to occlusion of the inter-villous space, thereby contribution to this condition.
As damage of the maternal endothelium is a key feature of preeclampsia, we have explored the interaction of NETS with endothelial cells (EC). These ongoing studies have indicated that the interaction of isolated PMN with pre-activated EC, will lead to netosis. The prolonged of exposure of EC to NETs lead to EC apoptosis. Of interest is that this cytolytic process required intact NETs, as it was abolished by concomitant treatment with DNAse.
In a new SNF funded study we are examining the molecular processes involved in aberrant trophoblast differentiation in PE. Here our focus is on possible epigenetic mechanisms. These studies are carried out in collaboration with Prof. M. Bühler, FMI, Basel.
In ongoing studies in collaboration with Prof. P. Hasler (Rheumatology, KSA, Aarau), we have assessed the release of cell-free DNA (cf-DNA) in auto-inflammatory conditions such as rheumatoid arthritis (RA). Here we observed that cf-DNA levels were significantly higher is cases with RA than in healthy controls. A striking feature of these analyses was that cf-DNA levels were much greater in serum of RA patients than in controls. This implies that more cf-DNA is being during the clotting of RA blood samples than in healthy blood samples. We also observed that the vast proportion of cf-DNA in RA was antibody associated. Since antibody-cf-DNA complexes have been shown to be capable of triggering rheumatoid factor production by B-cells, our observation may have significant clinical importance.

Connection to Clinical Practice

PD. Dr. med. Olav Lapaire
Prof. Dr. med. Irene Hoesli
University Women's Hospital, Basel

Development of new biomarkers for the detection of pregnancies at risk for preeclampsia

Currently no reliable tests exist to screen for pregnancies at risk for preeclampsia (PE). As a result the disorder only becomes obvious once the symptoms have become manifest, leaving very few options for therapeutic intervention other than frequent delivery of a very premature baby. As it has been suggested that PE involves a lengthy asymptomatic phase prior to clinical manifestation, it would be important to detect such pregnancies early in gestation, in order to develop effective intervention strategies. Since PE is characterised by aberrant trophoblast differentiation, and since the tissue is in direct contact with the maternal circulation, we have sought to determine whether proteomic analysis of maternal plasma samples could not assist with the detection of potential biomarkers.
For this purpose we developed appropriate quantitative strategies using isobaric labelling (iTRAQ) in combination with MALDI-TOF/TOF analysis. These analyses were carried out in collaboration with Prof. P. Jenö, Biozentrum, Basel. Our analysis of maternal plasma samples obtained in the 1st trimester of pregnancy, indicated that significant differences in a number of placentally derived proteins could be discerned between pregnancies which went on to develop PE and those who delivered normally. A similar analysis has been undertaken of pregnancies bearing Down syndrome fetuses, leading to a set of potential biomarkers. The veracity and usefulness of these biomarkers will be further examined in a large number of samples using SRM (selective reaction monitoring).
In collaboration with Prof. P. Hasler, KSA, Aarau, we have observed quantitative alterations in cf-DNA levels in RA patients in response to therapy with biologic agents such as Infliximab. In ongoing studies, we are no examining whether such analyses could assist in discriminating between patients who respond to therapy and those who don't. The development of such a theranostic tool would greatly assist with treatment strategies for affected patients.

Selected Publications

- Gupta, A.K., Joshi, M.B., Philippova, M., Erne, P., Hasler, P., Hahn, S., and Resink, T.J. (2010). Activated endothelial cells induce neutrophil extracellular traps and are susceptible to NETosis-mediated cell death. FEBS Lett 584, 3193-3197.
- Hahn, S., Jackson, L.G., and Zimmermann, B.G. (2010). Prenatal diagnosis of fetal aneuploidies: post-genomic developments. Genome Med 2, 50.
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- Ho, S.S., Chong, S.S., Koay, E.S., Ponnusamy, S., Chiu, L., Chan, Y.H., Rauff, M., Baig, S., Chan, J., Su, L.L., et al. (2010). Noninvasive prenatal exclusion of haemoglobin Bart's using foetal DNA from maternal plasma. Prenat Diagn 30, 65-73.
- Kolla, V., Jeno, P., Moes, S., Tercanli, S., Lapaire, O., Choolani, M., and Hahn, S. (2010). Quantitative proteomics analysis of maternal plasma in Down syndrome pregnancies using isobaric tagging reagent (iTRAQ). J Biomed Biotechnol. 2010;2010:952047.

T-cadherin

Endothelial dysfunction

Atherosclerosis

Angiogenesis

Skin cancer

Signal Transduction

Prof. Dr. Therese Resink
Department of Biomedicine
University Hospital Basel

Group Members
Dr. Maria Philippova (postdoctoral fellow)
Dr. Manjunath B. Joshi (postdoctoral fellow)
Dr. Dennis Pfaff (postdoctoral fellow)
Mr. Emmanouil Kyriakakis (PhD student)
Miss Ksenyia Maslova (PhD student)
Miss Katharina Rupp (technician)

T-cadherin – a guide and guard during tissue remodelling

Cadherins are a superfamily of cell-surface proteins involved in cell-cell interactions and signaling. They exhibit cell-type and developmental specificity in expression and are aberrantly regulated in several human malignancies. Atypical GPI-anchored T-cadherin (T-cad) is present in many tissues/cell types. While abnormal (high or low) expression has been associated with a variety of diseases, biomolecular characteristics of T-cad, its function in different cell types/tissues and mechanisms of signaling are poorly understood. Our studies suggest T-cad is multifunctional with tissue-specific and context-dependent facets.

Role of T-cad in the vasculature
Expression, function and signal transduction in endothelial cells (EC).
T-cad is expressed in the vessel and is increased during atherosclerosis, restenosis and pathological angiogenesis in vivo, and on proliferating EC and EC subjected to oxidative (OX) and endoplasmic reticulum (ER) stress in vitro. Upregulation on EC is thus characteristic of activation and stress. Collectively, our data suggest this offers a protective mechanism for limiting tissue damage during disease progression. T-cad influences many aspects of EC phenotype/behaviour, including proliferation, motility, angiogenesis and survival under conditions of OX and ER stress (Fig. 1). Intracellular signaling effectors for T-cad in EC include PI3K/Akt/ GSK3β, mTOR/S6K1, p38MAPK, β-catenin, RhoA and Rac1, integrin linked kinase (Fig. 1). Membrane adaptors enabling inward signaling by T-cad include Grp78/BiP and integrin β3 (Fig. 1).
We found T-cad present in culture media and human plasma as a surface component of activated/apoptotic EC-derived plasma membrane-derived vesicles, termed microparticles (MP), which are considered a circulating hallmark of EC activation/damage. Elevated levels of plasma T-cad associated with endothelium dysfunction (Fig. 2), even in non-significant atherosclerosis, implicating T-cad as a biomarker for early atherogenesis. MP-bound T-cad induces survival signaling and angiogenic behavior in target EC via homophilic interactions. Interaction of plasma-delivered MP-bound T-cad with the luminal endothelium, accompanied by upregulation of T-cad on activated/injured EC, represents a novel biological protective mechanism of action for T-cad. Ongoing studies address the role of T-cad in a broader context of cardiovascular diseases and their complications.

Biomolecular analyses.
By transducing EC with domain-deletion mutants of T-cad and comparison of proangiogenic functions/signaling, we found EC1 and EC5 domains of T-cad to be essential for its proangiogenic effects. Dominant-negative mutants of T-cad are potential tools targeting excessive angiogenesis.
Transcriptional regulation of T-cad is poorly understood. We identified redox-sensitive regulatory elements within the minimal promoter region of T-cad in EC and a requirement for Trx-1 (thioredoxin-1) in OX stress-induced T-cad expression. Trx-1-dependent activation of T-cad gene expression during OX stress represents a novel anti-apoptotic mechanism for Trx-1.

Role of T-cad in non-melanoma skin cancers
We initiated studies on the role of T-cad in keratinocytes and in progression and malignant transformation of non-melanoma skin cancers (NMSC). In the healthy epidermis T-cad expression is restricted to the basal keratinocyte layer. Staining patterns for T-cad in NMSC suggest crucial regulatory functions in tumor demarcation, directional invasion and progression. In particular, aberrant/absent T-cad associates with histologic features of a more malignant and invasive phenotype. Lentivector-based studies in keratinocyte and NMSC cell lines revealed that loss of T-cad is a major determinant in the acquisition of aggressive invasive behavior (Fig. 3). The functional outcome of change in T-cad expression in NMSC (loss = promigratory) is opposite to that observed for EC (gain = promigratory), but preliminary data suggest common mechanisms involving regulation of growth factor receptor activity/trafficking. In vitro/in vivo analyses on the role of T-cad in tumor expansion and angiogenesis and tumor cell extravasation/metastasis are ongoing.

Fig. 1

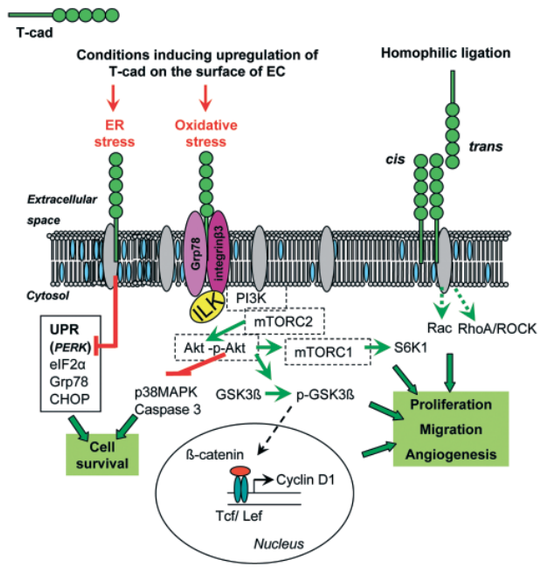


Fig. 2

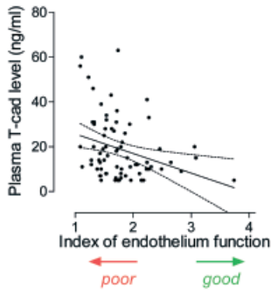
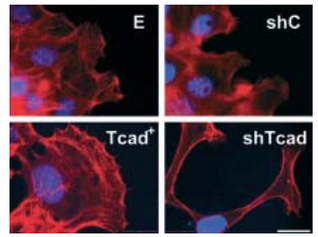


Fig. 3



Connection to Clinical Practice

Prof. Dr. Paul Erne
Division of Cardiology
Kantonsspital Luzern

Improving detection of early atherosclerosis and the vulnerable patient

Atherosclerosis is a common, chronic and progressive disease of large arteries and is a leading cause of morbidity and mortality. Its prevalence is predicted to rise due to the increase of diabetes and obesity. Myocardial infarction, stroke or other cardiovascular events identify vulnerable patients who suffer from symptomatic arteriosclerosis. However, atherosclerosis is clinically silent long before plaque rupture and ensuing cardiovascular events, and recent intravascular ultrasound (IVUS) studies show a high incidence of coronary atherosclerotic lesions even in asymptomatic teenagers and young adults. Detection of both the development of atherosclerosis at its non-significant stages as well as the shift from "indolent disease" to acute ischemic disease carries great clinical benefit, yet remains a diagnostic challenge. Atherosclerosis profiling using a multi-marker diagnostic paradigm comprising physical characteristics and lesional composition of vessels, endothelium function, plasma biomarkers of endothelial damage/dysfunction and inflammatory status and specific relationships between these parameters (e.g. Fig. 2) could improve risk stratification of patients and determination of treatment measures. We have compiled a wide-ranging clinical data base on a large cohort of study subjects (including healthy individuals, patients without cardiovascular risk factors, and patients with different stages of atherosclerosis defined on the basis of angiographic and IVUS data) and a corresponding bank of plasma samples and blood leukocyte isolates for biomarker analysis.

Selected Publications

- Joshi, M.B., Ivanov, D., Philippova, M., Kyriakakis, E., Erne, P., and Resink, T.J. (2008). A requirement for thioredoxin in redox-sensitive modulation of T-cadherin expression in endothelial cells. Biochem J 416, 271-280.
- Joshi, M.B., Kyriakakis, E., Pfaff, D., Rupp, K., Philippova, M., Erne, P., and Resink, T.J. (2009). Extracellular cadherin repeat domains EC1 and EC5 of T-cadherin are essential for its ability to stimulate angiogenic behavior of endothelial cells. FASEB J 23, 4011-4021.
- Kyriakakis, E., Philippova, M., Joshi, M.B., Pfaff, D., Bochkov, V., Afonyushkin, T., Erne, P., and Resink, T.J. (2010). T-cadherin attenuates the PERK branch of the unfolded protein response and protects vascular endothelial cells from endoplasmic reticulum stress-induced apoptosis. Cell Signal 22, 1308-1316.
- Philippova, M., Ivanov, D., Joshi, M.B., Kyriakakis, E., Rupp, K., Afonyushkin, T., Bochkov, V., Erne, P., and Resink, T.J. (2008). Identification of proteins associating with glycosyl-phosphatidylinositol- anchored T-cadherin on the surface of vascular endothelial cells: role for Grp78/BiP in T-cadherin-dependent cell survival. Mol Cell Biol 28, 4004-4017.
- Philippova, M., Suter, Y., Toggweiler, S., Schoenenberger, A.W., Joshi, M.B., Kyriakakis, E., Erne, P., and Resink, T.J. (2010). T-cadherin is present on endothelial microparticles and is elevated in plasma in early atherosclerosis. Eur Heart J DOI: 10.1093/eurheartj/ehq206.

Cartilage repair
Bone repair
Stem cells
Bioreactors
3D culture models
Engineered stromal tissues

Tissue Engineering

Prof. Dr. Ivan Martin
Department of Biomedicine
Institute for Surgical Research and Hospital Management (ICFS)
University Hospital Basel

Group Members
Dr. Andrea Barbero (project leader)
Dr. Arnaud Scherberich (project leader)
Dr. David Wendt (project leader)

Dr. Nunzia Di Maggio, Dr. Chiara Giovenzana, Dr. Anna Marsano, Dr. Sylvie Miot, Dr. Adam Papadimitropoulos, Dr. Karoliina Pelttari (postdoctoral fellows)

Paul Bourgine, Sinan Güven, Waldemar Hoffmann, Helena Lima, Elia Piccinini,Benjamin Pippenger, Rosaria Santoro, Beatrice Tonnarelli, Daniel Vonwil (PhD students)

Petra Bernegger, Andreas Trüssel (Master students)

Anke Wixmerten (scientific assistant)
Sandra Feliciano, Francine Wolf (technician)

Engineering of 3D cell culture models of developing skeletal tissues, toward manufacturing of clinical implants

The ultimate goal of the research group is to generate cellular grafts to repair cartilage and bone tissues, as well as complex osteochondral lesions. Beyond a potential clinical use as implants, the engineered constructs are also being considered as 3D model systems for cell differentiation and tissue development. The addressed scientific questions are related to (i) the characterization of different human cell sources (mature, progenitor, stem cells), (ii) the effect of specific environmental conditions (soluble factors, oxygen levels) on cell growth and differentiation, (iii) the identification of suitable characteristics of 3D porous scaffolds (architectures, compositions, surface and mechanical properties) and (iv) the cell response to controlled regimes of physical stimuli (flow-induced shear, compression) applied using bioreactor systems. The projects, at the interface between fundamental research and clinical translation, are based on a tight collaboration among biologists, engineers, material scientists and surgeons. Beyond national (SNF) and industrial programs, research is generously funded in the context of european consortia (EU FP VII), which have been instrumental in a strong international networking of the group.

Main recent achievements:

1. We have developed and validated the concept to generate skeletal tissues by direct expansion and differentiation of primary cells within the pores of 3D scaffolds using perfusion-based bioreactor systems. This approach allows to eliminate the typical procedure of monolayer cell expansion and to more efficiently maintain the tissue regenerative capacity of a variety of human cell sources (e.g., bone marrow- or adipose tissue-derived mesenchymal/endothelial progenitors or articular chondrocytes). The resulting engineered 3D stromal environments are also used to study interactions with other cellular systems, including tumour cells (collab. with Prof. G. Spagnoli), thymic epithelial cells (collab. with Prof. G. Holländer), osteoclastic and hematopoietic cells. As an example of such multi-cell co-culture models, Figure 1 displays the in vitro formation of tubular structures by endothelial cells, within the stromal tissue generated by adipose tissue-derived osteoprogenitors. Upon subcutaneous implantation, such blood vessel-like structures are capable to readily anastomose with the host vasculature, thereby offering a promising strategy for the rapid vascularisation of engineered bone grafts.
2. After establishing the critical role of oxygen percentage in the growth, differentiation and metabolic activity of cells from different skeletal tissues, we have set up a perfusion-based system to continuously monitor oxygen levels in medium and oxygen consumption by cells. The latter parameter has been positively correlated with the cell number in perfusion chambers, thus offering the possibility to non-invasively assess the cell growth kinetics during in vitro tissue development. The online quality control tool was integrated in a bioreactor system for the generation of cartilage grafts in a scaled-up size (i.e., 50 mm diameter, 4 mm thick patches) starting from a limited amount of human chondrocytes, corresponding to the number typically isolated from a small (i.e., about 100 mg) autologous biopsy (Figure 2). The process relies on direct cell expansion in the 3D environment (see point 1. above).
3. We have demonstrated that bone marrow-derived mesenchymal progenitors from adult individuals retain the capacity to generate bone tissue in vivo through an endochondral ossification process, corresponding to the typical route for bone formation during embryonic development (Figure 3). The process critically depends on the in vitro formation of mature, hypertrophic cartilaginous templates. In collab. with Prof. R. Zeller, we validated that the underlying morphogenetic process was structurally and molecularly similar to the temporal and spatial progression of limb bone development in embryos. Beyond offering a human model to study mechanisms governing bone development, this process could generate advanced grafts for bone repair by invoking a "developmental engineering" paradigm.

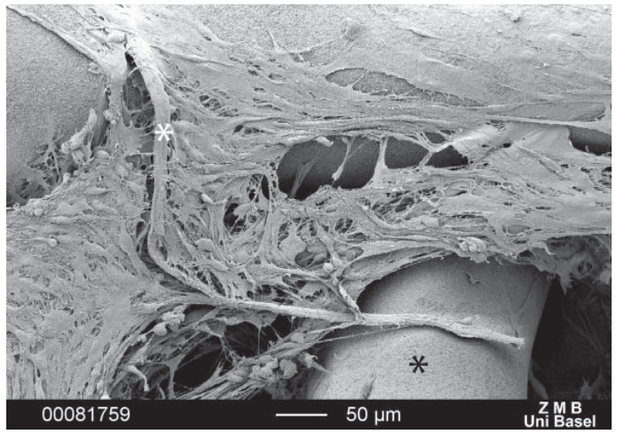


Fig. 1: In vitro engineered 3D stromal tissue containing human osteoprogenitor and endothelial cells. The black and white asterisks indicate respectively a synthetic scaffold fiber and a tubular, vessel-like structure, self-assembled by endothelial cells

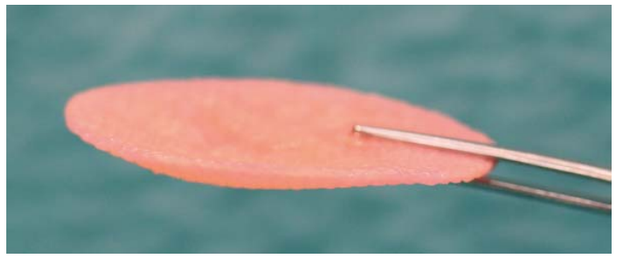


Fig. 2: In vitro engineered human cartilage disk, scaled up to 5 cm diameter and 4 mm thickness

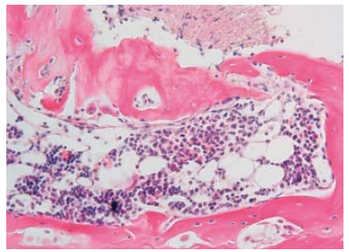


Fig. 3: Bone ossicle, including hematopoietic elements, generated in nude mice by ectopic implantation of human mesenchymal stromal cells pre-differentiated into hypertrophic chondrocytes

Connection to Clinical Practice

Prof. Dr. Marcel Jakob, Prof. Dr. Dirk J. Schäfer
Department of Surgery,
Behandlungszentrum Bewegungsapparat

Engineered skeletal tissue grafts in trauma, orthopaedic and reconstructive plastic surgery

The goal of the group is to translate the use of engineered cellular implants into specific surgical procedures and reconstructive indications. Currently targeted clinical applications:
Trial 1. Use of engineered cartilage for reconstruction of the alar lobule of the nose following tumour resection. A phase I clinical trial (5 patients) has been approved by Swissmedic. (PD Dr. M. Haug, Dr. I. Fulco)
Trial 2. Intra-operative transplant of adipose tissue-derived cells to enhance humeral fracture healing in osteoporotic patients. The study protocol is under prepration (PD Dr. C. Jaquiery, Dr. A. Mehrkens, Dr.A.M. Müller, Dr. F. Saxer, PD Dr. S. Schären, Dr. A. Kämpfen)
Trial 3. Use of nasal chondrocyte-based engineered cartilage for the treatment of joint defects. The specific indications and primary outcomes of the study are being planned in collaboration with Prof. V. Valderrabano and Prof. N. Friederich (PD Dr. M. Arnold, Dr. M. Barandun, Dr. A. Leumann)

Selected Publications

- Santoro, R., Olivares, A.L., Brans, G., Wirz, D., Longinotti, C., Lacroix, D., Martin, I., Wendt, D. (2010). Bioreactor based engineering of large-scale human cartilage grafts for joint resurfacing. Biomaterials 31: 8946-8952
- Scotti, C., Tonnarelli, B., Papadimitropoulos, A., Scherberich, A., Schaeren, S., Schauerte, A., Lopez-Rios, J., Zeller, R., Barbero, A., Martin, I. (2010). Recapitulation of endochondral bone formation using human adult mesenchymal stem cells as a paradigm for developmental engineering. Proc. Natl Acad Sci USA 107:7251-7256
- Martin, I., Smith, T., Wendt, D. (2009). A roadmap for the bioreactor-based translation of tissue engineering strategies into clinical products. Trends Biotech 27(9): 495-502.
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- Candrian, C., Vonwil, D., Barbero, A., Bonacina, E., Miot, S., Farhadi, J., Wirz, D., Dickinson, S., Hollander, A., Jakob, M., Li, Z., Alini, M., Heberer, M., Martin, I. (2008). Engineered cartilage generated by nasal chondrocytes is responsive to physical forces resembling joint loading. Arthritis Rheum 58:197-208.

DBM Focal Area Oncology

Focal Area Coordinators

Prof. Dr. G. Christofori
Department of Biomedicine
Institute of Biochemistry
and Genetics
University of Basel

Prof. Dr. R. Herrmann
Division of Clinical Oncology
University Hospital Basel

The major goal of this research program is to support and expand research in the field of molecular and clinical oncology in Basel. In particular, we aim at bridging the gaps between basic, translational, and clinical oncology research ongoing at the University of Basel and the non-University research institutes, biotech and pharmaceutical industry in the Basel area. Ultimately, the program should enforce collaborative efforts and common projects between various research groups, research institutes and pharma and between different disciplines. An added value is seen in innovative projects that eventually pay off by being transferred to a clinical setting. Apparently, the research program relies critically on the participating individuals' enthusiasm and initiatives.

The research program is currently led by Prof. Gerhard Christofori, head of the Institute of Biochemistry and Genetics, and Prof. Richard Herrmann, head of Clinical Oncology at the University Hospital. The program focuses on two major areas: first to support basic, translational, and clinical research by either generating additional positions or opportunities for oncology research by hosting new recruitments, such as SNF Assistant Professors and SCORE fellows within DBM. The second focus is to increase communication between the various researchers, clinicians and pharmaceutical company representatives in Basel and to generate and offer platforms for scientific exchange and technological collaboration. Towards this goal the program organizes seminars and one-day symposia with internal speakers. In a more clinical-oriented seminar series, named Onco-Lunch, newest insights into clinical oncology are being discussed. Outstanding international cancer researchers are invited to present lectures within the "DBM Oncology Program Seminars", and an impromptu guest seminar series completes the seminar activities of the research program. Thus far, these communication activities have led to a large number of successful collaborations and research networks, notably beyond the borders of institutes and pharmaceutical companies. Many of these efforts within the DBM Oncology program have been part of national and international research initiatives that cover innovative approaches to cancer research and treatment, including research on cancer genetics and genetic instability, cancer epigenetics, angiogenesis and metastasis, signal transduction, cancer stem cells, tumor vaccination and novel therapeutic regimen.

In the past years, the research program Oncology has been strengthened by the recruitment of additional faculty active in oncology research. For example, Prof. Luigi Mariani has been appointed head of neurosurgery and of the research group "Brain Tumor Biology" at DBM, and Proffs. Olivier Pertz and Alfred Zippelius moved as SNF-Assistant Professors from San Diego and Zürich, respectively, to join the DBM. Ongoing efforts in reorganization and recruitment have strengthened the research program in Oncology, and communication and collaboration within the Oncology program has improved despite the spatial separation of its member groups in different research buildings at Hebelstrasse, Petersplatz and Mattenstrasse. In the years to come, we need to further enforce scientific exchange between basic and patient-oriented research in order to facilitate the identification of clinical problems for the design of appropriate and innovative basic research approaches and, on the other hand, to improve on the rapid translation of basic research results into clinical application.

Brain

Glioma development

Tumor invasion

Biomarker

Stem cell

Brain Tumor Biology

New group since May 2009

Prof. Dr. Luigi Mariani
Department of Biomedicine
and Division of Neurosurgery
University Hospital of Basel

Group Members
Dr. Jean-Louis Boulay (project leader)
Dr. Gregor Hutter (postdoctoral fellow)
Dr. Marie-Françoise Ritz (postdoctoral fellow)
Dr. Martin Sailer (postdoctoral fellow)
Alexandra Gerber (technician)
Mr. Cristóbal Tostado (technician)

Glioma invasion: genetics, molecular mechanisms, biomarkers and local therapies

Malignant gliomas are among the deadliest malignancies, against which conventional therapies have not significantly improved patient survival. This is due to extremely high resistance of tumor cells to chemo-/radiotherapy and to high invasive capacity of gliomas into adjacent brain tissue, which compromizes total surgical resection. Glial tumors have been classified into histologic subtypes based on morphologic and antigen expression features. The finding of chromosomal alterations and gene mutations allowed identification of the glioma developmental pathways and refined classification into the molecular subsets summarized in Fig. 1. Through an active exchange between clinics and research laboratory, we are directly collecting in the operating room resected glioma biopsies of distinct grades and histologies for further analytic and experimental purposes.

Validation and discovery of biomarkers in gliomas
We are currently constructing a comprehensive, web-based glioma patient database containing personal (demographics, etiology, personal history); clinical (patient outcome, survival); MRI imaging (tumor size, location and infiltration grade), histopathological (tumor histology and WHO grade) and molecular annotations (genotyping, transcriptome, proteomics and activated signaling pathways). Altogether, results are expected to classify gliomas according to histologic, molecular and invasive features, and to allow identification of novel glioma biomarkers (Fig. 2).
Whenever possible, biopsies are taken from distinct areas of the tumor core and of the invasive rim at tumor periphery. Glioma cells isolated ex vivo are grown to establish long term glioma stem cell and differentiation cultures. Further, putative glioma stem cells are xenografted into immunocompromized mice to assess their tumorigenicity in vivo.

Molecular and genetic mechanisms of glioma invasion
We aim at identifying genetic determinants of glioma invasion by comparing on one hand expression profiles of invasive vs. non-invasive tumors and on the other hand, expression patterns of distinct areas within the same tumor.
In fact, genome-wide transcription analysis of invasive compared to non-invasive gliomas shows that tumor invasiveness is independent of a given histologic or a molecular subset shown in Fig. 1. Rather, invasiveness signature is associated with the differential regulation of a discrete number of genes only. We consistently found the gene for the mediator of glioma invasion BEHAB/brevican, and also the genes encoding transcription factors SOX2 and HEY1, suggesting for these genes a possible role in glioma invasion. Further, we provided evidence that SOX2 and HEY1 expressions are not strictly associated with the stem cell compartment of glioma lines, suggesting for them a role in glioma non-stem cells. The roles of SOX2 and HEY1 in glioma invasion are currently validated by siRNA-mediated inactivation in glioma cells and further migration / invasion assays in vitro and in vivo in orthotopically xenografted mice. Targets genes for SOX2 and HEY1 encoding potential effectors of glioma invasion are being defined by comparative genome-wide chromosome immuno-precipitation and transcription analyses of glioma cells with or without siRNA-mediated inactivation.
As a complementary approach, identification of invasion genes also involves the comparison of glioma cells extracted from the tumor periphery, where the invasive front is located, and from the center of the same tumor. First, glioma stem cells from these distinct areas of the tumor are being compared for their respective potentials to give rise to terminally differentiated glioma cells with distinct migration / invasion capacities in vitro and in vivo. Secondly, genes showing significant differential mRNA expression between the distinct zones will be validated for their potential roles in glioma invasion by siRNA-mediated inactivation in glioma cells and further migration/invasion assessment in vitro and in vivo. Results should provide clues on the molecular mechanisms of glioma invasion and designate potential targets for customized therapies to control glioma invasion.

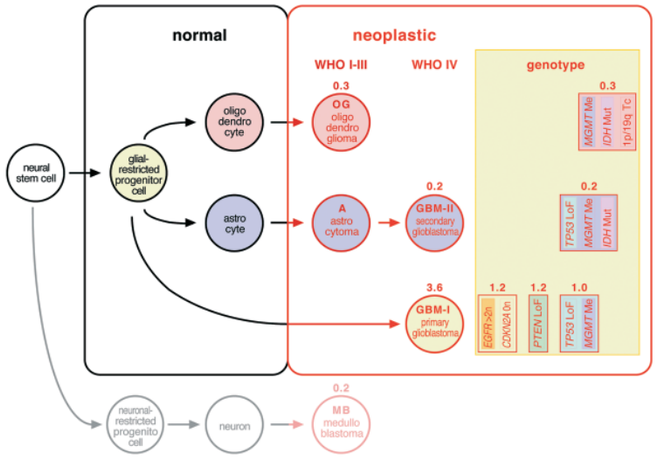
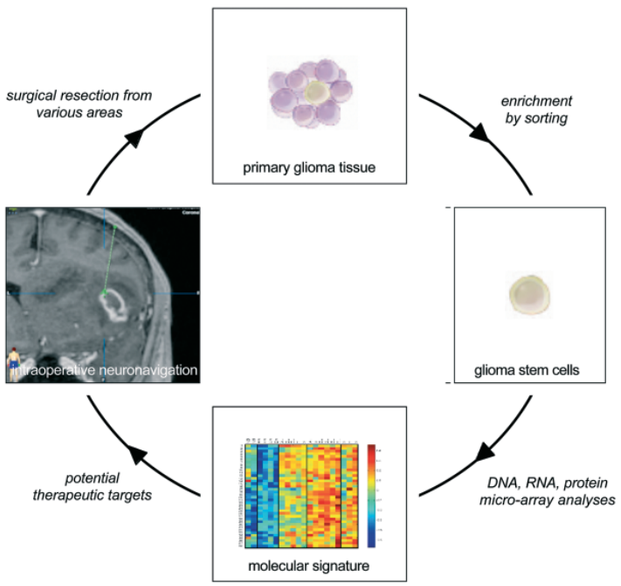


Fig. 1: Normal and neoplastic development within the glial lineage.
Histologic subtypes (left) and associations of genetic alterations among molecular subsets (right) are shown. Roman numerals indicate WHO tumor grades and Arabic numerals represent estimated incidences of glioma subsets among population for 100,000 hab/yr in Canton Zurich (Ohgaki & Kleihues 2005). The neuronal lineage is faded.



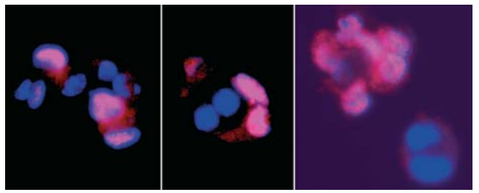
Connection to Clinical Practice

Dr. Dominik Cordier
Division of Neurosurgery
University Hospital of Basel

Experimental local therapy for gliomas

The current therapeutic standard of GBM consists in the surgical mass reduction of the tumor, followed by combined radiotherapy and chemotherapy. As innovative strategies, targeted local therapeutic approaches take advantage of surface molecules specifically expressed by tumor cells. As a result, cognate ligand binding and further internalization of a conjugated toxic compound may lead to tumor cell death. One of these glioma cell surface markers is NK1-R, the cognate receptor for Neurokinin type 1, a neuropeptide also named substance P. We are now developing an approach involving natural toxins covalently linked to substance P. Cholera toxin, a disruptor of the cAMP-cycle, Diphtheria toxin, an inhibitor of translation elongation and saporin, a blocker of ribosomal function, are currently evaluated in vitro for toxicity on GBM cell lines and planned to be tested in animal models. These compounds will be introduced into the brain through refined microcatheter systems we are currently developing to improve local delivery.

◀ **Fig. 2: Isolation of stem cells from primary gliomas and subsequent molecular analyses.**



▲ **Fig. 3: SOX2 Expression in neurosphere cells.**
Neurospheres were obtained from an oligo-astrocytoma and stained with DAPI (cell nuclei, in blue) and with anti-SOX2 antibodies (red). Some but not all nuclei show expression of SOX2 (purple as merger of blue and red).

Inflammation

Cancer

Lipid Signaling

Phosphoinositide 3-kinase

Growth

Cell migration

Cancer- and Immunobiology

Prof. Dr. Matthias Wymann
Department of Biomedicine
Institute of Biochemistry and Genetics
University of Basel

Group Members
Dr. Thomas Bohnacker (postdoctoral fellow)
Dr. Poppy Fotiadou (postdoctoral fellow)
Dr. Elena Gogvadze (postdoctoral fellow)
Dr. Romina Matter-Marone (postdoctoral fellow)
Fabrizio Botindari (PhD student)
Dominik Erhart (PhD student)
Anna Melone (PhD student)
Ann Mertz (PhD student)
Romy Walser (PhD student)
Miriam Zimmermann (PhD student)
Anna Baron (Master student)
Jan Völzmann (technician)

Inflammation and Cancer – Lipid Signaling Cascades

Overshooting cell activation leads to the deviation from normal cellular growth, proliferation and migration. This occurs in chronic inflammation and cancer alike, and most signaling cascades are shared in both disease groups. Lipid signaling cascades have been identified as important drug targets (Wymann and Schneiter, 2008). In particular the activation of a so-called phosphoinositide 3-kinase (PI3K) family was shown to play an important role in the control of cell growth, proliferation and migration (Marone et al. 2008). Class I PI3Ks are activated by cell surface receptors and produce the signaling lipid PtdIns(3,4,5)P3. This lipid is thought to be exclusively localized in the plasma membrane and serves as a docking site for protein kinases, guanine nucleotide exchange factors (GEFs), and facilitates membrane fusion processes. Protein kinase B (PKB/Akt) is one of the prominent signaling molecules binding to PtdIns(3,4,5)P3 via its pleckstrin homology (PH) domain, and links the PI3K to multiple downstream signaling cascades including the target of rapamycin complex (mTOR). Simplified, class I PI3Ks can be subdivided into complexes activated downstream of growth factor receptors and protein tyrosine kinases (class IA) and the PI3K IB, operating downstream of G protein-coupled receptors (GPCRs).

We have shown earlier that the class IB PI3Kγ isoform plays an important role in chronic inflammation and allergy, as confirmed by genetic and pharmaceutical targeting of PI3Kγ in mouse models for rheumatoid arthritis, systemic lupus, and passive anaphylactic responses. Moreover, the ablation of PI3Kγ activity also alleviated atherosclerosis in low-density lipoprotein (LDL) receptor and apolipoprotein E (ApoE)-deficient mouse models (Fougerat et al. 2008). While the latter disease involved the recruitment of macrophages and T-cells, anaphylactic responses are controlled by mast cells.

PI3Ks in mast cells can be triggered by the clustering of high affinity receptors for immunoglobulin E (IgE receptors, FcεRI) and GPCRs. Interestingly, efficient mast cell activation requires PI3Kγ downstream of GPCRs (Laffargue et al. 2002, Immunity). An initial clustering of the high affinity IgE receptor activates a protein tyrosine kinase cascade and class IA PI3Ks, but also leads to the autocrine stimulation of adenosine receptors on mast cells. These activate PI3Kγ by liberating Gβγ subunits from trimeric G proteins. Using mast cell from PI3Kγ null mice, we could show that these loose not only the catalytic subunit of PI3Kγ (p110γ), but also a p84 adapter subunit that sensitizes the PI3Kγ complex for GPCR activation. Investigating the activation process of PI3Kγ, it became clear that its relevant cellular output signals like chemotaxis and degranulation required the presence of a functional adapter subunit. Interestingly, a p84-related PI3Kγ adapter subunit called p101 could substitute for p84 in chemotactic responses, but did not reconstitute PI3Kγ-dependent mast cell degranulation. These observations lead to the definition of two specific pools of PtdIns(3,4,5)P3, one in cholesterol-rich membrane micro-domains, and a pool of PtdIns(3,4,5)P3 prone to internalization (for details see (Bohnacker et al. 2009) and Fig. 1). In a collaborative effort, it could be subsequently shown, that of the p84•p110γ and p101•p110γ PI3Kγ complexes only p84•p110γ required the interaction with activated Ras (Kurig et al. 2009, PNAS), which provides a first rational explanation of the specific function of p84 and p101 PI3Kγ complexes in physiology and disease.

PI3K are best known their role in cancer and metastasis. The PI3K pathway can be over-activated by mutations, increased upstream inputs from mutated growth factor receptors, Ras, or the loss of the lipid phosphatase PTEN, which normally degrades PtdIns(3,4,5)P3. Until recently, the major PI3K isoform believed to be involved in tumor progression was PI3Kα. In collaboration with E. Hirsch (Torino), we have investigated the role of PI3Kβ in cancer and metabolic control. As opposed to earlier studies generating PI3Kβ null mice, mice expressing a catalytically kinase inactive PI3Kβ (KI) were viable. Homozygous PI3KβKI/KI mice developed a type II diabetes-like phenotype at advanced age, as monitored by glucose tolerance and insulin tolerance tests. Interestingly, PI3KβKI/KI mice were significantly protected in a Her2-drived breast cancer mouse model, which could be associated with a requirement of PI3Kβ in tumor cell autonomous signaling. Moreover, it could also be established, that the PI3Kβ protein was required for membrane recycling and sorting in a Rab5-associated compartment, and that some functions of PI3Kβ were independent of its lipid kinase activity (Ciraolo et al. 2008). PI3Kβ could then also be linked to c-kit signaling in the testis, which explained the male sterility in PI3KβKI/KI mice (Ciraolo et al. 2010, MBC).

The fact that the c-kit receptor is coupled to PI3Kβ in testis, but selectively activates PI3Kδ in mast cells, nicely illustrates cell-specific PI3K isoform signaling. We believe that such differences can be exploited to more specifically target PI3Ks in tumor autonomous processes, tumor/stroma and tumor/immune system interactions, with the aim to control tumor progression and metastasis.

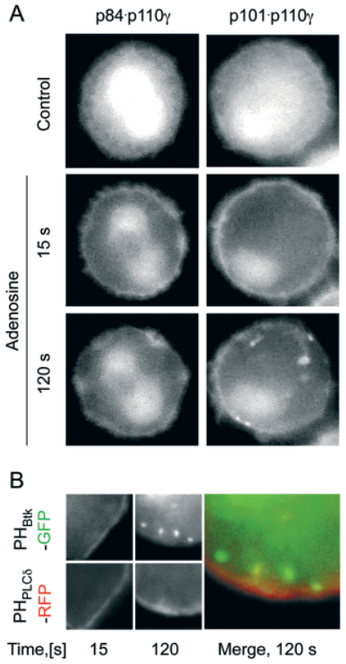


Fig. 1: PI3Kγ generates two pools of PtdIns(3,4,5)P3 with specific fates depending on which adapter subunits (p84 or p101) are associated with the catalytic subunit (p110γ):
1A) p84•p110γ supports degranulation, while p101•p110γ complexes generate PtdIns(3,4,5)P3 that is translocated to perinuclear locations. PtdIns(3,4,5)P3 was detected using a fusion protein of the Bruton's tyrosine kinase pleckstrin homology domain and GFP (PHBtk-GFP).
1B) Surprisingly, p101•p110γ generated PtdIns(3,4,5)P3 vesicles that do not contain PtdIns(4,5)P2, although PtdIns(4,5)P2 is 100x more abundant than PtdIns(3,4,5)P3 in the plasma membrane (PtdIns(4,5)P2 was detected with the PH domain of PLCδ).

Connection to Clinical Practice

Prof. Dr. Bernd Giese, Dept. Chemistry
Dr. Flaurent Beaufils, Dr. Vladimir Cmiljanovic
Dr. Olivier Jacques, Natasa Cmiljanovic (PhD student)
Prof. Dr. Ed Constable, Dept. Chemistry
Dr. Pirmin Rösel, Ruben Cal (PhD student)

PI3K inhibitors have entered phase I and phase II clinical trials in oncology, and programs to develop PI3K isoform-specific drugs for applications in chronic inflammation and allergy are progressing (Marone et al. 2008). As the number of available candidate compounds grows, it becomes apparent that the specific inhibitor profiles matter, and significantly affect efficiency, adverse effects, and the induction of signaling feedback loops. In this respect, the selectivity for PI3K versus mTOR inhibition seems to be of interest, and is currently investigated further.

Selected Publications

- Bohnacker, T., Marone, R., Collmann, E., Calvez, R., Hirsch, E., and Wymann, M. P. (2009). PI3Kgamma adaptor subunits define coupling to degranulation and cell motility by distinct PtdIns(3,4,5)P3 pools in mast cells. Sci Signal 2, ra27.
- Ciraolo, E., Morello, F., Hobbs, R. M., Wolf, F., Marone, R., Iezzi, M., Lu, X., Mengozzi, G., Altruda, F., Sorba, G., Guan, K., Pandolfi, P. P., Wymann, M. P., and Hirsch, E. (2010). Essential role of the p110beta subunit of phosphoinositide 3-OH kinase in male fertility. Mol Biol Cell 21, 704-711.
- Marone, R., Cmiljanovic, V., Giese, B., and Wymann, M. P. (2008). Targeting phosphoinositide 3-kinase: moving towards therapy. Biochim Biophys Acta 1784, 159-185.
- Marone, R., Erhart, D., Mertz, A. C., Bohnacker, T., Schnell, C., Cmiljanovic, V., Stauffer, F., Garcia-Echeverria, C., Giese, B., Maira, S. M., and Wymann, M. P. (2009). Targeting melanoma with dual phosphoinositide 3-kinase/mammalian target of rapamycin inhibitors. Mol Cancer Res 7, 601-613.
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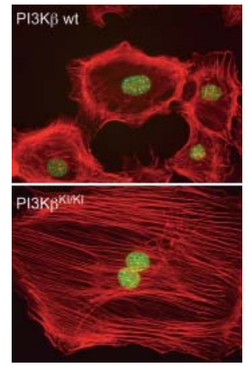

Fig. 2: Although mice without a functional PI3Kβ are viable, PI3KβKI/KI mouse embryonic fibroblasts (MEFs) show prominent phenotypes like increased cell size, senescence and defects in cytokinesis. F-actin was stained red with rhodamin-phalloidin, and nuclear DNA is depicted in green.

Anti-tumor immunity
Tumor antigen
Specific T cell response
Immunotherapy
Tumor microenvironment
Cytotoxic therapy

Cancer Immunology

New group since January 2010

Prof. Dr. Alfred Zippelius
Departments of Biomedicine and Oncology
University Hospital Basel

Group Members
Dr. Philipp Müller (postdoctoral fellow)
Dr. Grzegorz Terszowski (postdoctoral fellow)

Regulation and modulation of immune responses against tumors

In the last decade substantial evidence has accumulated that T cells can modulate cancer development. The concept of "cancer immunoediting" has been validated in elegant studies using knockout mouse models. In humans, several clinical observations strongly support the process of cancer immunosurveillance, including the prognostic relevance of tumor-infiltrating lymphocytes. Because T cells directed against tumor antigens are frequently found at the tumor site, the identification and characterization of those antigens has been a major progress in the field of tumor immunology. However, though anti-tumor T cell responses develop either spontaneously or upon immunization, these cells fail on most occasions to eradicate or even control malignant cells. Major obstacles to effective anti-tumor immunity include the ability of tumor cells to generate an immuno-modulating local microenvironment, to which diverse cell subsets, co-inhibitory molecules and soluble factors are thought to contribute. We investigate anti-tumor immunity in an inducible tumor model based on a conditionally activatable oncogene. This model also provides the platform to experimentally perturb the tumor microenvironment by different anti-tumor agents. In addition, we investigate the immune response in the tumor microenvironment of cancer patients at different stages of tumor progression and treatment. To this end, we perform a comprehensive analysis on the cellular and molecular immune interactions at the tumor site.

Connection to Clinical Practice

Cytotoxic anti-cancer therapies, i.e. chemotherapy, ionizing radiotherapy and targeted agents, are the most commonly used treatment modalities for cancer patients with both advanced disease and minimal residual disease after local surgery. However, their clinical efficacy may be limited by several factors including the development of therapy-resistant variants, a dormant tumor state of micrometastatic cells, and the inherent biology of cancer-initiating cells with high tumoricidal capacity. Very recently, mechanisms including the concomitant induction and/or enhancement of anti-tumor immunity have been proposed to considerably contribute to their efficacy. Clinical observations further support a concept that cytotoxic therapies enhance the efficacy of immunotherapy. Detailed knowledge of their immunostimulating effects are currently poorly defined. The aim of our research is to improve our understanding of the immuno-modulating capacities of cytotoxic anti-cancer therapies and pave the way for a rationale design of treatment algorithms combining cytotoxic anti-tumor agents with immunotherapy.

Selected Publications

- Knights AJ, Nuber N, Thomson CW, Tiercy JM, Jäger E, van den Broek M, Pascolo S, Knuth A, Zippelius A (2009). *Tumour antigen-encoding mRNA for the analysis of spontaneous and vaccine-induced immune responses in cancer patients*. Cancer Immunol Immunother. 58: 325-338
- Curioni Fontecedro A, Knights A, Tinguely M, Nuber N, Schneider C, Thomson CW, von Böhmer L, Pahlich S, Gehring H, Moch H, Renner C, Knuth A, Zippelius A (2008). *MAGE-C1/CT7 is the dominant Cancer-Testis antigen targeted by humoral immune responses in patients with multiple myeloma*. Leukemia. 22: 1646-1648
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- Walton S, Gerlinger M, Levy F, Gati A, Frei C, Taverna C, Jager E, Old LJ, Knuth A, Jager D, Zippelius A (2006). *Spontaneous CD8 T cell responses against the melanocyte differentiation antigen RAB38/NY-MEL-1 in melanoma patients*. J Immunol 177: 8212-8218
- Zippelius A, Batard P, Rubio-Godoy V, Bioley G, Lienard D, Lejeune F, Rimoldi D, Guillaume P, Meidenbauer N, Mackensen A, Rufer N, Speiser D, Cerottini J-C, Romero P, Pittet MJ (2004). *Effector function of humna tumor-specific CD8 T cells in melanoma lesions: a state of local functional tolerance*. Cancer Research 64: 2865-2873

Cell Migration
Neurite Outgrowth
Systems biology
Rho GTPase
Local mRNA translation
Live cell imaging
Signaling

Cell migration and Neurito-genesis

Prof. Dr. Olivier Pertz
Department of Biomedicine
Institute of Biochemistry and Genetics
University of Basel

Group Members
Dr. Michel Letzelter (postdoctoral fellow)
Daniel Feltrin (PhD student)
Katrin Benakovitsch (PhD student)
Ludovico Fusco (PhD student)
Georgios Fengos (PhD student)
Erika Fluri (technician)

Spatio-temporal signaling programs during cell migration and neurite outgrowth

The ability of vertebrate cells to directionally migrate is critical to development, the immune response and wound healing, and its regulation is compromised in pathologies such as metastatic cancer and vascular disease. The capacity of neurons to directionally extend neuronal processes is crucial for the proper wiring of the brain. A detailed understanding of the signaling events that regulate these complex morphogenetic processes is therefore likely to contribute important insights that could be used to target a number of different pathologies. We are broadly interested in the signaling events that regulate the cytoskeleton and the cell polarity mechanisms during the two processes mentioned above. Importantly, the activation status of these signaling switches is likely to be highly regulated in space and time. For this purpose, we are developing novel tools to grasp the spatio-temporal dimension of these signaling processes.

Spatio-temporal signaling programs during directed cell migration
To study spatio-temporal signaling during cell migration, we have devised genetically-encoded fluorescence resonance energy transfer-based biosensors for a wide variety of signaling molecules. This has led to novel models of Rho GTPase signaling during cell migration. We also developed an assay that allows for the purification of pseudopods from the cell body of migrating cells. Combined with proteomics approaches, this allowed us to examine the subcellular location of thousands of proteins at one time (pseudopod/cell body) in three prototypical cell directional migration modes. In one of these modes, cells migrate to a gradient of adhesion sites involving solely integrin signaling. In another mode, cells migrate in response to a gradient of soluble chemokines that signal either through a receptor tyrosine kinase or a G-coupled protein receptor. We find that different signaling programs occur at the leading edge in response to the different cues. Especially important, we find that different trafficking machineries relocalize to the front in the cell in the different migration modes. We are currently studying how these signaling programs might regulate the precise morphodynamics of the cell migration process and how this results in directional movement. For that purpose, we also developed a new microfluidic assay that allows to challenge migrating cells with precise gradients of chemoattractants. This provides a tractable system for live cell imaging of the cell migration process allowing to test some of the predictions provided by the proteomics data. The combination of these approaches will provide an integrated view of signaling during directed cell migration.

Spatio-temporal signaling programs during neurite outgrowth
We have also devised a method to biochemically purify the neurite from the soma of neurons. This has allowed a large scale proteomic analysis of the neurite and soma proteomes and enabled us to identify a complex Rho GTPase centered signaling network that is localized in the neurite. Importantly, we find that neurite outgrowth is controlled by modular, spatio-temporal Rho GTPase signaling units that perform different functions in space and time (regulation of neurite pathfinding, of filopodia stability, of neurite initiation or elongation) that co-operate to fine tune this process. We are currently dissecting this signaling network using a medium scale RNA interference screen using the dynamics of the neurite outgrowth process as a readout. Using the neurite outgrowth purification trick, we also have performed a genome-wide screen for mRNAs that are enriched in the neurite and found that 50 mRNAs are enriched at this location. These might be transported and translated in the neurite to perform highly specialized and localized functions. We are currently dissecting how local translation of a MAPKK that is upstream of the Jun kinase (JNK), a classic regulator of cellular stress, might locally switch the function of this kinase to regulate cytoskeletal dynamics.

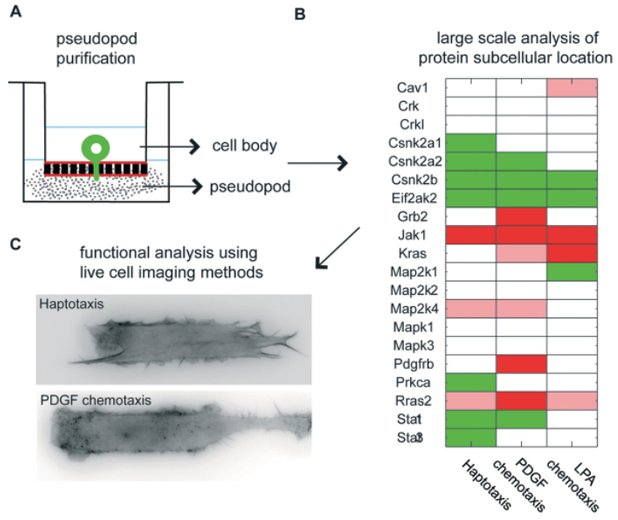

Fig. 1: **A.** Method for pseudopod purification. **B.** Heatmap of subcellular protein distribution in different cell migration modes. **C.** Fluorescence micrographs of cell directionally migrating in response to different cues.

Connection to Clinical Practice

Signaling to the cytoskeleton in cell migration and neurite outgrowth

The ability of vertebrate cells to directionally migrate is critical to development, the immune response and wound healing, and its regulation is compromised in pathologies such as metastatic cancer and vascular disease. The capacity of neurons to directionally extend neurites that will subsequently differentiate in axons and dendrites is crucial for the proper wiring of the brain. These complex morphogenetic processes depend on a very tight control of the cell's skeleton: the actin cytoskeleton. By example, at the front of a migrating cell, specific signaling molecules control actin polymerization to push the membrane forward. In contrast, at the back of the cell, other signaling events enable the contraction of the actin cytoskeleton to pull the cell's tail. Similar spatio-temporal signaling events are also observed during the extension of neuronal processes.
Until now many of these signaling events have been studied using classical biochemical techniques in which, by example, populations of cells are lyzed in a dish for biochemical studies. This cannot resolve the complexity mentioned above, and the lack of methods that enable to study these cellular processes in time and in space has made many of these signaling events elusive. Using novel tools that give access to the spatio-temporal dimension of signaling, we are exploring cell migration and neurite outgrowth in normal and pathological situations. We anticipate that this will give essential insights in how deregulated signaling confers invasive potential to cancer cells or in how to make nerves regenerate after spinal cord injury.

Selected Publications

- Pertz, O., Hogdson, L., Klemke, R.L., Hahn K.M. Spatio-temporal dynamics of RhoA activation in migrating cells. Nature. 2006 Apr 20;440(7087):1069-72.
- Pertz O., Wang Y., Yang F., Wang W., Gay L.J., Gristenko M.A., Clauss T.R., Anderson D.J., Liu T., Auberry K.J., Camp D.G., Smith D., Klemke R.L. Spatial Mapping of the Neurite and Soma Proteomes Reveals a Functional Cdc42/Rac Regulatory Network. Proc Natl Acad Sci U S A. 2008 Feb 12;105(6):1931-6.
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Acute leukemia

Molecular genetics

PIM kinases

MLL1

Mouse models

Childhood Leukemia

G. von Meissner Foundation

Prof. Dr. Jürg Schwaller
Department of Biomedicine
University Hospital Basel and
University Children's Hospital Basel

Group Members
Dr. Vaia Stavropoulou (postdoctoral fellow)
Dr. Laurent Brault (postdoctoral fellow)
Ellivasset Paraskevopoulou (PhD student)
Helene Mereau (PhD student)
Janine Zankl (Master student)*
Sarah Thommen (Master student)
Sabine Ehret (technician)
Ting Liu (PhD student)*
Dragana Jankovic (PhD student)*
Christelle Gasser (PhD student)*

* left during report period

Dissection of molecular alterations underlying acute leukemia to develop novel therapeutic strategies

Acute leukemia is the most common cancer in childhood. Current strategies provide a curative treatment for up to 80% of acute lymphoblastic leukemia (ALL), but for less than half of patients with acute myeloid leukemia (AML), and even less for infants with leukemia. Therefore we are searching for novel targeted therapeutic strategies. Acute leukemia is characterized by expansion of immature hematopoietic cells, which is the product of multiple functionally cooperating genetic lesions. Hereby, mostly gain of function mutations of protein kinases (like FLT3) and related signaling mediators drive clonal expansion without affecting differentiation. In addition, mutations of transcriptional regulators of normal hematopoietic cell differentiation (such as MLL1) result in a maturation block and provide aberrant self-renewal. Functional collaboration of leukemogenic alterations also involves epigenetic mechanisms such as histone modifications, DNA methylation and micro RNAs (Fig. 1).

We have previously identified the PIM family of serine/threonine kinases as potential therapeutic target in hematopoietic cells transformed by protein tyrosine kinases like the FLT3-ITD mutant frequently found in AML. Upon addressing the role of PIM kinases for leukemia induction, we unexpectedly found that bone marrow cells from PIM1$^{-/-}$ mice were severely impaired in homing to the hematopoietic organs. Interestingly, PIM1$^{-/-}$ cells expressed significantly lower levels of the CXCR4 chemokine receptor on their surface than wildtype or PIM2$^{-/-}$ cells. Interaction of the CXCL12 ligand with CXCR4 is known to be essential for proper homing and migration of normal and malignant hematopoietic stem cells. Interestingly, blocking of PIM1 by expressing a dominant-negative mutant, siRNAs, or with a small molecule inhibitor resulted in down regulation of CXCR4 surface expression in normal and leukemic cells. Further analysis revealed that PIM1 regulates the recycling process of the CXCR4 receptor through phosphorylation of its intracellular C-terminal domain at Serine 339. These observations not only provided novel insights into the role of PIM kinases for normal hematopoiesis but also suggested that blocking PIM1 might help to mobilize leukemic cells from their protecting microenvironment (Grundler et al., 2009, Brault et al., 2010).

Alterations of the mixed lineage leukemia 1 (MLL1) gene on chromosome 11 are a hallmark of acute leukemia in infants (<1 year of age). The most frequent ones are chromosomal translocations t(4;11), t(9;11) and t(11;19) leading to MLL/AF4, MLL/AF9 and MLL/ENL respectively. Expression of MLL fusion such as MLL/ENL in the mouse hematopoietic system induces an acute leukemia phenotype that closely recapitulates the human disease. However, it is not clear whether expression of an MLL-fusion is indeed sufficient to induce acute leukemia. To identify cooperating events, we have cloned viral integration sites in blasts in mice that developed acute leukemia after reconstitution of bone marrow cells retrovirally expressing MLL/ENL. We identified viral insertion-mediated increased expression of the meningioma 1 (MN1). Interestingly, co-expression of MN1 with MLL/ENL cooperated in leukemic transformation *in vitro* and in vivo. Elevated levels of MN1 seem to induce a distinct genetic program that results in expansion of leukemia-initiating cells (Liu et al., 2010).

Like MLL lesions, alteration of the nucleoporin-98 (NUP98) gene is a poor prognostic marker in acute leukemia. We have recently identified and functionally characterized a chromosomal translocation t(10;11)(q23;p15) associated with AML that leads to a fusion of NUP98 to the hematopoietically regulated homeobox gene (HHEX). Expression of the NUP98/HHEX fusion blocked hematopoietic differentiation *in vitro*, and induced an acute leukemic phenotype in vivo. Comparative gene expression profiling suggested that NUP98 fusion genes might induce acute leukemia by a genetic program that is highly overlapping to those mediated by MLL-fusions (Jankovic et al., 2008).

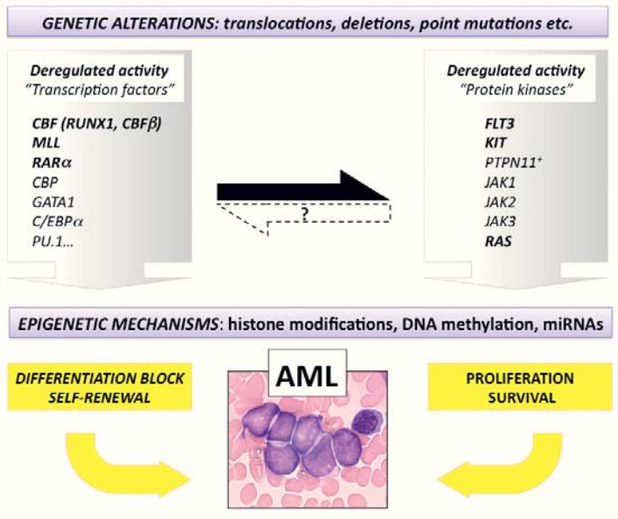

Fig. 1: Cooperation of (epi)genomic alterations leading to acute leukemia
Alterations targeting transcriptional regulators of normal hematopoiesis (e.g. MLL fusions) impose a block in differentiation and result in aberrant self-renewal. Aberrant activities of protein kinases (like the FLT3-ITD mutant) and related signaling regulators provide a proliferation and survival advantage leading to clonal expansion. Several epigenetic mechanisms like histone modification, DNA methylation or microRNAs are direct or indirect executors of the genomic lesions. The black and dashed arrows reflect the existing and putative cross-talks between the different types of (epi)genomic alterations respectively.

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Genomics
Proteomics
Theragnostics
Personalized medicine
Hormone dependent malignancies

Gynecological Oncology

Prof. Dr. Xiao Yan Zhong
Department of Biomedicine and Women's Hospital
University Hospital Basel

Group Members
Zeinab Barekati (PhD student)
Corina Kohler (PhD student)
Bessie Zhang (PhD student)
Ramin Radpour (PhD student)
Lei Fang (PhD student)
Fengfeng Cai (PhD student)
Kiefer Vivian (technician)
Hongbo Chen (statistician)
Wenxiu Zhou (MD student)
Navin Thomas (Master student)

Using Omic-Technologies to Develop Theragnostics for Hormone Dependent Malignancies: Example I – Methylation and Breast Cancer

Our aim is to develop theragnostics combining therapeutics with diagnostics for hormone dependent malignancies, such as breast cancer (BC), ovarian cancer (OVC) and endometrial cancer (EC), using omic-technologies, such as, genomics, transcriptomics and proteomics, in personalized medicine.
The first successful development of a theragnostics was the HER-2/neu based treatment of using Trastuzumab, especially for BC, however only benefiting 20-25% of the patients. Therefore, more cancer specific biomarkers are expected to develop new drugs and strategies for targeted therapy.
We apply high-throughput assays to analyse DNA (nDNA, mtDNA and DNA methylation), RNA (mRNA and microRNA) and protein changes in cancer for discovering new biomarkers. Herewith, we show our partial research data on DNA methylation status in BC as an example.
We developed a MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) -based assay to analyse DNA methylation status of 22 genes (APC, BIN1, BMP6, BRCA1, BRCA2, CADHERIN 1, CST6, DAPK1, EGFR, ESR2, GSTP1, NES1, Nm23-H1, P16, P21, PR, Prostasin, RAR-b, RASSF1, SRBC, TIMP3, TP53). They are mostly tumor suppressor genes (TSGs) involved in cancerogenesis, metastasis, drug resistance and response to hormone therapy in BC.
In order to understand the diagnostic value of methylation changes of the genes, we quantified the methylation status in paired cancerous and normal breast tissues, as well as in paired / unpaired blood samples. Using the bioinformatic tools, such as two-way hierarchical cluster analysis, one-way ANOVA test, Mann-Whitney test, paired-wise euclidean distances and linkage algorithm analysis, 10 TSGs (APC, BIN1, BMP6, BRCA1, CST6, ESRb, GSTP1, P16, P21 and TIMP3) were identified as hypermethylated in BC, which enabled distinguishing between cancerous and non-cancerous tissues, suggesting a classification value. High levels of hypermethylated circulating cell free DNA (ccf DNA) from most of the selected genes were found in patients plasma/serum samples. Correlation of TSG hypermethylation could be found between cancerous tissues and circulation in overlapping, but not between normal tissues and circulation, suggesting a possible diagnostic value in developing blood based test useful for facilitating early diagnosis and monitoring of therapies (Fig. 1).
In order to clarify the therapeutic value of using the identified genes as targets, we developed CpG island methylator phenotype (CIMP) criteria for epigenetic therapy. A methylation inhibitor 5-azacitidiene led to increased apoptosis/toxicity and decreased viability of BC cells in-vitro, and reactivated TSG expression based on the CIMP. Effect of the CIMP criteria based-treatment on tumour seeding, growth and metastasis will be confirmed through in-vivo mouse experiments. While demethylating TSG hypermethylation, the drugs may reactivate proto-oncogene, promoting development and progression of tumour metastasis. Therefore, we perform transcriptomic and proteomic studies to analyse gene expression profile and protein profile before and after treatment in cooperation with Novatis and Prof Lefkovits to understand the mechanism. A long-term in-vitro study to investigate the correlation between transient or reversible changes of the methylation signature and relapses/drug resistance has been scheduled.
In order to explain the interactions between gene-gene, mutation-methylation and mtDNA-nDNA, we analysed the network of genes, for example, the relationship between methylation profile of P14ARF/MDM2/TP53/PTEN/P21/P16Rb pathways and mtDNA alterations, as well as telomere length in BC. Indeed, we could find "cross-talking" between gene changes, which should be taken into consideration during theragnostics (Fig. 2).
In order to validate our observations, several international networks, such as "CANgene" for BC, "EUROTROP" for OVC, and one for EC have been built together with several Universities and Companies in USA, Europe and China. The figure 3 shows our research schedule to gaining our final goal of clinical applications.

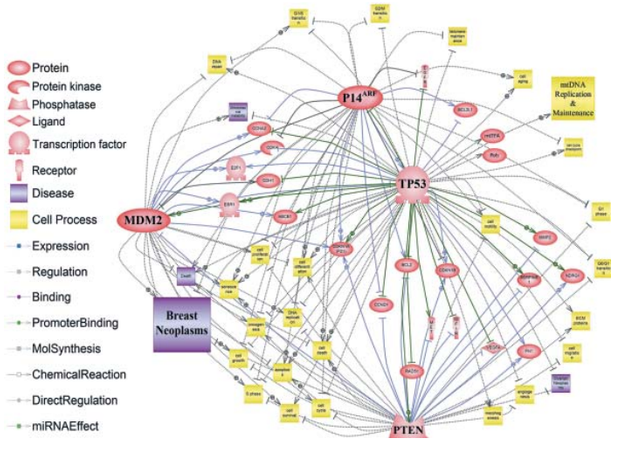

Fig. 2: Interactions between gene-gene, mutation-methylation and mtDNA-nDNA: P53 pathways as an example

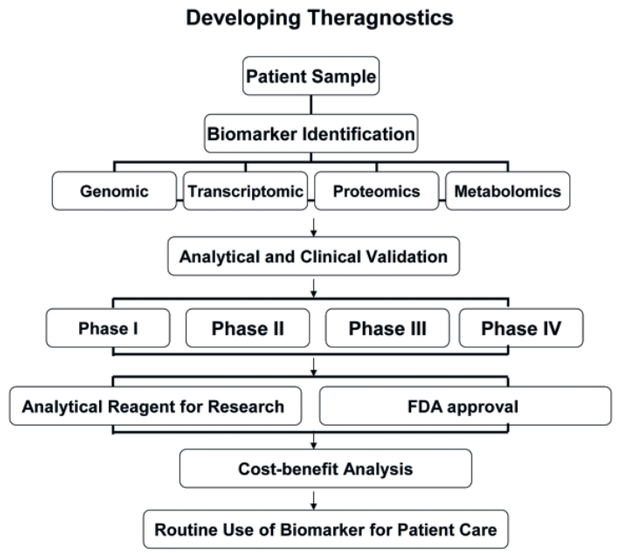

Fig. 3: Work plan for developing theragnostics

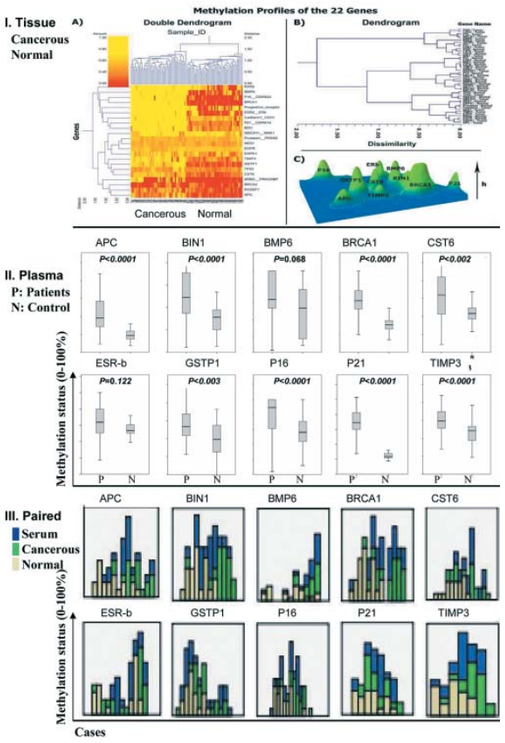

Fig. 1: Methylation quantification in tissue and/or circulation of patients with BC

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Hereditary colorectal cancer
Genotype-phenotype correlations
Genetic testing
Chromosome abnormalities
Array-CGH
Copy number variations

Human Genetics

PD Dr. Karl Heinimann
Department of Biomedicine and
Division of Medical Genetics
University Children's Hospital Basel

Group Members
Dr. phil. Robert Blatter
Dr. med. Isabel Filges
Dr. phil. Michal Kovac
Dr. phil. Judith Luz*
Dr. phil. Martina Plasilova
PD Dr. med. Nicole Bürki (external collaborator)
Salvatore Piscuoglio (PhD student)
Zoe Alvarado (MD student)*
Céline Gerber (MD student)
Mathis Grehn (MD student)*
Lucie Gautier (MD student)*
Stephan Zürcher (Master student)
Jan Sidler (Master student)
Vanessa Klug (Master student)*
Michèle Attenhofer (technician)
Marianne Häusler (family study professional)

Clinical Collaborators
Prof. Dr. med. Peter Miny
Prof. Dr. med. Hansjakob Müller
Prof. Dr. med. Walter Weber (external collaborator)

*left during report period

Genotype-phenotype correlations in hereditary colorectal cancer and patients with copy number variations

The research activities during 2008 to 2010 focused on the clinical and molecular characterisation of hereditary colorectal cancer syndromes and, with the introduction of array-based comparative genomic hybridization, of patients with copy number variations.
Fifteen to 20% of all colorectal cancers (CRC) are familial in origin. Familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer and familial colorectal cancer are estimated to account for about 0.5-1%, 2-5% and 10% of all CRC cases, respectively, with the latter being a heterogeneous, poorly understood entity. Our research group aims to characterize the molecular (epi)genetic basis of adenoma-carcinoma formation in patients with CRC predisposition syndromes. The activities include a) identification and genetic characterization of hereditary CRC patients b) assessment of genotype-phenotype correlations and c) characterisation of (epi)genetic somatic alterations in cancers from mutation carriers. The following excerpts briefly illustrate results from two collaborative studies.

Common genetic variants at the HMPS locus on 15q13.3 influence colorectal cancer risk. In a large multi-center study led by Ian Tomlinson, Cancer Research London, and with our group contributing to the mutation analysis and bioinformatic assessment of the 15q13.3 locus, a high-penetrance gene (CRAC1) associated with CRC was mapped to a 0.6-Mb region on chromosome 15. Subsequent SNPs nearby were found to be strongly associated with an increased CRC risk (for rs4779584, P=4.44 x 10-14).

Attenuated FAP: Results from an international collaborative study. Phenotypic and genotypic information from 12 polyposis registries from 9 countries was gathered on 254 AFAP patients. Median adenoma number was 25 with a uniform distribution of colorectal adenomas and CRC. Age at diagnosis was delayed by 15 years compared to classic FAP. Notably, APC gene mutations usually associated with an AFAP phenotype were only present in 52% of patients. Based on these observations, clinical diagnostic criteria for AFAP and surveillance recommendations were proposed.

Chromosome abnormalities are the most frequent and heterogeneous group of genetic diseases accounting for about 0.5-1% of multiple congenital anomalies and mental retardation syndromes. The advent of array-CGH allows the precise determination of submicroscopic chromosome alterations and enables accurate genotype-phenotype correlations as illustrated in the following observations.

Mosaic Ring Chromosome 8: Clinical and Array-CGH Findings in Partial Trisomy 8. In a 20 months old girl with developmental delay, facial dysmorphism and minor organ malformations we identified mosaicism for a supernumerary ring chromosome (SRC). Spectral karyotyping and FISH confirmed the SRC to be derived from chromosome 8, present in about 47% of cells. Array-CGH precisely determined the extent of the duplication (43.8 Mb, 8p11.21 to 8q21.2, Fig. 1) illustrating the potential of this method to replace laborious conventional cytogenetic methods.

Familial 14.5 Mb interstitial deletion 13q21.1 -13q21.33: A benign phenotype in a three-generation family. In a family an interstitial familial 13q21 deletion was identified with molecular karyotyping confirming a large 14.5 Mb deletion identical in all 3 healthy carriers (Fig. 2). The region appears to be a large euchromatic variant or benign copy number variation without phenotypic consequences. Our data underline the importance of a phenogenetic approach combining clinical and laboratory evidence in the interpretation of segmental chromosomal anomalies especially in prenatal diagnosis.

Interstitial deletion 1q42 in a patient with agenesis of corpus callosum: A contiguous 1q4 syndrome? In a girl with minor anomalies, midline defects including agenesis of the corpus callosum, epilepsy and developmental delay a de novo 5.45 Mb deletion located within 1q42 was found. In contrast to patients with 1q41q42 deletion syndrome, the SHH-pathway gene DISP1 was not deleted in our patient (Fig. 3, red bar), arguing against haploinsufficiency of single genes in the 1q4 region to cause complex malformation syndromes.

Fig. 1

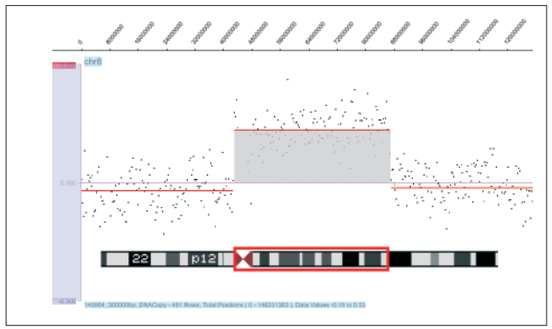


Fig. 2

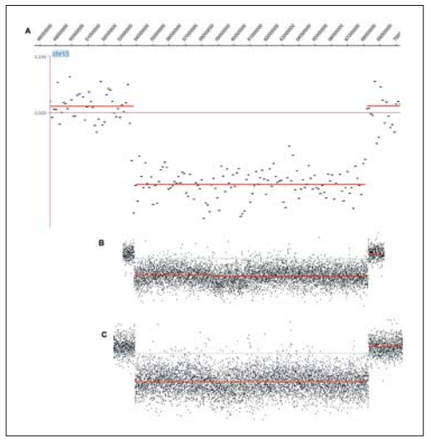
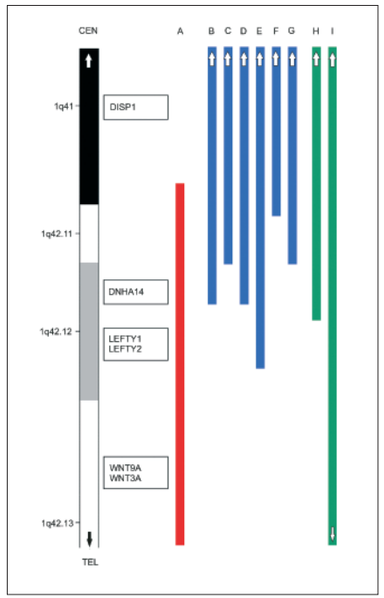


Fig. 3



Selected Publications

- Filges, I., Rothlisberger, B., Wenzel, F., Heinimann, K., Huber, A. R., and Miny, P. (2008). Mosaic ring chromosome 8: clinical and array-CGH findings in partial trisomy 8. Am J Med Genet A 146A, 2837-2841.
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- Filges, I., Rothlisberger, B., Boesch, N., Weber, P., Wenzel, F., Huber, A. R., Heinimann, K., and Miny, P. (2010). Interstitial deletion 1q42 in a patient with agenesis of corpus callosum: Phenotype-genotype comparison to the 1q41q42 microdeletion suggests a contiguous 1q4 syndrome. Am J Med Genet A 152A, 987-993.
- Knudsen, A. L., Bulow, S., Tomlinson, I., Moslein, G., Heinimann, K., and Christensen, I. J. (2010). Attenuated Familial Adenomatous Polyposis (AFAP) Results from an international collaborative study. Colorectal Dis. 2010 Jan 22.

Liposome, Immunoliposomes, Antibody, Drug Delivery
EGFR, VEGFR2, VEGFR3
DNA microarrays, Tumor Stroma, Cell-cell Interaction
Breast cancer

Medical Oncology

Prof. Dr. Christoph Rochlitz
Department of Biomedicine
and Division of Medical Oncology
University Hospital Basel

Group Members
PD Dr. Christoph Mamot (MD)
PD Dr. Martin Buess, (MD, PhD)
Dr. Andreas Wicki, (MD, PhD)
Dr. Annette Orleth (postdoctoral fellow)
Michal Rajski (PhD student)
Matyas Ecsedi (MD student)
Gregor Stehle (MD student)
Reto Ritschard (technician)
Brigitte Vogel (technician)

Expanding immunoliposomal strategies towards vascular endothelial cells and vascular endothelial tip cells.

Gene expression profiling.

Site-specific delivery of anti-cancer therapeutics is paramount for both reducing nonspecific toxicities and increasing efficacy of chemotherapeutic agents. Encapsulation of cytotoxic drugs inside lipid-based carrier systems (so-called liposomes) results in selective targeting of the compounds to solid tumors. The preferential delivery of liposomal drugs to cancerous tissue is mostly due to altered barrier-properties of tumor-associated vessels. This results in both an improved delivery and at the same time a significantly milder toxicity profile. Recently, we have further increased the specificity of delivery by attaching monoclonal antibodies to the surface of liposomes (=immunoliposomes). Our area of interest is tumor-associated angiogenesis, which is critical for tumor growth, invasion, and metastasis. VEGF receptor-2 (VEGFR-2) has been recognized as a main signaling transducer in tumor-associated angiogenesis, and therapeutic approaches against VEGFR-2 activity have been designed. VEGFR-3 has been thought to play a role in lymphangiogenesis rather than blood vessel angiogenesis.
Recent evidence suggests that VEGFR-3 is specifically functional in endothelial sprouts and plays a crucial role in the formation of tumor-associated vessels. We hypothesize that targeting of immunoliposomes to vascular endothelial receptors, such as VEGFR-2 or VEGFR-3 leads to disruption of neoangiogenesis and thus to tumor shrinkage. First results in an animal model of human pancreatic cancer indicate that vessel-targeted immunoliposomes indeed induce involution of tumor-associated vessels and significantly reduce tumor volume.
Another approach we are following is to load immunliposomes with siRNA (short interfering RNA). siRNAs interact with the homologous mRNA in a sequence-specific manner, resulting in the degradation of target mRNA and hence decreased production of the corresponding protein. Thereby, we plan to silence oncogenes in tumor cells using immunoliposomes against different targets of the tumor itself and the tumor stroma/vasculature. Combining the advantages of (1) promising cytotoxic compounds or siRNA stably encapsulated into liposomes and (2) the specific targeting function of monoclonal antibodies is expected to result in a specific delivery system for anticancer agents. This should increase the efficacy of the therapy while cutting down on unwanted side-effects. The final goal is to translate this research into the clinic and to establish new treatment protocols based on the insights we hope to gain through the proposed study.
Gene expression profiling studies with DNA microarrays have produced a detailed picture of the molecular features involved in human cancer. Over the last few years, gene expression profiles were determined for most common human cancers, allowing the identification of novel molecularly defined disease subtypes with distinct clinical outcome. The major challenge raised by these large amounts of detailed results is now identifying the pathophysiology underlying the specific gene expression patterns. The long-term goal is to identify mechanisms underlying the gene expression profiles of breast cancer. Considering the contributions of the microenvironment for the development of a tumor we will focus our study on the interaction between the tumor cells and their stromal host cells. That the interaction between tumor cells and stromal cells of the host plays an essential role in the development cancer has been shown in multiple studies. However, the effects on global gene expression due to heterotypic cell-cell interaction are not yet well characterized. We speculate that the effects of heterotypic interaction, which are expressed by specific gene signatures, are important for cancer development and the course the disease takes. To elucidate the basic principles in the gene expression effects of heterotypic interaction between breast cancer cells and a panel of stromal cells, we will analyze an in vitro co-culture model system using DNA microarrays and define their in vivo relevance by comparing the data to large publicly available datasets of breast cancer with annotation of clinical parameters.

Connection to Clinical Practice

Prof. Dr. Richard Herrmann, MD
Division of Medical Oncology, University

First phase I clinical trial with anti-EGFR-immunoliposomes in cancer patients.

The 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 (=immunoliposomes, IL). In fact, we demonstrated that by targeting the epidermal growth factor receptor (EGFR) using anti-EGFR ILs, the specificity and efficacy of various anticancer drugs was clearly improved. A worldwide first phase I clinical trial of immunoliposomal, anti-EGFR-targeted therapy was started in January 2007 and was completed in April 2010. A total of 26 patients suffering from different EGFR-expressing solid tumors were treated with EGFR-coated, doxorubicin-containing pegylated liposomes at doses increasing from 5mg/kg to 60 mg/kg. Preliminary results of both toxicity and efficacy have been reported at international meetings and look very promising.

Selected Publications

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- Wicki, A., Rochlitz, C., Ritschard, R., Orleth, A., Albrecht, I., Herrmann, R., Christofori, G., Mamot, C. Targeting tumor-associated endothelial cells: anti-VEGFR2-immunoliposomes mediate tumor-vessel disruption and reduce tumor burden. Cancer Res. 2010. Accepted pending minor routine and communicated revisions.

Genome Stability
DNA Repair
Cancer
Epigenetics
DNA Methylation

Molecular Genetics

Prof. Dr. Primo Schär
Department of Biomedicine
Institute of Biochemistry and Genetics
University of Basel

Group Members
Dr. Daniel Cortazar (postdoctoral fellow)
Dr. Frauke Focke (postdoctoral fellow)
Dr. Olivier Fritsch (postdoctoral fellow)
Dr. Christophe Kunz (postdoctoral fellow)
Dr. Faiza Noreen (postdoctoral fellow)
Dr. Joëlle Rüegg (Ambizione)
Dr. David Schürmann (postdoctoral fellow)
Angelika Jacobs (PhD student)
Claudia Krawczyk (PhD student)
Stefan Weis (PhD student)
Alain Weber (PhD student)
Annika Wirz (PhD student)
Barbara Gruberski (technician)

(Epi)Genome Maintenance

Reactive agents of endogenous and environmental origin pose a constant threat to the integrity of our genomic material, the DNA. DNA damage destabilizes genomes and, thereby, increases the risk of cancer. We explore biological processes that enforce genetic and epigenetic stability at the level of DNA damage response and repair. Our objective is to provide a thorough understanding of the molecular mechanisms involved and the consequences of their dysfunction for cancer development and therapy.

DNA Base Excision Repair (BER)
C->T substitutions are a prevalent type of mutation found in the DNA of human cancers. Most of them occur through deamination of cytosine or 5-methylcytosine, a frequent event that generates non-matching U•G and T•G base pairs in the DNA. Thymine DNA-Glycosylase (TDG) is a DNA repair enzyme capable of hydrolyzing mispaired U or T bases from the DNA backbone and may thus play a key role in the excision repair of such lesions. Pursuing biochemical and genetic approaches, we have been exploring the role of this enzyme in DNA repair, carcinogenesis, and cell differentiation. We discovered that dynamic modification of TDG with small ubiquitin-like peptides (SUMO) is required to coordinate its interactions with DNA and other repair proteins in the repair process. These investigations led to the first description of a role of SUMO-modification in DNA repair. Through work with yeast and mouse genetic models, we learned that TDG-mediated base excision contributes critically to the DNA-directed effects of chemotherapeutic drug 5-FU and to spontaneous chromosomal instability (Fig. 1). The mouse project also revealed an essential function of TDG in embryonic development, apparently in the control of epigenetic states during cell differentiation.

DNA double strand-break repair (DSBR)
DNA double-strand breaks are the most severe form of DNA damage. They arise through genotoxic insult or as a result of DNA transactions accompanying cell proliferation or differentiation. Cells utilize two distinct modes of DSBR; homology directed repair and non-homologous-end-joining (NHEJ). Both are critical for genome stability. We pioneered work on NHEJ in yeast with the discovery of Dnl4 and Lif1. The two proteins form a complex to constitute the DNA ligase operating in NHEJ. In a search for regulatory factors of DSBR, we also isolated Nej1 and Ntr1, both as interaction partners of Lif1. While Nej1 turned out to be a regulator of cell-type specific NHEJ, the function of Ntr1 in DSBR has remained enigmatic. We found Ntr1 to interfere with the formation of an active DNA ligase complex by occupying the Dnl4 binding site of Lif1, and to localize to telomeres and nucleoli (Fig. 2). These and other findings led us to propose that Ntr1 may engage to suppress NHEJ at these sites to avoid chromosomal aberrations. Current work focuses on the characterization of a newly identified role of Dnl4 in the stabilization of the ribosomal DNA array at sites of pausing DNA replication.
Cancer Epigenetics Aberrant CpG methylation contributes to tumorigenesis by dysregulating gene expression. Exactly why, how and when changes in DNA methylation arise during carcinogenesis is unknown. We aim to identify physiological conditions promoting DNA hypermethylation and, thereby, to assess the underlying molecular mechanisms. To this end, we examined the normal appearing colorectal mucosa of healthy individuals for the presence of cancer-prone methylation changes in the promoters of the hMLH1 and MGMT genes. We detected aberrant methylation in a gene-, age-, and gender-specific manner. Methylation levels were significantly elevated in females, but not in males, and only at the hMLH1 promoter in biopsies from the proximal colon of women above 60 (Fig. 3). Remarkably, sporadic hMLH1 deficient colorectal cancers also present preferentially in the proximal colon of females of advanced age, suggesting a causal relationship between hMLH1 hypermethylation in the normal mucosa and colorectal carcinogenesis. These striking observations are being validated and pursued with a larger cohorts and at a genomic scale.

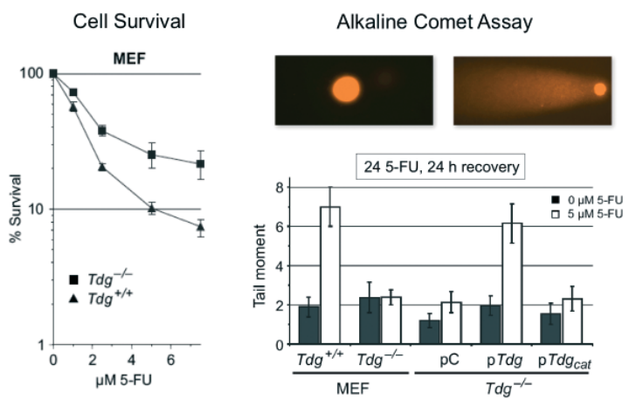

Fig. 1: Tdg dependent DNA base excision is responsible for 5-FU induced DNA strand-breaks and DNA-directed cytotoxicity of the drug.

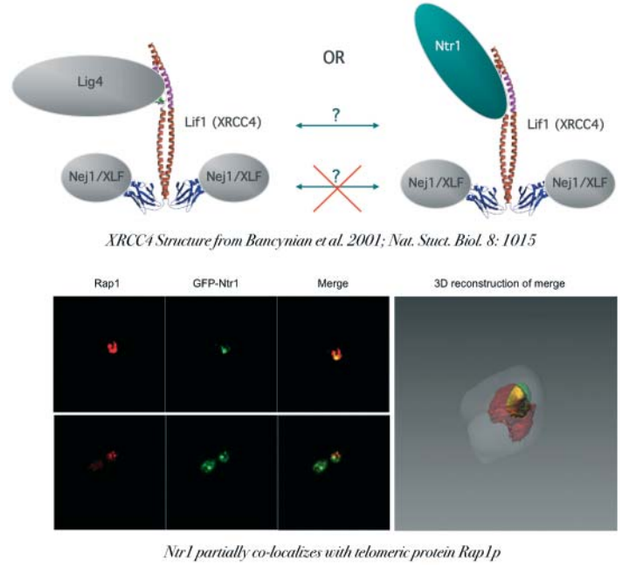

Fig. 2: NHEJ factors and protein complexes identified and functionally characterized in the Schär laboratory.

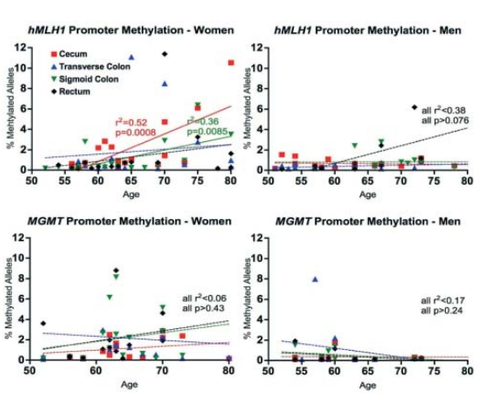

Fig. 3: Gender and anatomic location specific occurrence of cancer relevant CpG island methylation in the colorectal mucosa of healthy individuals

Selected Publications

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Glioblastoma
Notch2
Pro-apoptotic drug synergism
Stem cells
GSK 3 beta
Radiopeptide therapy

Neuro-Oncology

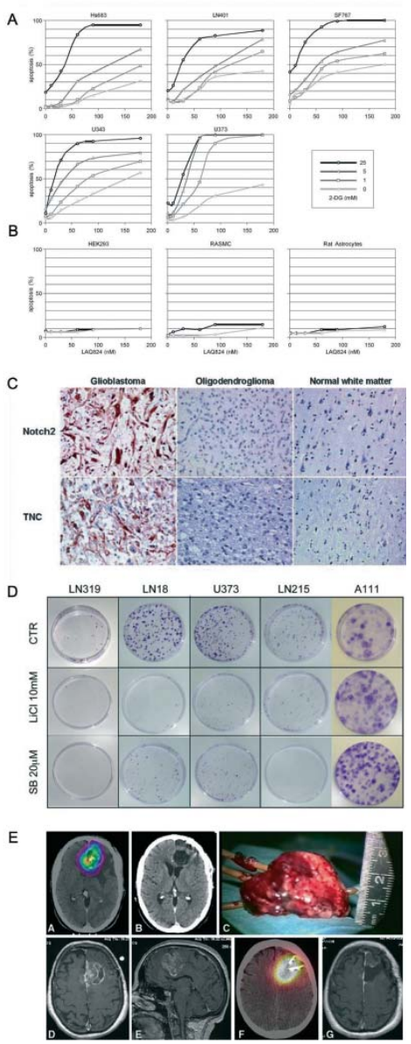
Prof. Dr. Adrian Merlo*
Department of Biomedicine
University Hospital Basel

Group Members
Dr Maria Maddalena Lino (postdoctoral fellow)
Dr. Serdar Korur (postdoctoral fellow)
Dr Jean-Louis Boulay (postdoctoral fellow)*
Dr. Balasubramanian Sivasankaran (postdoctoral fellow)*
Roland Huber (PhD student)
Beatrice Dolder (technician)
Elisabeth Taylor (technician)
Jaqueline Rauch (technician)
Marie Christine Müller (technician)*

*left during report period

Notch2 pathway in GBM and development of combinatorial therapeutic interference

High-grade glioma remains one of the most difficult cancers to treat. Since an accumulation of alterations is required for the onset of tumor development, combinations of compounds that inhibit non-overlapping pathways have become attractive strategies to treat gliomas. HDAC inhibitors (HDIs) have proven antiproliferative effects by promoting differentiation, cell cycle arrest, or apoptosis in tumor cells. We have shown that the glycolytic inhibitor 2-deoxy-D-glucose (2-DG), combined with low doses of the HDI LAQ824, induces strong apoptosis, in a p53-independent manner, in gliomas cell lines. Further, we found that 2-DG neutralized the LAQ824-dependent p21 up-regulation (Fig. A-B). In the same way other HDI, such as trichostatin (TSA) or sodium butyrate (NaB), when combined with 2-DG induce strong apoptosis and decreased p21 levels. Similarly, the combination of 2-DG and LAQ824 synergize in non glioma cell lines such as breast and cervix cancer cell lines. These results propose that the energetic and the histone acetylation pathways are targets to be considered for novel combined therapies against gliomas that could also be extended to other tumor types.
We further identified new pathways involved in migration and cancer stem cell regulation in GBM: Notch-Tenascin C and BMI1-GSK 3 beta.
Tenascin-C (TNC) expression is known to correlate with malignancy in GBM. In these malignant gliomas as well as in GBM cell lines, we found Notch2 protein to be strongly expressed. In a GBM tumor tissue microarray, RBPJk protein, a Notch2 cofactor for transcription, was found to be significantly coexpressed with TNC (Fig. C-D). We show that the TNC gene is transactivated by Notch2 in an RBPJk-dependent manner mediated by an RBPJk binding element in the TNC promoter. The transactivation is abrogated by a Notch2 mutation, which we detected in the glioma cell line Hs683 that does not express TNC. This L1711M mutation resides in the RAM domain, the site of interaction between Notch2 and RBPJk. In addition, transfection of constructs encoding activated Notch2 or Notch1 increased endogenous TNC expression identifying TNC as a novel Notch target gene. Overexpression of a dominant negative form of the transcriptional coactivator MAML1 or knocking down RBPJk in LN319 cells led to a dramatic decrease in TNC protein levels accompanied by a significant reduction of cell migration. Because addition of purified TNC stimulated glioma cell migration, this represents a mechanism for the invasive properties of glioma cells controlled by Notch signaling and defines a novel oncogenic pathway in gliomagenesis that may be targeted for therapeutic intervention in GBM patients.
Cancers are driven by a population of cells with the stem cell properties of self-renewal and unlimited growth. These cells are believed to constitute a tumor cell reservoir. Pathways controlling the renewal of normal stem cells are deregulated in cancer. The polycomb group gene Bmi1, which is required for neural stem cell self-renewal and also controls anti-oxidant defense in neurons, is upregulated in several cancers, including medulloblastoma. We have found that Bmi1 is consistently and highly expressed in GBM. Downregulation of Bmi1 by shRNAs induced a differentiation phenotype and reduced expression of the stem cell markers Sox2 and Nestin (Fig. E). Interestingly, expression of glycogen synthase kinase 3 beta (GSK3β), which was found to be consistently expressed in primary GBM, also declined. This suggested a functional link between Bmi1 and GSK3β. Interference with GSK3β activity by siRNA, the specific inhibitor SB216763 or lithium chloride (LiCl) induced tumor cell differentiation. In addition, the formation of neurospheres was impaired, and clonogenicity reduced in a dose-dependent manner. GBM cell lines consist mainly of CD133-negative (CD133-) cells. Interestingly, ex vivo cells from primary tumor biopsies allowed the identification of a CD133- subpopulation of cells that express stem cell markers and are depleted by inactivation of GSK3β. Drugs that inhibit GSK3, including the psychiatric drug LiCl, may deplete the GBM stem cell reservoir independently of CD133 status.



A-B: Synergistic induction of apoptosis by 2-DG and HDAC inhibitor LAQ824 in glioma cell lines. Glioma cell lines Hs683, LN401, SF767, U343 and U373 (A), non-tumor lines HEK and rat aorta smooth muscle cell, and normal rat astrocytes (B) were precultured for 48 h in standard medium and were exposed to various concentrations of LAQ824 in the presence of 2-DG for 72 h.

C: Immunostaining of GBM, oligodendroglioma, and normal white matter biopsies with anti-Notch2 and anti-TNC.

D: GSK3β inhibition reduced colony formation of GBM cells. A colony formation assay was performed on GBM cell lines treated with 10 mM LiCl or 20 mM SB216763 for 14 days.

E: a–c: Patient 10: a Dose distribution as assessed by CT-SPECT at the pretherapeutic intratumoral test injection. b Contrast-enhanced postoperative CT-scan. c En bloc removal of the GBM after internal decompression. Note the capsule-like surface of the resected tumor. The three catheter systems have been left in situ as anatomical landmarks. d–g Patient 4: (d, e) Large left frontal GBM in preoperative T1-weighted and contrast-enhanced MR imaging. (f) Dose distribution by CT-SPECT at the second therapeutic intratumoral injection. (g) T1-weighted and contrast-enhanced MR imaging after resection of the tumor.

Connection to Clinical Practice

Targeted alpha-radionuclide therapy of functionally critically located gliomas with (213) Bi-DOTA-[Th

GBM carry the worst brain tumor prognosis. The resection of GBM, followed by combined radiochemotherapy, is the current therapeutic standard and positively correlated with prolonged time to tumour recurrence. Besides treatment of the main tumour mass, therapy of the infiltration zone needs to be addressed as a major goal, because 95% of gliomas exhibit local recurrence. The local intratumoural injection of radiolabelled substance P, the physiological ligand of NK-1 receptors (overexpress by GBM), can be used for diagnostic or therapeutic applications. Alternatively, α-particle emitting radionuclides may be powerful candidates: allowing a highly cytotoxic radiation dose to be delivered to targeted cells while sparing adjacent healthy tissue. We performed a pilot study including five patients with critically located gliomas. After diagnosis , (213)Bi-DOTA-substance P was locally injected, followed by serial SPECT/CT and MR imaging and blood sampling Targeted radiopeptide therapy using (213) Bi-DOTA-substance P was tolerated without additional neurological deficit. No local or systemic toxicity was observed. (213)Bi-DOTA-substance P showed high retention at the target site. MR imaging was suggestive of radiation-induced necrosis and demarcation of the tumours, which was validated by subsequent resection. This study show that targeted local radiotherapy using (213)Bi-DOTA-substance P is feasible and may represent an innovative and effective treatment for critically located gliomas. Primarily non-operable gliomas may become resectable with this treatment, thereby possibly improving the prognosis.

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- Sivasankaran, B., Degen, M., Ghaffari, A., Hegi, M.E., Hamou, M.F., Ionescu, M.C., Zweifel, C., Tolnay, M., Wasner, M., Mergenthaler, S., et al. (2009). Tenascin-C is a novel RBPJkappa-induced target gene for Notch signaling in gliomas. Cancer research 69, 458-465.
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- Cordier, D., Forrer, F., Bruchertseifer, F., Morgenstern, A., Apostolidis, C., Good, S., Muller-Brand, J., Macke, H., Reubi, J.C., and Merlo, A. Targeted alpha-radionuclide therapy of functionally critically located gliomas with (213)Bi-DOTA-[Thi (8),Met(O (2)) (11)]-substance P: a pilot trial. Eur J Nucl Med Mol Imaging. 2010 Jul;37(7):1335-44.
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Cancer
Immune response
Immunotherapy
Tumor associated antigens
Tumor microenvironment
Translational oncology

Oncology Surgery

Prof. Dr. Giulio C. Spagnoli
Department of Biomedicine
Institute for Surgical Research and Hospital Management (ICFS)
University Hospital Basel

Group Members
Elke Schultz-Thater (technician)

Dr. Paul Zajac, Dr. Chantal Mengus,
Dr. Giandomenica Iezzi (postdoctoral fellows)

Nermin Raafat, Clementine Le Magnen,
Manuele G. Muraro, Volker Lorber,
Francesca Amicarella, Emanuele Trella (PhD students)

Charlotte Sedowski-Cron (guest surgeon)
Raoul Droeser, Xaver Huber (surgeon in training)
Valentina Mele (guest grad. student)
Juniy Han (guest surgeon)
Marzieh Ebrahimi (guest scientist)

Cancer-immune system interactions: between active antigen specific immunotherapy and the analysis of tumor microenvironment.

The "Oncology" lab of the ICFS is primarily interested in the clinical application of basic biology advances to surgical oncology. The main field of investigation is represented by tumor immunology with its diagnostic, prognostic and therapeutic implications.
During the past ten years the lab has developed immunotherapy protocols addressing the treatment of advanced melanoma by using a recombinant vaccinia virus (rVV) encoding multiple HLA-A0201 restricted epitopes from tumor associated antigens (TAA) and CD80 and CD86 co-stimulatory molecules. In 2009 we have closed a phase I/II clinical trial based on intranodal administration of this vector in stage III/IV melanoma. No major toxicity was observed following repeated rVV injection. Virus administration was associated with the induction of cytotoxic T lymphocyte (CTL) responses against at least one of the three epitopes from different TAA encoded by the vector. Interestingly, promising clinical results were observed, including one complete response (Fig. 1) of the duration of 19 months in a patient with a stage IV tumor and prolonged overall survival in additional immunologically responsive patients. Capitalizing on these advances similar strategies are presently being developed to address immune-mediated treatments of other cancers, and, in particular, in those expressing cancer/testis TAA of the MAGE-A family in significant percentages of cases (Sadowski-Cron et al., in preparation).
Pre-clinical studies have focused on the optimization of conditions favouring the generation of TAA specific CTL responses. In particular, we have demonstrated the superior ability of dendritic cells (DC) generated upon culture of peripheral blood monocytes in the presence of IFNα and GM-CSF in the induction of CTL and we have addressed the role of homeostatic cytokines (CK) binding the common γ-chain receptor in the elicitation of anti tumoral responses. We could demonstrate that whereas pre-incubation of CD8+ T lymphocytes in the presence of IL-15 favours the expansion of antigen specific memory cells, culture in the presence of IL-2 predisposes naïve CD8+ lymphocytes to react to TAA derived HLA-restricted epitopes.
The expertise acquired in the characterization of TAA specific immune responses has also been utilized to address the definition of immunogenic epitopes from virus of potential oncogenic significance. We have identified "universal" antigenic peptides derived from human cytomegalovirus (HCMV) pp65 protein, capable of stimulating both HLA class I and class II restricted immune responses, in CD8+ and CD4+ T cells across a wide range of HLA specificities. These reagents might qualify as synthetic immunogens for potentially large populations exposed to HCMV infection or reactivation.
An additional productive research line has investigated, in collaboration with the Institute of Pathology of our University, the characteristics of the tumor microenvironment, as related to cancer progression and its clinical features. We have shown that renal cell carcinomas (RCC) do express MICA/B ligands of the natural killer (NK) cell activation marker NKG2D. Importantly, the interaction between tumor and NK cells leads to mutual induction of apoptosis, resulting in a lack of NK cell infiltration into RCC. In other tissues additional immunosuppressive strategies are implemented within tumors to favour escape from immune responses. For instance, we have been able to detect expression of the gene encoding indoleamine 2,3-dioxygenase (IDO), a tryptophan metabolizing enzyme in endothelial and tumor cells in prostate cancers (PCA). By local tryptophan depletion and generation of toxic metabolites this enzyme may contribute to the creation of an immunosuppressive tumoral microenvironment.

Taken together our results underline progress in the "in vitro" and "in vivo" induction of TAA specific immune responses, but also the emerging increasing complexity of the interactions occurring between cancer and innate and adaptive immune system. The challenge for the next future is clearly represented by the translation of the knowledge acquired into clinical protocols of therapeutic relevance.

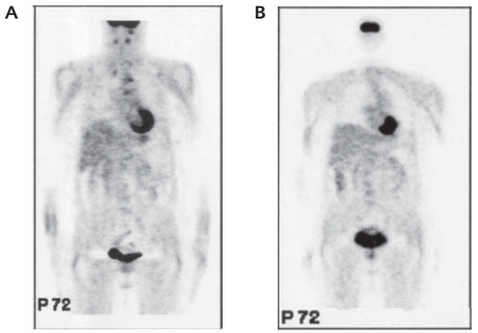

Fig. 1: A 72 years old HLA-A0201+ patient with stage IV melanoma (panel A) was treated with two cycles of active specific immunotherapy based on the administration of a recombinant vaccinia virus encoding gp100$_{280\text{-}288}$, Melan-A/MART-1$_{27\text{-}35}$ and tyrosinase$_{1\text{-}9}$ HLA-A0201 restricted epitopes and CD80 and CD86 co-stimulatory molecules, followed by injection of the corresponding synthetic peptides in the presence of GM-CSF (Adamina et al., 2010). PET showed evidence of a complete response following treatment (panel B). A progression free time of 19 months could be recorded.

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Connection to Clinical Practice

From left to right:
Prof. Dr. Daniel Oertli,
Prof. Dr. Alexander Bachmann,
Prof. Dr. Didier Lardinois
Departments of Visceral Surgery, Urology and Thoracic Surgery, University of Basel

Translational science in surgical oncology

The "oncology" lab of the Institute for Surgical Research and Hospital Management enjoys a close relationship with Clinical Surgery Departments. This interaction is consolidated by the presence of clinicians participating full time to the research activities of the lab for periods of time ranging between six months and two years. Clinicians from the Surgical Departments have run clinical trials of active specific immunotherapy in advanced melanoma from the selection of patients to the vaccination procedures and to the comparative evaluation of the clinical course of the disease and the immunological monitoring. Capitalizing on this model of cooperation, surgeons from different clinics have taken advantage of the technologies and reagents developed within the lab to explore the expression of TAA in lung cancers, to analyze the potentially immunosuppressive features of the tumor microenvironment in the prostate and to address the prognostic relevance of the expression of phenotypic markers of cancer initiating cells in colorectal cancers. In this context, the tight interaction with the Department of Pathology is also proving of critical relevance. Taken together, these studies provide the indispensable background for the development of basic research projects. Furthermore, they allow envisaging innovative strategies of potential clinical relevance as related to the stratification of patients undergoing established treatments and to the implementation of novel immunotherapeutic protocols.

Angiogenesis
Cancer,
Lymphangiogenesis,
Metastasis,
Signal transduction
Tumorigenesis

Tumor Biology

Prof. Dr. Gerhard Christofori
Department of Biomedicine
Institute of Biochemistry and Genetics
University of Basel

Group Members
Dr. Imke Albrecht (postdoctoral fellow)
Helena Antoniadis (technician)
Vanessa Baeriswyl (PhD student)*
Raphael Bieri (Master student)*
Dr. Miguel Cabrita*
Maren Diepenbruck (Master student)*
Dr. Ernesta Fagiani
Dr. Anna Fantozzi
Michael Flori (Master student)*
Chantal Heck (PhD student)
Dr. Ulrike Hopfer
Dr. François Lehembre*
Dr. Akiko Kunita
Dorothea Maaß (PhD student)
Lukas Mannhart (bioinformatician)
Dr. Nathalie Schlegel
Ursula Schmieder (technician)
Petra Schmidt (technician)
Dr. Tibor Schomber*
Karin Strittmatter (technician)*
Lorenz Waldmeier (PhD student)
Mahmut Yilmaz (PhD student)*
Adrian Zumsteg (PhD student)*

* left during report period

Molecular dissection of tumor angiogenesis, lymphangiogenesis, and metastasis

90% of cancer patients die of metastasis. The major objective of our research is the identification and characterization of the molecular events underlying malignant tumor progression and metastasis formation, potential targets for innovative cancer therapies. In particular, we focus on the contribution of tumor angiogenesis and lymphangiogenesis to tumor progression and on the molecular mechanisms underlying the transition from benign neoplasia to malignant cancers and the metastatic dissemination of tumor cells. In addition to tumor cell lines in vitro, we employ transgenic mouse models of tumorigenesis to determine causal connections between the expression of particular genes and tumor progression in vivo.

The development of malignant tumors is in part characterized by a tumor cell's capability to overcome cell-cell adhesion and to invade surrounding tissue. In most epithelial cancers, loss of the cell-cell adhesion molecule E-cadherin underlies the conversion of epithelial, differentiated cells to mesenchymal, migratory and invasive cells, a process referred to as epithelial-mesenchymal-transition (EMT). In the past years, we have learned that EMT occurs in multiple stages and is regulated by sophisticated molecular networks regulating the expression of a large number of protein- and miRNA-encoding genes. Notably, we have identified a number of transcription factors that appear critical not only in the initiation and execution of the morphogenic process of EMT but also in providing survival signals to cancer cells. We investigate the direct target genes of such transcription factors and their functional contribution to tumor metastasis. These transcription factors may also define "cancer-initiating cells" which are able to seed metastasis, and we study them also in the context of the epigenetic regulation of gene expression, such as histone modifications and DNA methylation. Finally, we assess the role of miRNAs and their target genes in the regulation of EMT and metastatic dissemination. With these experimental approaches we aim at the identification of the master regulators of EMT and metastasis and we plan to scrutinize their potential as therapeutic targets for preventing metastatic disease.

In a second line of research, we investigate the molecular regulation of tumor blood vessel angiogenesis and tumor lymphangiogenesis. We have generated a number of mouse models that offer the unique opportunity to study the pathological, physiological and molecular consequences of different qualities and quantities of angiogenesis and lymphangiogenesis for tumor progression and metastasis. For example, employing these mouse models we have identified novel cellular and molecular markers for tumor angiogenesis and lymphangiogenesis, markers that are desperately needed for the diagnosis, prognosis and clinical monitoring of cancer patients being treated with anti-angiogenic therapies. Moreover, in the past years we have employed a combination of adoptive cell transfer and genetic lineage tracing experiments to determine the contribution of bone marrow-derived cells to tumor angiogenesis and lymphangiogenesis. While we have not found any bone marrow-derived cell integrating into tumor blood vessels, we have demonstrated that cells of the myeloid lineage trans-differentiate into lymphatic endothelial cells and by integrating into lymphatic vessels contribute to tumor lymphangiogenesis.

Finally, we employ various transgenic mouse models for the design and testing of innovative cancer therapies, either based on anti-angiogenic strategies or by directly targeting cancer cells. For example, in collaboration with Dr. Andreas Wicki, PD Dr. Christoph Mamot, and Prof. Christoph Rochlitz, Clinical Oncology, University Hospital Basel, we are testing immunoliposomes that are designed to target the tumor vasculature. This approach has been highly successful in the preclinical setting and is now being adapted for clinical use (see textbox on the right). Finally, in collaboration with pharmaceutical companies we are investigating the efficacy and biological consequences of various anti-angiogenic cancer treatments.

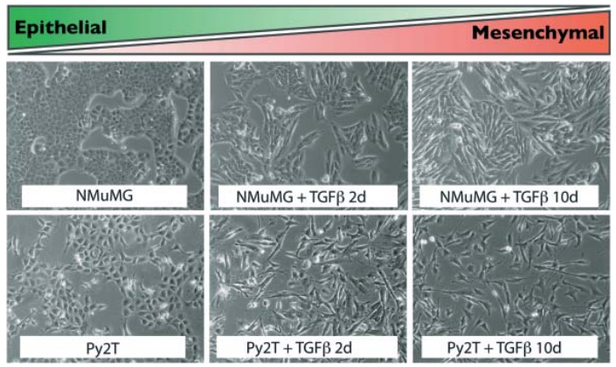

Fig. 1: TGFβ-induced epithelial-mesenchymal transition (EMT) of cultured normal murine mammary gland epithelial cells (NMuMG) and epithelial breast cancer cells derived from a breast tumor of a MMTV-Polyoma Middle T transgenic mouse (Py2T). Note the epithelial to mesenchymal transition (EMT) upon exposure to TGFβ after 2 days and 10 days.

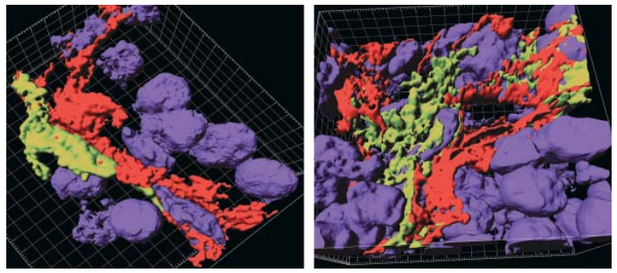

Fig. 2: Confocal three-dimensional reconstruction of pericytes (green) attaching to tumor endothelial cells (red) in pancreatic β-cell tumors of Rip1Tag2 transgenic mice. Note that transgenic expression of angiopoietin-1 in tumor cells induces maturation of tumor vessels (left panel), while transgenic expression of angiogepoietin-2 prevents vessel maturation (right panel). Blue = nuclei of endothelial cells, pericytes and tumor cells.

Connection to Clinical Practice

Dr. Andreas Wicki, PD Dr. Christoph Mamot, Prof. Christoph Rochlitz
Clinical Oncology, University Hospital Basel

Targeting tumor-associated endothelial cells with immunoliposomes

Angiogenesis is a key process in tumor progression. By binding vascular endothelial growth factor (VEGF), VEGF receptor-2 (VEGFR2) is a main signaling transducer in tumor-associated angiogenesis. Accordingly, therapeutic approaches against the VEGF/VEGFR2 signaling axis have been designed and a number of small chemical compounds or neutralizing antibodies interfering with VEGFR2-mediated signaling are in clinical use or trial. However, an efficient and specific chemotherapeutic targeting of tumor-associated endothelial cells has not been achieved. In collaboration with the Department of Clinical Onocology of the University Hospital Basel, we have employed anti-VEGFR2 antibodies covalently linked to pegylated liposomal doxorubicin (PLD) to specifically ablate tumor-associated endothelial cells in the Rip1Tag2 mouse model of insulinoma, in the MMTV-PyMT mouse model of breast cancer, and in the HT29 human colon cancer xenograft transplantation model. In each model, anti-VEGFR2-targeted immunoliposomes loaded with doxorubicin (anti-VEGFR2-ILs-dox) are superior in therapeutic efficacy to empty liposomes, empty anti-VEGFR2, and PLD. Detailed histopathological and molecular analysis reveal a strong anti-angiogenic effect of anti-VEGFR2-ILs-dox, and the observed anti-angiogenic therapy is significantly more efficient in repressing tumor growth in well-vascularized transgenic mouse models as compared to the less-vascularized xenograft model. In conclusion, anti-VEGFR2 immunoliposomes provide a highly efficient approach to selectively ablate VEGFR2-expressing tumor vasculature and thus offer a novel and promising anti-cancer strategy for patient treatment.

Selected Publications

- Lehembre, F., Yilmaz, M., Wicki, A., Schomber, T., Strittmatter, K., Ziegler, D., Kren, A., Went, P., Derksen, P., Berns, A., Jonkers, J., and Christofori, G. (2008) NCAM-induced focal adhesion assembly: a functional switch upon loss of E-cadherin. EMBO J. 27, 2603-2615.
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- Schomber, T., Zumsteg, A., Strittmatter, K., Crnic, I., Antoniadis, H., Littlewood-Evans, A., Wood, J., and Christofori, G. (2009) Differential effects of the VEGF receptor inhibitor PTK787/ZK222584 on tumor angiogenesis and tumor lymphangiogenesis. Mol. Cancer Ther. 8, 55-63.
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- Zumsteg, A., Strittmatter, K., Klewe-Nebenius, D., Antoniadis, H., and Christofori, G. (2010) A bioluminescent mouse model of pancreatic β-cell carcinogenesis. Carcinogenesis 31, 1465-1474.

DBM Focal Area Immunology

Focal Area Coordinators

Prof. Dr. A. Rolink
Department of Biomedicine
University of Basel

Prof. Dr. Chr. Hess
Department of Biomedicine
Medical Outpatient Department
University Hospital Basel

During evolution an immune system has been generated for protection against life-threatening infections. However, the high versatility and complexity of the immune system also harbors the danger of developing various diseases like immunodeficiency's and autoimmune diseases. These diseases most often arise as a consequence of defects in the development of the immune system and/or as a consequence of aberrant immune reactions.

Within the Department of Biomedicine the Immunology Focus is comprised of 12 research groups. Four of these groups focus their efforts on developmental aspects of the immune system. In particular, these studies seek to unravel the molecular and cellular mechanisms that guide (i) the development of T and B cells and with special emphasis on how central and peripheral T and B cell tolerance is achieved; and (ii) the formation of primary and secondary lymphoid organs. These studies are aimed to provide new insights in the development of various types of effector cells as well as the involvement of the microenvironment in this differentiation.

About 20 years ago a T cell that is able to suppress the function of effector T cells was first described. Nowadays these T cells are called regulatory T cells. However, up to now the mechanism by which these T cells execute their suppressive action is still unknown. One research group is studying this using an organ transplantation model system.

The majority of T cells expressing an α/β T cell receptor recognize MHC/peptide complexes. However, a considerable part of these T cells recognize lipids, phosporylated metabolites and sugars presented by CD1 molecules. The research of one group is focused on the physiology of these non-conventional T cells and seeks to elucidate their potential role in immunopathology. Recently it was observed that various circulating cells could release small vesicles by budding from the cell surface. These vesicles are called ectosomes. One group has convincing evidence that these ectosomes can block inflammatory responses. Currently the mechanism by which they execute this inhibitory action is analyzed.

Complement is required to combat infections and to clear the body from necrotic and apoptotic cells. However, schistosomes seem to be able to block complement activation. One research group is analyzing the mechanism by which this parasite exerts its inhibitory action. Complement deficiencies in man and mice can result in autoimmunity. For example, the occurrence of systemic lupus erythematosis is strongly associated with the presence of anti-C1q autoantibodies. One group is studying the pathogenic role of these types of antibodies in human diseases.

Toll-like receptors play a crucial role in the defense against bacterial infections. The analysis of the role of these receptors in the context of staphylococcal infections constitutes another research focus in the Department.

Viral infections constitute a life-threatening challenge especially in individuals with primary or secondary immunodeficiencies. Three research groups within the Department focus their efforts on the immune system's early recognition of viral infection and ways by which an anti-viral response can be enhanced.

Taken together a wide variety of basic translational immunological research activities are ongoing in the Department. Moreover a network of laboratory-based research with strong links to clinical medicine and other institutes of the University of Basel has been established.

Complement

Autoantibodies

Systemic lupus erythematosus

Ischaemia-reperfusion injury

Clinical Immunology

PD Dr. Marten Trendelenburg
Department of Biomedicine
Clinic for Internal Medicine

Group Members
Dr. Dominique Vanhecke (postdoctoral fellow)
Dr. Michael Osthoff (clinical reseach fellow)
Hedwig Niederer (technician)

The pathogenic role of complement MBL and autoantibodies against complement C1q in human diseases

Systemic lupus erythematosus (SLE) is considered an archetype of systemic autoimmune diseases. However, the causes and pathogenic mechanisms of SLE are still not fully understood. A major hypothesis of the pathogenesis of SLE assumes that the disease is driven by a defective clearance of dead and dying cells. In the context of an altered clearance these dying cells could become antigenic and initiate an autoimmune response. The complement system has been shown to play an important role in the clearance of apoptotic cells and the deficiency of one of the early components of the classical pathway of complement is strongly associated with the development of SLE. However, most SLE patients have no primary complement deficiency. In contrast, hypocomplementemia in SLE patients is a secondary event and most often associated with antibodies against the first component of the classical pathway of complement (C1q). As we and others have shown, autoantibodies against C1q (anti-C1q) strongly correlate with renal flares in SLE patients. Our studies suggest that the occurrence of anti-C1q in SLE patients is necessary but not essential for the development of proliferative lupus nephritis. It is possible that anti- C1q interfere with the normal function of the complement system including the clearance of apoptotic cells. As we could show, anti-C1q specifically target C1q when bound to the surface of early apoptotic cells.
However, the role of anti-C1q in other diseases is not yet established and the potential pathogenic mechanism of anti-C1q remains to be elucidated. Furthermore, the importance of regular anti-C1q measurements as a clinical follow-up marker in SLE patients is not yet established.
Therefore, our group aims to further examine the pathological role and the clinical relevance of anti-C1q antibodies in a double approach based on experimental studies of anti-C1q and clinical studies of patients with SLE. The experimental part includes the generation of human monoclonal anti-C1q and the investigation of their interference with physiologic functions of the complement system in vitro and in vivo. In our clinical studies we aim to establish anti-C1q as an important follow-up parameter in SLE patients.

Independently, we are studying the role of complement mannose-binding lectin (MBL). MBL, that is strongly related to C1q, has been shown to play an important role in the defence against infectious agents. More recent studies suggest that MBL also binds to apoptotic cells and plays a pro-inflammatory role in experimental settings of ischaemia-reperfusion injury. The high frequency of functional MBL deficiency in the general population (about 25%) predestinates MBL for clinical studies investigating its role in human diseases. In a large trial on patients with acute myocardial infarction undergoing catheter intervention to reopen the occluded artery, we could show that low serum MBL levels were associated with reduced mortality. In ongoing studies, we are investigating the role of complement MBL in other settings of human ischemia-reperfusion injury as well as in infectious diseases.

Selected Publications

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- Bigler C, Schaller M, Perahud I, Trendelenburg M. Autoantibodies against complement C1q specifically target C1q bound on early apoptotic cells. J Immunol 2009; 183: 3512-3521.
- Schaller M, Bigler C, Danner D, Ditzel HJ, Trendelenburg M. Autoantibodies against C1q in systemic lupus erythematosus are antigen driven. J Immunol 2009; 183: 8225-8231.
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T cell development
B cell development
Plastic Thymus
Notch
BAFF
BAFF-Receptor

Developmental and Molecular Immunology

Prof. Dr. Antonius Rolink
Department of Biomedicine
University of Basel

Group Members
Dr. Jan Andersson
Dr. Rhodri Ceredig (visiting scientist)
Dr. Nabil Bosco (postdoctoral fellow)*
Dr. Roxane Tussiwand (postdoctoral fellow)
Lee Kim Swee (PhD student)
Angèle Bénard (PhD student)
Nadine Gehre (PhD student)
Matthias Kreuzaler (PhD student)
Anja Nusser (PhD student)
Marianne Spalinger (Master student)*
Reto Ziegler (Master student)*
Jamil Wenzel (Master student)
Nicole von Burg (Master student)
Corinne Demolliere (technician)
Giuseppina Capoferi (technician)
Hannie Rolink (technician)
Ernst Wagner (technician)
Patricia Thimm (animal caretaker)

* left during report period

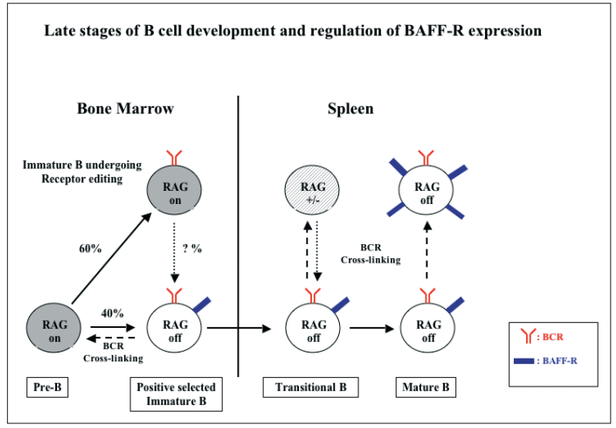
Molecular mechanisms guiding lymphocyte development

T cell development
We and others have shown that early progenitors from the bone marrow (BM) that home to the thymus still posses the capacity to generate B-, NK-, Dendritic- and other myeloid cells. Upon a brief Notch signal these cells quickly loose their B cell developmental potential. Based on these findings we have been able to estimate that the thymus is colonized by about 10 progenitors from the BM per day. However, DN1 and DN2 cells who are the direct progeny of these early BM progenitor still posses the capacity to give rise to NK-,Dendritic and other myeloid cells. At the DN2-DN3 transition commitment to the T cell lineage is achieved. The molecular mechanisms that guide this commitment are still poorly understood.

We have now generated a stromal cell free culture system that allows the differentiation of lineage negative, Sca-1 positive CD117 high (LSK) cells from the BM into the T cell lineage. This culture system is loosely called "The Plastic Thymus". The in vitro differentiation of LSK's into the T cell lineage is achieved by culturing them on Delta like 4 – human IgG1-Fc fusion protein coupled to a tissue culture well via a mAB against human IgG1-Fc. Moreover this proliferation and differentiation of LSK's requires the addition of IL-7 and SCF. Thus, cultured LSK's divide every 20-30 hrs and can be propagated for more then 6 months. With time they acquire a DN2–DN3 phenotype and loose the capacity to generate B-, NK-, Dendritic- and other myeloid cells. Upon transfer these cells can efficiently but exclusively reconstitute the T cell compartment with functional cells. Therefore these cells are committed to the T cell lineage. Currently they are subjected to detailed molecular analysis in order to shed light on the mechanisms that guide this commitment.
Previously we showed that DN3 when cultured on the OP9 stromal cells expressing the Notch ligand Delta like 1 differentiate into DP thymocytes. Now we showed that plate bound Delta like 4 – human IgG1-Fc fusion protein also very efficiently induce the differentiation of DN3 cells into DP thymocytes. This differentiation is preTCR dependent, improved by CXCL12 signaling and inhibited by IL-7 signaling. This culture system will be an ideal tool to study positive and negative selection of T cells in vitro.

B cell development
Immature B cells generated in the BM bearing an autoreactive B cell receptor (BCR) or a BCR of which the heavy and the light chain badly pair will either die by apoptosis or will undergo secondary light chain rearrangement (receptor editing). Up to now it ha not been possible to distinguish receptor editing immature B cells from those bearing a good BCR and thus not undergoing editing (positively selected immature B cells). We now have shown that based on the expression of the BAFF receptor (BAFF-R) immature BM B cells can be subdivided into two populations. By FACS about 40% of these express the BAFF-R and 60% do not. The BAFF-R negative immature B cells still express the RAG enzymes and spontaneously undergo receptor editing in vitro while the BAFF-R positive ones do not express RAG and do not change their BCR upon in vitro culture. Thus BAFF-R marks the positive selected immature B cells in the BM. However, upon BCR cross-linking positively selected immature B cells down-modulate the expression of the BAFF-R and gain RAG expression and as a consequence of this undergo receptor editing. Immature B cells that migrated to the spleen (also called transitional B cells) also down-modulate BAFF-R expression upon BCR cross-linking and gain RAG expression. However, the RAG induction and as a consequence of this the receptor editing in immature splenic B cells is less then in their BM counterparts. In marked contrast to the immature B cell compartments cross-linking of the BCR on mature B cells results in a dramatic up-regulation of BAFF-R expression. Thus BAFF-R expression underlies a very fine tuned regulation, which very well could be envisaged to play a crucial role in the establishment and maintenance of B cell tolerance (Fig. 1).

Fig. 1



Connection to Clinical Practice

B cell development in humans

In mice, BAFF-R signaling plays a crucial role in the establishment and maintenance of the mature B cell compartments. The finding that patients with a BAFF-R deficiency have very low numbers of B cells suggest a similar role for this signaling pathway in human B cell development. We have established a very sensitive anti-BAFF ELISA. BAFF levels were determined in the serum of over 100 healthy donors. In these, the BAFF concentrations varied from 0.2-5 ng/ml. Moreover, the BAFF concentrations in the serum of 583 patients with primary immunoglobulin deficiencies were determined (Collaboration with Dr. H. Eibel, University of Freiburg, Germany). About 70% of these had BAFF levels comparable to healthy donors indicating that their deficiency was BAFF independent. About 30% of the patient had BAFF levels of 10 ng/ml or higher i.e. two or more times higher then in healthy controls. In all of these patients peripheral B cell numbers were dramatically reduced suggesting that the increased BAFF concentrations might be due to less consumption. Up to now 5 patients with BAFF levels below the detection limit have been identified. However, B cell numbers in the blood of these patients are within the range found in healthy donors. Currently these patients are analyzed in more detail.
In near future BAFF concentrations will be determined in patients with various autoimmune diseases and in patients with various B cell neoplasias in order to elucidate whether BAFF might play a role in the pathogenesis of these disorders.

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- Transient decrease in interleukin-7 availability arrests B lymphopoiesis during pregnancy. Bosco N, Ceredig R, Rolink A. Eur J Immunol. 2008 Feb;38(2):381-90.PMID: 18203141 [PubMed – indexed for MEDLINE]

Lymph node
Peyer's patch
Lymphoid tissue inducer cell
Cytokine
Development
Immune response

Developmental Immunology

Prof. Dr. Daniela Finke
Department of Biomedicine
University of Basel

Group Members
Dr. Stephane Chappaz (postdoctoral fellow)
Sandrine Schmutz (PhD student)*
Adeline Stiefvater (Master student)*
Claudia Gärtner (technician)
Caroline Bornmann (technician)*
Isabel Seibert (technician)*

* left during report period

The development and function of lymphoid tissues in ontogeny and disease

The focus of our research is to identify the cellular and molecular requirements for the generation of lymphoid tissues. Our main interest is to understand the role for lymphoid tissue inducer (LTi) cells in the development of secondary lymphoid organs. In particular, we investigate the mechanisms, which regulate both LTi cell generation and function from fetal to adult life. We use various mouse models to study cytokines and cytokine receptors that are mandatory for the life cycle of LTi cells and their precursors. Moreover, we address the responsiveness of LTi cells to inflammatory signals and their contribution to the innate and adaptive immune responses.

Secondary lymphoid organs such as lymph nodes (LNs) and Peyer's patches (PPs) are tissues where immune responses are generated towards foreign antigens (Ags). In addition, inducible lymphoid tissues can develop at sites of infection and inflammation. It is unclear whether these "tertiary lymphoid organs (TLO)" are beneficial for protective immune responses or whether they maintain chronic inflammation, which can be involved in several diseases, e.g. autoimmunity and tumor formation. The analysis of mouse models and *in vitro* cultures of LTi cells and mesenchymal cells provide us with important information regarding the remodeling and formation of lymphoid tissue in infection and chronic inflammation.

We and others have identified fetal $CD4^+$ IL-$7R\alpha^+$ $CD3^-$ cells as LTi cells, which activate mensenchymal organizer cells. The LTi-organizer cell cross-talk induces the expression of chemokines, thereby allowing the recruitment of lymphocytes and the development of organized lymphoid compartments necessary for the generation of adaptive immune responses. We have now identified the adult counterpart of fetal LTi cells in mice. Adult LTi cells are derived from bone marrow (BM) precursor cells and are found in all secondary lymphoid organs. Increasing Il7 availability in wild type mice either by Il7 transgene (Tg) expression or treatment with Il7/α-Il7 complexes increased adult LTi cell numbers through *de novo* generation from BM precursor cells and increased survival and proliferation of LTi cells. BM-derived adult LTi cells contribute not only to the formation of isolated lymphoid follicles in the gut (Fig. 1), but also to the restoration of lymphoid stroma after viral infection.

Known for its role in triggering allergic diseases in human and mice, thymic stromal lymphopoietin (TSLP) is a cytokine, which binds to the Il7Rα chain. Using K14 TSLP Tg mice we found that Il7 and TSLP had overlapping functions in lymphoid development. Both cytokines were important for the generation and maintenance of B and T cells in primary and secondary lymphoid organs. In Il7-/- mice, TSLP Tg expression rescued the disorganized thymic architecture and restored LN and PP development.

RAG γ_c double deficient mice lack B lymphoctes, T lymphoctes and NK cells and are devoid of almost all LNs. We used TSLP Tg mice on a RAG γ_c double deficient background for understanding the role for lymphocytes in LN organogenesis. We show that TSLP Tg expression was sufficient to induce LN formation through enlarging the pool of LTi cells, and that LN development occured independent of B lymphoctes, T lymphoctes and NK cells (Fig. 2). In addition, the development of high endothelial venules and segregated B and T cell areas with production of B (CXCL13) and T (CCL19) zone chemokines occured independent of lymphocytes in $RAG^{-/-}\gamma c^{-/-}$ K14-TSLP mice. A mature LN architecture with development of follicular dendritic cells was however dependent on peripheral lymphocytes.

LTi cells express the Il7 receptor and the receptor tyrosine kinase Kit, while organizer cells express their cognate ligands. We found that Kit ligand (KitL) collaborated with Il7 in generating LTi cells *in vitro*. To determine the relative significance of Il7 and Kit in PP and LN development, we analyzed mice deficient for Kit ($Kit^{W/Wv}$), Il7 ($Il7^{-/-}$), or both ($Il7^{-/-}$ $Kit^{W/Wv}$). Unlike $Kit^{W/Wv}$ and $Il7^{-/-}$ single mutants, $Il7^{-/-}$ $Kit^{W/Wv}$ mice were almost devoid of LTi cells in their mesenteric LN anlage. Kit and Il7 were acting synergistically in LN organogenesis (Fig. 3), while Kit signaling, but not Il7, critically regulated PP organogenesis and LTi cell numbers in the intestine. Consistent with these differential growth factor requirements for PP and LN development, PP organizer cells expressed higher KitL and lower Il7 levels than LN organizer cells. Collectively, these results demonstrate that Kit and Il7R signalling differentially control PP and LN organogenesis through the local growth factor driven regulation of LTi cell numbers.

Using Il7 and KitL, we have developed an *in vitro* assay to efficiently generate large numbers of LTi cells from fetal liver precursors. This now allows us to study their cell biology and function during infection and inflammation. We are currently analyzing their responsiveness to various microbial and inflammatory products. We attempt to identify the specific stimulatory conditions required for their polarization towards cytokine production that plays a role in infection and inflammation. We further test their lineage relationship with other cells of the hematopoietic system, and investigate their role in the mucosal immune system in mouse and man.

Selected Publications

- Chappaz, S., Gärtner, C., Rodewald, H.,R., and Finke, D. (2010). Kit ligand and Il7 differentially regulate Peyer's patch and lymph node development. J Immunol *185*, Epub ahead.
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- Schmutz, S., Bosco, N., Chappaz, S., Boyman, O., Acha-Orbea, H., Ceredig, R., Rolink, A. G., and Finke, D. (2009). Cutting edge: IL-7 regulates the peripheral pool of adult RORgamma+ lymphoid tissue inducer cells. J Immunol *183*, 2217-2221.
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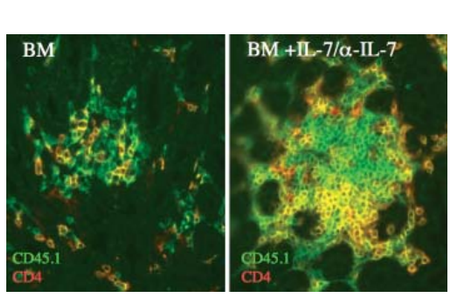
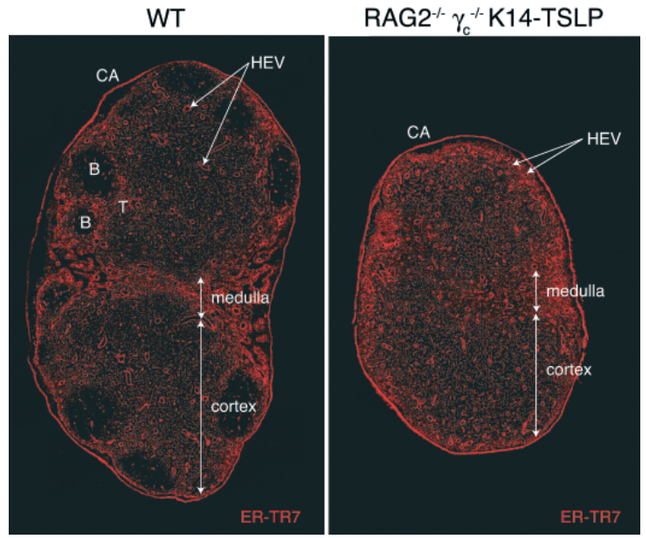
- Scandella, E., Bolinger, B., Lattmann, E., Miller, S., Favre, S., Littman, D. R., Finke, D., Luther, S. A., Junt, T., and Ludewig, B. (2008). Restoration of lymphoid organ integrity through the interaction of lymphoid tissue-inducer cells with stroma of the T cell zone. Nat Immunol *9*, 667-675.



▲ **Fig. 1**: Figure 1 $RAG2^{-/-}$ mice were reconstituted with 10^7 BM cells (CD45.1) and treated with Il7/α-Il7 or left untreated. Isolated lymphoid follicles from individual mice were counted per section using immunofluorescence microscopy.



▶ **Fig. 2**: Inguinal LNs from 6 weeks old WT and from $RAG2^{-/-}$ $\gamma_c^{-/-}$ K14-TSLP Tg mice were stained for the fibroblastic reticular cell marker ER-TR7. CA, capsule; B, B cell zone; T, T cell zone; HEV, High Endothelial Venule.

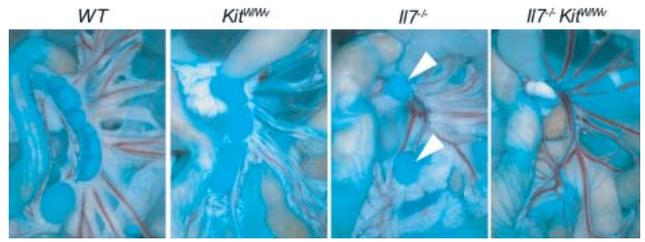


Fig. 3: Mesenteric region of adult WT, $Kit^{W/Wv}$, $Il7^{-/-}$, $Il7^{-/-}$ $Kit^{W/Wv}$ mice. mLN are dissociated in 2 small nodes in $Il7^{-/-}$ mice (indicated by arrowhead) and absent in $Il7^{-/-}$ $Kit^{W/Wv}$ littermates.

Glucose

Insulin

Obesity

Cytokine

Interleukin-1

Interleukin-6

Diabetes Research

New group since December 2010

Prof. Dr. Marc Y. Donath
Departments of Biomedicine and
Endocrinology, Diabetes and Metabolism
University Hospital Basel

Group Members
Dr. Marianne Böni (PhD)
Dr. Helga Ellingsgaard (PhD)
Dr. Nadine Sauter (PhD)
Dr. Eleonora Seelig (MD)
Dr. Katharina Timper (MD)
Daniel Meier (PhD student)
Erez Dror (PhD student)
Patrizia Zala (study nurse)
Marcela Borsigova (academic technician)
Kaethi Dembinski (technician)
Richard Prazak (academic technician)
Noemi Thum (Master student)

Islet inflammation in type 2 diabetes

Our research focuses on the mechanisms and therapy of decreased insulin production by the pancreatic islets in the obesity associated type 2 diabetes. In previous studies we demonstrated that the metabolic stress evoked by high glucose and saturated fatty acids (contained in animal fat) may induce death of the insulin producing beta-cells of the islets. Subsequently we identified interleukin 1 beta as a key mediator of these deleterious effects and showed that it is produce by human beta-cells in type 2 diabetes. More recently we published several additional studies supporting the concept that this mechanism leads to an inflammatory process and underlies the failure to produce sufficient amount of insulin in type 2 diabetes. On the basis of this we initiated clinical trials in patients with type 2 diabetes that vindicates this hypothesis and opens the way for a causative treatment. The overall goal of the present projects aim at understanding the precise role and regulation of the uncovered islet inflammation in type 2 diabetes and test therapeutic intervention.

Connection to Clinical Practice

Based on preclinical studies, we hypothesize that components of islet inflammation are initially an attempt of the islet to adapt and repair itself in response to stressors inducing beta cell death. If this initially physiological response is sustained over a prolonged period of time at a high level of activity it becomes deleterious. Therefore, remodeling this response may promote beta-cell survival and regeneration. Understanding the putative beneficial role of these islet-derived cytokines and chemokines in islet regeneration is the scientific problem that is addressed. It opens the door to therapeutic strategies aiming at remodeling this response both in type 1 and 2 diabetes. Several drugs which modulate the action of cytokines and chemokines are presently in clinical trials in our clinical research team.

Selected Publications

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T lymphocytes
Antigen recognition
Infection
Autoimmunity
Cancer
Vaccines

Experimental Immunology

Prof. Dr. Gennaro De Libero
Department of Biomedicine
University Hospital Basel

Group Members
Dr. Lucia Mori
Dr. Marco Cavallari (postdoctoral fellow)
Dr. Marco Lepore (postdoctoral fellow)
Dr. Pauline Cullen Baumann (postdoctoral fellow)
Dr. Federica Facciotti (postdoctoral fellow)
Dr. Seetaraman Gundimeda (postdoctoral fellow)
Dr. Stefano Vavassori (postdoctoral fellow)
Dr. Hüseyin Duyar (postdoctoral fellow)
Dr. Alessia Colone (postdoctoral fellow)
Simon Hostettler (Master student)
Melissa Manser (Master student)
Lena Angman (technician)
Sebastiano Sansano (technician)

T cells specific for non peptidic antigens: role in infection, autoimmunity, tumor surveillance and immunoregulation

We study how T lymphocytes recognize antigens and become active during the immune response.
T cells recognize as antigens peptides, lipids, and phosphorylated non-peptidic metabolites. Our research focus is the study of a population of human T cells that recognize lipid antigens presented by CD1 molecules. One area of investigation is the identification of lipids relevant for human diseases. Three Mycobacterium tuberculosis lipids were identified with potential relevance during mycobacterial infections. Lipid-specific T cells kill mycobacteria-infected cells and intracellular mycobacteria, thus exerting protective functions. We identified a new mycobacterial lipid, di-acylated sulfotrehalose, which induces a strong specific immune response in infected individuals. This lipid is only generated by virulent mycobacteria and detection of specific immune response might represent a novel diagnostic tool of latent infection. Analogs of this lipid have been synthesized and are being evaluated as diagnostic tests in M. tuberculosis-infected individuals and as subunit vaccine in small animals.
The second lipid antigen is hexamannosylated phosphatidyl-myo-inositol. We found that CD1e is absolutely required for PIM6 processing, thus attributing the first known function to this CD1 molecule.
The third lipid antigen is glycerol-monomycolate. This lipid has also adjuvant properties and therefore it represents a unique molecule, which combines the two important functions of antigen and adjuvant. Combinations of this lipid with other immunogenic lipids is being investigated for optimal induction of specific response in small animals.

Lipid antigens derived from human samples are also under investigation. We are studying the nature of self-lipids that induce selection in thymus of invariant Natural Killer T cells their expansion in the peripheral lymphoid organs, and stimulate them in different diseases. A novel technique has been established, which allows characterization by mass spectrometry of HPLC-purified lipids with T cell-stimulatory capacity. The same strategy is being used to identify self-lipids stimulating specific T cells accumulating in atherosclerosis plaques, in tumor infiltrates and during bacterial infections.

Transgenic mice expressing human CD1b and CD1e have been generated and are being used to investigate how lipid-specific T cells are selected within the thymus, how they are primed in the periphery, and whether they generate classical memory T cells. These studies in animal models will provide indications on the possible use of lipids as tuberculosis vaccines. CD1b transgenic mice are also investigated for their increased susceptibility to experimental autoimmune encephalomyelitis, possibly due to the increased presentation of self-lipids.

A second area of interest is determination of human CD1 structures. We have found that native CD1b contains a long spacer, which slides upon antigen binding, thus adapting to the variable acyl chains present in lipid antigens. The modification of the spacer's position also leads to a conformational change in CD1b structure, which is absolutely required for T cell recognition. Thus, the non-polymorphic CD1b molecule adapts to different lipid antigens by changing its conformation and showing an unpredicted flexibility in its structure. Adaptation of CD1 antigen-presenting molecules represents a novel strategy, alternative to polymorphism of MHC molecules, to make presentation of different lipid antigens possible.

Another major focus of our research is the immune response of human TCR γδ cells to non-peptidic antigens. We have shown that the major population of TCR γδ cells, which uses a Vγ9-Vδ2 heterodimer, recognizes self metabolites, generated in the mevalonate pathway. Different stress conditions, including tumor transformation or bacterial infection, dysregulate the mevalonate pathway and induce the accumulation of the stimulatory antigens. These are small phosphorylated metabolites presented to T cells by dedicated antigen-presenting molecules, which remain unknown. We are studying the cellular mechanisms that allow these antigens to cross cell membranes and to interact with the TCR γδ.

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Human Immunology

T Cell Physiology

Natural Killer Cells

Killer Immunoglobulin-like Receptors

Influenza-Vaccine

Latent Viral Infection

Immunobiology

Prof. Dr. Christoph Hess
Department of Biomedicine
Medical Outpatient Department
University Hospital Basel

Group Members
Dr. Glenn Bantug (postdoctoral fellow)
Dr. Olivier Gasser (postdoctoral fellow)
Dr. Matthias Mehling (postdoctoral fellow)
Dr. Bojana Durovic (postdoctoral fellow)
Dr. Georg Funk (postdoctoral fellow)
Stefanie Fritz (Phd student)
Patrick Gubser (MD PhD student)
Nicola Krähenbühl (MD student)
Dominik Eichin (Master student)
Gideon Hönger (technician)

Learning from the patient; basic and translational aspects of human immunology

Our lab is concerned with basic and translational aspects of human immunology. Three primary areas of interest have been developed over the past few years.

(i) T cell physiology
Basic T cell physiology has become a recent focus of interest in our lab, initially triggered by the serendipitous observation that T cells expressing receptors that mediate homing into lymphnodes produce more heat than their non-lymphnode homing counterpart (Figure 1). Searching for the molecular mechanism(s) and functional significance of this phenomenon we have started to characterize pathways influencing mitochondrial energy efficiency, cellular mobility and immunological synapse formation.

(ii) Immunology and immuno-pathology in transplant recipients
Organ transplantation has become a standard medical procedure. The central issue in organ transplantation remains suppression of allograft rejection. Contribution of innate immune mechanisms to allo-immunity and to the control of infectious pathogens in the immuno-suppressed host remains ill understood.
In a prospective cohort of renal transplant recipients we assessed homeostatic secretion and allo-specific induction of acute-phase cytokines and the dynamics, phenotype and reactivity of allo-specific NK cells, and related allo-specific reactivity to transplant rejection episodes.
On the other hand we have been interested in how innate immune mechanisms contribute to the control of viral infections and virus-associated malignancy. These studies have established a protective role for activating Killer Immunoglobulin-like Receptors (KIR) in the control of Cytomegalovirus after renal transplantation. Along the same line of investigation, in the to date largest cohort of patients suffering from post-transplant lymphoproliferative disease –a dreaded, often Epstein Barr Virus-associated malignancy– a major influence on survival of a compound genotype including an Fc-gamma receptor polymorphism and distinct KIR genes was uncovered (Figure 2). The functional significance of these genetic associations is now being assessed.

(iii) Influenza-vaccine specific immunity
Vaccination is providing a simple yet powerful tool to study the induction of antigen-specific immunity in humans. We have initiated cohort-studies aiming to characterize cellular and humoral influenza-vaccine specific immunity among individuals with specific immunological conditions. In HIV infected individuals characterizing vaccine-specific immunity uncovered a surprising relation between CD4+T cell counts, influenza-specific CD4+T cell frequencies and antibody production. In healthy individuals, studying vaccination-induced immunity has further provided insight into the relation between genes encoding innate immune receptors and the magnitude of the vaccine-specific T cell response, and into homing properties of antigen-triggered T cells. These studies are ongoing.

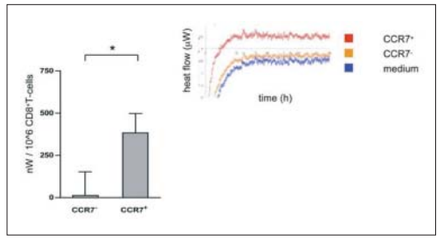

Fig. 1: In calorimetric analyses heat production of sorted CCR7- and CCR7+CD8+ T cells was quantified. After a calibration period of 24 hours, heat production was quantified every minute for 12 hours. On the right a heat flow diagram of a representative experiment is shown. * p<0.05

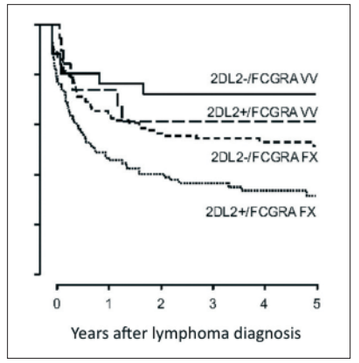

Fig. 2: Survival of transplant recipients after lymphoma diagnosis is influenced by KIR and FCGR3A genotype. Stratifying patients by both KIR2DL2 and FCGR3A yields four prognostic groups, where patients carrying KIR2DL2 and the FCGR3A alleles FF/VF show lowest survival (28 ± 5%), patients not carrying KIR2DL2 with FCGR3A VV genotype best survival (71 ± 9%), and the remaining patients intermediate survival.

Selected Publications

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- Zenhaeusern, G., Gasser, O., Hoenger, G., Durovic, B., Stern, M., and Hess, C. (2009). HLA C Allotypes Differentially Support Regulatory Allo-Specific NK Cell-Function. Am. J. Transplant., 9, 2624–30.
- Stern, M., Opelz, G., Doehler, B., and Hess, C. (2010). Natural Killer Cell Receptor Polymorphisms and Post-Transplant non-Hodgkin Lymphoma. Blood. 2010 May 13; 115 (19): 3960-5

Innate Immunity
Ectosomes
Macrophages
Complement smTOR
Inflammation.

Immuno-nephrology

Prof. Dr. Jürg A. Schifferli
Department of Biomedicine
and Division of Internal Medicine
University Hospital Basel

Group Members
Dr. Ceylan Eken (postdoctoral fellow)
Dr. Salima Sadallah (postdoctoral fellow)
Dr. Daniel Zecher (postdoctoral fellow)
Corinne Lochmatter (PhD student)
Arun Cumpelik (PhD student)
Marius Zimmerli (MD student)
Corina Metaxas (Master student)
Michèle Walch (Master student)
Verena Widmer (technician)

Inflammation and ectosomes

The regulation of inflammation is of primordial importance to combat infection, and to get rid of necrotic and apoptotic material without producing harm to self. Thus, although powerful cascades increasing the inflammatory reactions with enhancement of the immune responses are necessary, it is evident that these strong mechanisms of inflammation have to be controlled as well.

Our present investigations are based on our recent observations that different circulating cells release small vesicles (erythrocytes, leukocytes, platelets) by budding from the cell surface. This budding corresponds to a reaction described 20 years ago as "ectocytosis", thus we named these vesicles "ectosomes". Structurally, these ectosomes express surface proteins in a different ratio than found on the originating cell suggesting a specific selection process at the time of budding. In addition phosphatidylserine (PS) is present on the outer leaflet of the ectosome membrane as found for apoptotic cells. PS serves as receptors for many proteins including C1q, Gas6 and others, which might bridge ectosomes to phagocytes. We have now established that these vesicles have biological functions. Our initial data indicated that ectosome of PMN and erythrocytes down modulate the inflammatory reaction of macrophages and dendritic cells. Our present goals are to define the properties of ectosomes, in particular their capacity to interfere with the function of cells involved in inflammation and immunity. The specific aims are:

1) To define the uptake and intracellular processing of ectosomes by different cells
2) To study the cellular responses induced by ectosomes
3) To study the changes in the cellular programs induced by ectosomes
4) To analyze the possible anti-inflammatory properties of ectosomes *in vivo* in mice, as well as their capacity to block an immune response.

SmTOR: regulator of complement in schistosomes

SmTor is a transmembrane protein of schistosomes initially described in 1999. A fragment of the extracellular domain has homologies with the beta chain of complement C4. The corresponding peptide of smTOR binds C2, inhibits the cleavage of C2 by C1s, and blocks classical pathway activation. In vivo, the same peptide reduces inflammation in a mouse model of reverse Arthus reaction. These data suggest that the schistosome is capable of blocking the complement attack at the time of penetration through the skin. The aim of our further investigations will be:

1) To define the capacity of CRIT to inhibit human complement on the schistosome surface.
2) To see whether CRIT is a target of the immune response in humans, and if so, whether antiCRIT specific antibodies interfere with the function of CRIT.

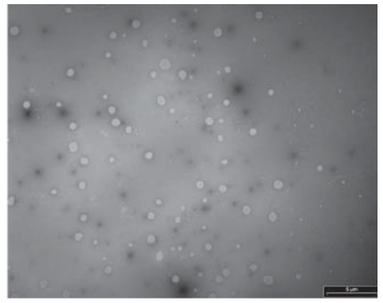

Fig. 1: Electron microscopy of thrombocyte-derived ectosomes released during storage.
Electron microscopy of ectosomes purified from the supernatant of stored platelets (PLT) show that PLT-Ect represents a heterogeneous population of vesicles with sizes between 100 nm and 1 m.

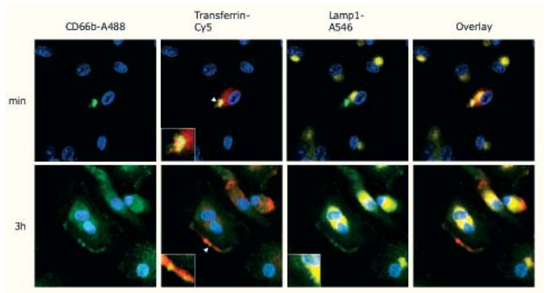

Fig. 2: PMN-Ect specific protein CD66b follows recycling and degradative pathway.
To follow endocytic and recycling pathway of PMN-Ect, we used human monocyte-derived macrophages that were preincubated with PMN-Ect and Transferrin-Cy5 (red) during 10 min at 37°C .The preparation was washed and chased during 30 min or 3h. Immunofluorescence was performed, cells were incubated with biotinylated CD66b antibody followed by strep-Alexa488 (green). Labeling of lysosomes was performed by incubation with mouse anti-lamp1 followed by anti-mouse Alexa546 (yellow). At 30 min, CD66b is colocalized with transferrin but not lysosomes showing that it takes recycling pathway. At 3h, CD66b is colocalized with transferrin at the cell surface, showing the recycling route, but some also with Lamp1 showing that part of CD66b joins the degradative pathway.

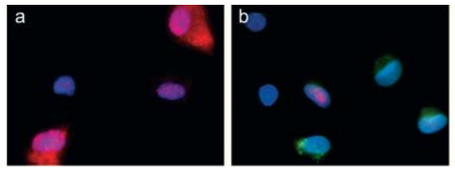

Fig. 3: Ectosomes induce the immediate release of TGF-β by macrophages.
Human monocyte-derived macrophages were incubated with (a) medium alone or (b) CD66b-FITC pre-labeled PMN-Ect, for 30 min. Cells were then fixed, TGF-β staining was performed with polyclonal pan anti-TGF-β, followed by Cy5 donkey anti-rabbit secondary Ab (red), and analyzed by immunofluorescence microscopy.
a- TGF-β, stained in red is present in cytoplasmic compartments of human macrophages. b- In presence of PMN Ect, green dots present in the cytoplasm, the TGF-β is significantly decreased.

Selected Publications

- Lochmatter C, Schifferli JA, Martin PJ. Schistosoma mansoni TOR is a tetraspanning orphan receptor on the parasite surface. Parasitology. 2009 Apr;136(5):487-98.
- Sadallah S, Eken C, Schifferli JA. Erythrocyte-derived ectosomes have immunosuppressive properties. J Leukoc Biol. 2008 Nov;84(5):1316-25.
- Eken C, Gasser O, Zenhaeusern G, Oehri I, Hess C, Schifferli JA. Polymorphonuclear neutrophil-derived ectosomes interfere with the maturation of monocyte-derived dendritic cells. J Immunol. 2008 Jan 15;180(2):817-24.

Transplantation
Tolerance
Regulatory T cells
Stroma cells
Immune privileged Site

Immuno-regulation

Prof. Dr. Simona Rossi Girard
Department of Biomedicine
University Hospital Basel

Group Members
Dr. Mathias Schmaler (postdoctoral fellow)
Maria Broggi (PhD Student)
Daniele Riva (Master student)

Treg and tolerance induction: single players or team work?

The success of solid organ transplantation is determined by the ability to control rejection and establish tolerance. Currently this problem is overcome by treating the patients with immunosuppressive agents, which involve a large number of side effects that compromise the patients' quality of life and graft survival; for this reasons tolerance is the ultimate goal in transplantation. Over the last few years, transplantation tolerance has been established in mice using regulatory T cells (Tregs). Tregs are the cellular component of the adaptive immune system with the ability to control the activity of effector T cells. The aim of our research is to examine how Tregs collaborate with the grafted tissue and the different cell types involved in tolerance/rejection. For this purpose, we use an animal model of skin transplantation where Tregs induce stable tolerance to allogeneic skin.
We hypothesize that Tregs effectively modulate the cytokine/chemokine milieu in both the lymph node (Ln) and the graft microenvironment. These changes may result in the creation of an immuno-privileged site, due to decreased graft antigenicity and an attenuate activation of the effector T cells.

In the first year we focused on the characterization of the model. We studied Tregs, effector T cells and donor dendritic cells (DC) in Ln and skin graft to define their migration pattern and their phenotype at different time points post transplantation. Tregs are detectable in the Ln very early after adoptive transfer and their number increase in the presence of effector T cells. Tregs infiltrate and circulate in the skin graft independent from effector T cells. In the presence of Tregs, effector T cells do not proliferate or infiltrate the graft, suggesting suppression or impared activation of effector T cells functions. Furthermore, we studied the activation profile of effector T cells in presence or absence of Tregs in the Ln and in the skin graft. We were not able to dissect differences in early and late activation markers of effector T cells. In absence of Tregs, effector T cells accumulate in the skin graft (Fig. 1) and reject it within 20 days, whereas it is tolerated in the presence of Tregs (Fig. 2). The mechanism by which effector T cells reject the graft is currently under investigation.
DC of graft origin can be detected in the recipient Ln and their number is constant during the entire experimental period. This indicates that Tregs and effector T cells can be exposed directly to the antigen in the Ln and not only in the graft.
During the last years it has been suggested from different studies, that other cellular players, generally defined as stroma cells, could also take part in tolerance establishment. A more precise look to stroma cells shows a variety of cell type with different functions. We aim to study the role of stroma cell subpopulations in induction and maintenance of tolerance in the Ln as well as in the grafted skin.

To characterize the immunoreactions of stroma with adaptive immune cells, we designed a 3 dimensional ex vivo model for skin transplantation and Ln. Tregs, effector T cells, skin or Ln stroma cells are isolated from mice tissues and co-cultured at different proportions (Fig. 3). The cells clustered together and form aggregates, which we analyze at different time points to better understand the development of the immune reaction/suppression/cellular interactions of the different cellular components. Interestingly, we observed in phenotypical analysis that this ex vivo system is comparable to the in vivo transplanted grafts. We plan to further use this co-culture system to screen for molecules potentially involved in induction and maintenance of tolerance.

Our experiments will help to better understand the interactions between different cells in induction of tolerance, which is required for successful transplantation and better life quality in humans.

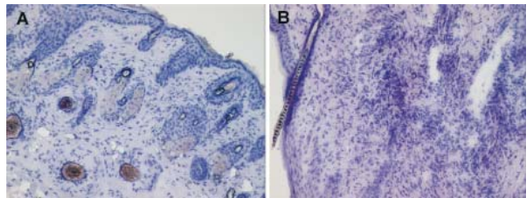

Fig. 1: Grafted tissue sections stained with Haematoxylin and Eosin. A. Healthy graft, B. Rejected graft

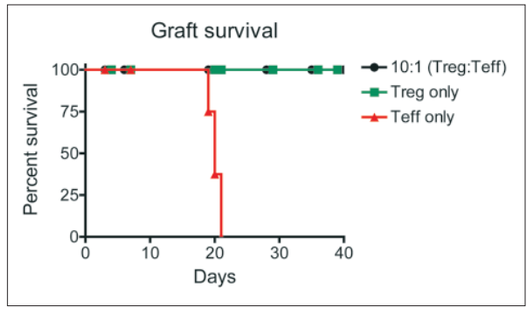

Fig. 2: Graft survival. *10:1:* Tregs were injected in a ratio of 10:1 respect to effector T cells. *Treg only:* Only regulatory T cells were adoptively transferred into the grafted mice. *T effector (Teff)* only: Only effector T cells were adoptively transferred into the grafted mice.

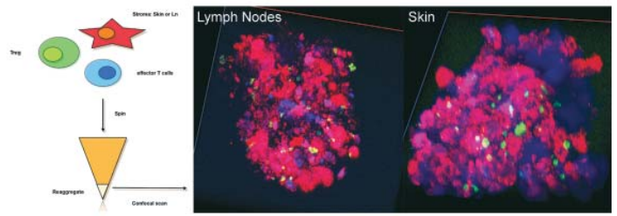

Fig. 3: Ln and Skin reaggregates scanned using confocal microscopy for cell interactions studies. Green: Tregs, Blue: effector T cells, Red: stroma cells.

Selected Publications

- Rossi, S., Blazar, B. R., Farrell, C. L., Danilenko, D. M., Lacey, D. L., Weinberg, K. I., Krenger, W., and Hollander, G. A. (2002). Keratinocyte growth factor preserves normal thymopoiesis and thymic microenvironment during experimental graft-versus-host disease. Blood 100, 682-691.
- Rossi, S. W., Jenkinson, W. E., Anderson, G., and Jenkinson, E. J. (2006). Clonal analysis reveals a common progenitor for thymic cortical and medullary epithelium. Nature 441, 988-991.
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- Rossi, S. W., Kim, M. Y., Leibbrandt, A., Parnell, S. M., Jenkinson, W. E., Glanville, S. H., McConnell, F. M., Scott, H. S., Penninger, J. M., Jenkinson, E. J., et al. (2007). RANK signals from CD4(+)3(-) inducer cells regulate development of Aire-expressing epithelial cells in the thymic medulla. J Exp Med 204, 1267-1272.

Hematopoietic stem cell transplantation

Multiple myeloma

Immune reconstitution

Donor lymphocyte infusion

Natural killer cells

Cytomegalovirus

Immunotherapy

New group since November 2010

Prof. Dr. Martin Stern
Department of Biomedicine, University Hospital Basel

Group Members
Karol Czaja (PhD student)
Karin Schmitter (technician)
Hojjatollah Nozadcharoudeh (postdoctoral fellow)

Natural Killer Cells in the control of Disease Relapse and Infection in Transplanted Patients

Natural killer (NK) cells are a subgroup of lymphocytes that – unlike B- and T-lymphocytes – do not possess rearranged surface receptors but instead are regulated by integration of signals derived from an array of activating and inhibitory receptors. While much progress has been made over the last 10 years in the characterization of NK cell surface receptors and their ligand, the function and ligands of several NK cell receptors are still unknown.
NK cells are of particular importance in patients under pharmacological immunosuppression, e.g. after solid organ or hematopoietic stem cell transplantation. These patients with compromised adaptive immunity are therefore predestined to study the role of natural killer cells in the control of malignant and viral transformation.
Our studies focus on one family of NK cell receptors termed Killer-cell Immunoglobulin-like receptors (KIR). KIR are transmembrane proteins and come in an inhibitory or activating flavor. While the function of inhibitory KIR is clear (providing NK cell tolerance through binding to HLA-class I) both function and ligands of activating KIR are so far undefined. Studies in transplanted patients have hinted that patients carrying activating KIR have a reduced rate of viral infection, pointing to viral proteins as potential activating KIR ligands. Through in vitro experiments and analyses of immune reconstitution of patients undergoing transplantation we aim to define the function of activating KIR ligands. In parallel, we plan to further study the impact of inhibitory KIR in various types of transplant.

Selected Publications

- Stern, M., Opelz, G., Dohler, B., Hess, C. Natural killer-cell receptor polymorphisms and posttransplantation non-Hodgkin lymphoma. Blood 2010; 115(19): 3960-5.
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Staphylococcus aureus
Lipoproteins
Cathelicidin
Toll-like receptor 2
Implant infection
Silver

Infection Biology

Prof. Dr. Regine Landmann*
Department of Biomedicine
University Hospital Basel

Group Members
Anne-Kathrin John (PhD student)
Fabrizia Ferracin (technician)
Zarko Rajacic (technician)
Naja Jann*
Mathias Schmaler*
Olivier Gordon*

* retired November 2009

** left during report period

Pathogen-host interaction in staphylococcal infection

Staphylococcus (S.) aureus is a most important pathogen causing severe systemic infections like sepsis. It expresses multiple virulence factors, which contribute to its survival in the host and help its evasion from immune responses. Neutrophils can kill S. aureus by antimicrobial peptides (AMPs) including cathelicidins, reactive oxygen species and neutrophil extracellular traps (NETs).
The mechanism of AMP action remained unidentified, but it was known that S. aureus exhibits enhanced resistance to AMP in part due to alanylation of teichoic acids by the dlt operon. We took advantage of the Cathelin-related (CR)AMP-susceptible phenotype of S. aureus ΔdltA to study the impact of the murine cathelicidin CRAMP on staphylococcal killing, its regulation by TLR2 and to identify its key site of action in murine neutrophils.
We could demonstrate that CRAMP remained intracellular during PMN exudation from blood and was secreted upon PMA stimulation. It was not regulated by TLR2. Early in infection, it was recruited to phagolysosomes in neutrophils and exhibited intracellular activity against S. aureus. Later in infection, CRAMP was associated with S. aureus in NETs, where it had however a weak bactericidal activity, which was regained activity after DNase treatment. Our study unravels that granulocytes use CRAMP in a timed and locally coordinated manner in defense against S. aureus.
Membrane Lipoproteins (Lpp), as part of the bacterial cell envelope, are involved both in nutrient acquisition for S. aureus and in binding to the host pattern recognition receptor TLR2 and signaling for inflammation through the adaptor MyD88.
In granulocytes we did not find any effect of the Lpp-TLR2 interaction upon CRAMP activity, phagocytosis or chemotaxis, but we found that TLR2 has a central role in killing of S. aureus by murine granulocytes via enhancement of NADPH oxidase activity. This TLR2 effect on killing was caused by accelerated NADPH-oxidase assembly.
We next studied the impact of Lpp function in systemic staphylococcal infection by measuring the effect of Lpp on S. aureus growth and on TLR2-MyD88 activation in vitro and in a murine sepsis model. We used S. aureus deficient in mature Lpp, by lack of the enzyme encoded by the prolipoprotein diacylglyceryl transferase gene (Δlgt), which attaches the lipid anchor to pro-Lpp.
Lpp in S. aureus induced early and strong cytokines by TLR2-MyD88 signaling in murine peritoneal macrophages. Lpp contributed via TLR2 to the pathogenesis of sepsis in C57BL/6 mice with chemokine-mediated inflammation and high bacterial numbers. Lpp improved iron acquisition of S. aureus in vitro and in vivo. This effect was counteracted by MyD88-mediated inflammation, as shown by a strong Lpp-dependent bacterial growth in MyD88-/- mice. Thus lipid anchoring is an evolutionary advantage for S. aureus to retain essential proteins for better survival in infection, and Lpp serve to oppose the TLR2-MyD88 mediated innate immune response, which improves bacterial clearing and disease outcome.
We then investigated the role of dendritic cells (DC) and T cells in Lpp-MyD88 mediated immune activation and the function of T and B cells in defense against S. aureus infection. We showed that Lpp enhances via TLR2-MyD88 DC activation, which promotes the release of IFN-γ and IL-17 in CD4+ T cells in vitro. This effect was independent of superantigens and MHC class II. We next evaluated the function of T cell-derived IFN-γ and IL-17 in infection in vivo. IFN-γ, IL-17 and IL-10 production in total spleen cells were MyD88-dependent and their levels were increasing from day 6 until 21. The comparison of CD3-/-, Rag2-/- and C57BL/6 mice after infection revealed that IFN-γ and IL-17 originated from T cells and IL-10 from innate immune cells. Furthermore the presence of T and/or B cells was related neither to the extent of bacterial clearing from kidneys and knees nor to disease outcome. In conclusion, while the innate effector systems of the MyD88-mediated response are crucial for defense against systemic S. aureus infection, neither T cells nor their MYD88-regulated products or B cells affect pathogen elimination.

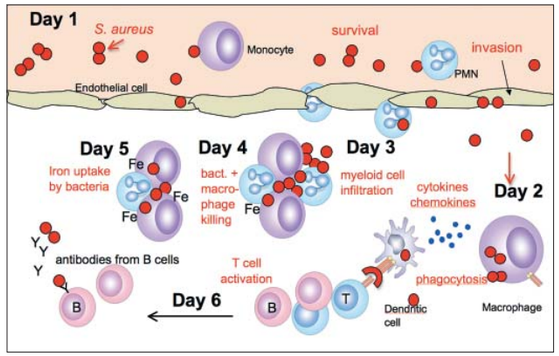

Fig. 1: ***S.aureus* sepsis**
S.aureus survives in blood, then invades tissue, is phagocytosed by PMN, or by dendritic cells and macrophages, which secrete cytokines, and -via IL-1b -chemokines. Thereafter myeloid cells are attracted and *S.aureus* can hide in host cell infiltrates, being killed by host cells or surviving within infiltrates and even killing macrophages. *S.aureus* is able to take up and use iron released in the abscesses. T cells are activated by dendritic cells and activate primed B cells to antibody production. The staphylococcal enzyme Lgt causes maturation of membrane lipoproteins. Lipoproteins are ligands of host toll-like receptor 2, which induces many defense effects (drawn in red). Despite T cell activation through TLR during *S.aureus* infection, neither T nor B cells affect bacterial clearing.

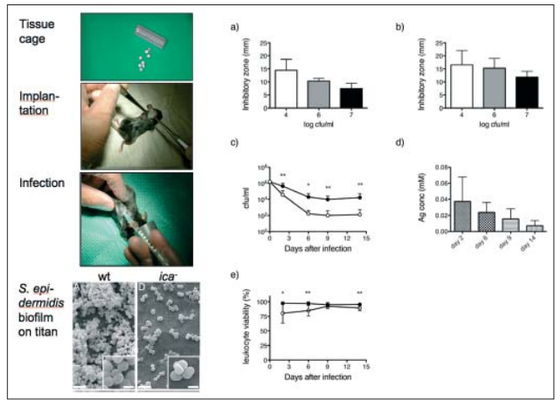

Fig. 2: **Foreign body infection**
The laboratory has longstanding experience with a murine foreign body model. Three images left: The tissue cage -made from teflon or titanium- contains eg. glass beads to enhance the surface for adhering bacteria, it is subcutaneously implanted and peri- or postoperatively infected. 4th image: SEM pictures of *S. epidermidis* on titanium cage surface, biofilm-forming wild type (wt); ica- mutant deficient in enzymes for biofilm formation.
Images right: a) Gold plates and (b) titan beads coated with Ag coordination compound cause *S. epidermidis* killing as shown by an agar inhibition assay with different bacterial inocula *in vitro*. Ag treatment of tissue cages reduces bacterial load (untreated: filled symbols; Ag treated empty symbols) after infection with *S. epidermidis*. d) decreasing silver concentration and (e) slightly reduced viability of leukocytes are observed in cages over two weeks after infection.

Connection to Clinical Practice

Pathogenesis of Staphylococcal implant infection and new therapeutic options

Prosthetic joint replacements are used to alleviate pain and improve mobility of the progressively older and more obese population. Implant infection occurs in about 5% of patients and is most often caused by staphylococci. It is difficult to treat due to biofilm formation and antibiotic resistance
We first addressed the question, how biofilm protects *Staphylococcus (S.) epidermidis* from host defense by using staphylococcal mutants lacking thegenes, which encode biofilm exopolysaccharide biosynthesis.
We then investigated the effect of biofilm on susceptibility to staphylococcal infection of different implant materials *in vivo*. We showed that the metal played a minor role in susceptibility to and persistence of infection; ica genes had a strong effect on biofilm *in vitro* and a weak effect *in vivo*. *S. epidermidis* was more pathogenic when introducedduring than after implantation.
We finally investigated the effect of implant coating with two non antibiotic-type antiinfective substances, furanones and silver polymers, upon staphylococcal infection. We found surface-grafted furanone ineffective and free furanone bactericidal for staphylococci, but at similar concentrations as it was toxic for fibroblasts. Silver coordination polymers on titanium exhibited strong biofilm-independent bactericidal activity *in vitro* and prevented murine staphylococcal implant infection *in vivo* with slow release of silver ions and limited leukocyte cytotoxicity. Thus new silver compounds are promising candidates for infection prevention.

Selected Publications

- Kristian S., T. Birkenstock, D. Mack, F. Goetz, R. Landmann. 2008. Biofilm-formation induces C3a release and protects Staphylococcus epidermidis from IgG and complement deposition and neutrophil-dependent killing. J Infect. Dis.197:1028-35.
- Karaüzüm H., T. Ferry, G. Lina, M. Bes, F. Vandenesch, J.Etienne, R. Landmann. 2008. Comparison of adhesion and virulence of two predominant hospital-acquired MRSA clones and clonal MSSA isolates. Infect. Immun.76: 5133-5138.
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- Gordon O., T. Vig Slenters, P. Brunetto, A.E. Villaruz, D.E.Sturdevant, M. Otto, R.Landmann, K. M. Fromm. Silver coordination polymers for the prevention of implant infection: thiol interaction, impact on respiratory chain enzymes and hydroxyl radical induction. Antimicrob Agents Chemother. 2010 54:4208-18.

Immunity to fungi

Invasive aspergillosis

Hematopoietic stem cell transplantation

Implant infection

Staphylococcus aureus and epidermidis

Infection Biology

Prof. Dr. Manuel Battegay
Department of Biomedicine
and Division of Infectious Deseases and Hospital Epidemiology
University Hospital Basel

Group Members
Dr. med. Nina Khanna (project leader)
Anne-Kathrin John (PhD student)
Justyna Nowakoska (PhD student)
Fabrizia Ferracin (technician)
Zarko Racajic (technician)

Interaction between innate and adaptive immunity to *Aspergillus fumigatus* in Healthy Donors and in Patients after Allogeneic Hematopoietic Stem Cell Transplantation

Invasive aspergillosis in patients after allogeneic stem cell transplantation (SCT) is associated with a substantial morbidity and mortality. A significant feature of this infection is that everyone has been exposed to *Aspergillus* spores but only a minority of immunosuppressed patients develops invasive disease. Thus, understanding host protection and interaction with the organism is critical. The innate and the adaptive immunity to *Aspergillus* play a pivotal role controlling the infection during the post-transplant period. $CD4^+$ T_H1 cells are protective by improving the effector function of innate immune cells through the release of pro-inflammatory cytokines. Recent results in murine models indicate that regulatory T-cells and T_H17 T-cells might play an important role in host response to the fungus. In an attempt to clarify disease susceptibilities, the immunity to *A. fumigatus* after HSCT will be studied. We have previously identified *Aspergillus*-specific T-cell epitopes of the Crf1 protein a cell wall glucanase that can be presented by common MHC class II alleles and induce memory $CD4^+$ T_H1 cells with a diverse T-cell receptor repertoire. We are aiming at assessing the quality and quantity of *A. fumigatus*-specific adaptive immunity, establishing methods to measure the interplay between adaptive immunity and innate immunity and investigating the *A. fumigatus*-specific immune reconstitution after HSCT.

Staphylococcal implant infection and antimicrobial surface platforms

Device-associated staphylococcal infections are associated with significant morbidity and social costs. They are difficult to treat due to the formation of a polysaccharide biofilm. Therefore, infection prevention by prosthesis coating with new antiinfective substances is an attractive therapeutic strategy. Within a "competence center for material science and technology" (CCMX) project biocompatible surface coatings are developed and equipped with covalently coupled or releasable antibacterial substances. Our main goal is to characterize a series of new antimicrobials, which form part of the bioactive compounds, and elucidate their mechanism of action.

Selected Publications

- Khanna N, Widmer AF, Decker M, Steffen I, Halter J, Heim D, Weisser M, Gratwohl A, Flückiger U, and Hirsch HH. Respiratory Syncytial Virus Infection in patients with hematological diseases: Single Center Study and Review of the Literature. Clin Infect Dis, 46(3):402-412, 2008
- Khanna N, Wolbers M, Müller NJ, Garzoni C, Du Pasquier R, Fux CA, Vernazza P, Bernasconi E, Viscidi R, Battegay M, and Hirsch HH for the Swiss HIV Cohort Study. JCV-Specific Immune Responses in HIV-1 Patients with Progressive Multifocal Leukoencephalopathy. J Virol, 83(9): 4404-4011, 2009.
- Kristian S., T. Birkenstock, D. Mack, F. Goetz, R. Landmann. 2008. Biofilm-formation induces C3a release and protects Staphylococcus epidermidis from IgG and complement deposition and neutrophil-dependent killing. J Infect. Dis.197:1028-35.
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- Gordon O, Vig Slenters T, Brunetto PS, Villaruz AE, Sturdevant DE, Otto M, Landmann R, Fromm KM. Silver coordination polymers for prevention of implant infection: thiol interaction, impact on respiratory chain enzymes, and hydroxyl radical induction. Antimicrob Agents Chemother. 2010 Oct;54(10):4208-18.

HIV
Viral Tropism
Diagnostics
DNA integration
Viral entry
Resistance

Molecular Virology

Prof. Dr. Thomas Klimkait
Department of Biomedicine
Institute for Medical Microbiology
University of Basel

Group Members
Dr. Séverine Louvel (postdoctoral fellow)
Heinz Stucki (Master student)
Suzanne Edwards (Master student)
Krischan Bäumli (Master training)
Sarah Wagner (technician)
Isabell Seibert (technician)

On cellular determinants for the cell tropism of HIV and on cellular processes dealing with HIV DNA prior to integration

The great successes of combination therapy have completely changed the face of HIV/AIDS in most countries of the world. However, new challenges arise from the development of viral resistance or in the context of the newly introduced, molecularly not yet fully understood drugs to entry- and integration events. Our research contributes to a treatment-relevant understanding of viral escape mechanisms as well as to the elucidation of molecular details of new drug principles.
HIV uses for entry one of the two chemokine surface receptors on human leukocytes, CCR5 or CXCR4. The recent approval of selective CCR5-antagonists has opened a field of research for sensitive, predictive diagnostic tools. Our efforts focus on the characterization of clinical HIV isolates and on the validation of tools to study the cellular tropism and to predict their therapy-responsiveness. Furthermore, using PCR-driven cloning and mutagenesis approaches as well as cellular phenotyping methods for characterization, we collaborate with the Swiss HIV cohort study towards longitudinal profiling of viral tropism in patients over time.

In a second line of research we target another "early event" of the HIV life cycle in that we follow the retroviral genome into the infected host cell. The advent of specific integration inhibitors in the clinics has raised our interest. Since this novel class of antiviral drugs for the first time leaves retroviral DNA unintegrated in the target cell we study aspects of the fate of this unique viral DNA over time and its possible impact on therapy response.
When the integrase inhibitor raltegravir was analyzed in our replicative cellular phenotyping system, we consistently noted that above the inhibitory concentration 50 (IC50) the inhibition of viral replication did not reach the 100% inhibition level. Inhibition rather reached a plateau at below 100% inhibition (Fig. 2a, bottom right: RGV). This was NOT observed with any of the other enzyme inhibitors for HIV targeting protease, RT, or Env gp41 (Fig. 2a, top row for Fuzeon T20 and the protease inhibitor Darunavir; or bottom left for the non-nucleosidic RT inhibitor Efavirenz).
This observation was unexpected and seems to contradict the other observation that raltegravir is known to be a highly potent inhibitor in vivo, associated with a remarkably steep and rapid decline of viral replication in patients as shown in clinical studies of patients under monotherapy: with a dose-independent slope the viral burden dropped by up to 2 logs within less than 2 weeks (as GS-9137, Fig. 2b).
Among the possible explanations for this puzzling contradiction trivial ones such as assay shortcomings of a partially integrase-independent read-out have to be ruled out.
It remains possible that the mildly chelating properties of raltegravir have a certain contribution in the overall antiviral effect of the compound. HIV depends on transactivating proteins such as Tat, which depends on binding to bi-cationic salts or that budding events could be affected.
In a pilot study we assessed principal feasibility by building a set of highly selective assessment tools for the sensitive dissection of the viral life cycle.
We were able to show that the integrase inhibitor had not significant impact on the isolated Tat driven gene transactivation when Tat protein was expressed under a CMV-promoter. We further showed that the plateau effect vanishes when the number of infection cycles is increased. This finding is compatible with the assumption that also residual expression from unintegrated DNA should get diluted with every cell division in the presence of drug.

Based on these initial observations we will attempt to fill gaps in the knowledge about the fate of chemotherapeutically induced unintegrated viral DNA and possible consequences fort he clinics. We are aware that this is a disputed field and that data of others using different cell systems may also suggest that unintegrated HIV DNA is rapidly degraded and has therapeutically no meaning. – The heat is on, and our update will follow…

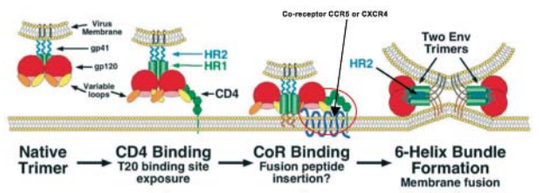

Fig. 1: Steps of HIV-1 entry – CD4-binding → chemokine-receptor-binding → Env-triggered cell fusion

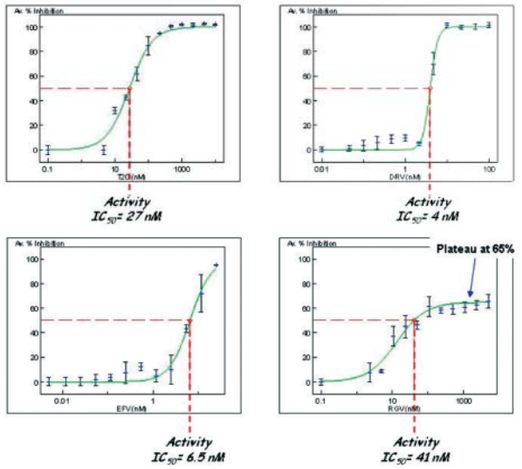

Fig. 2a: Various inhibition profiles for selective HIV inhibitors targeting different viral genes; T20 – fusion; DRV – Protease; EFV – reverse transcription; RGV – DNA integration

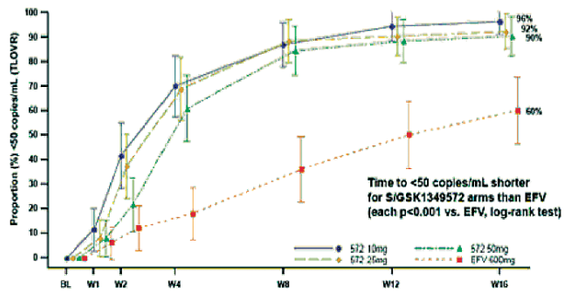

Fig. 2b: HIV-1 Viral load decline in patients' blood over time after administration of the integrase inhibitor RGV. Different dose given as different colors as indicated.

Connection to Clinical Practice

Novel HIV tropism test and understanding integrase inhibition – tools for clinical use

The interest of my research group focuses on aspects of HIV entry and on the integration of proviral DNA in the presence HIV tropism & integrase. Currently there is no diagnostic system available in Switzerland that permits to assess, which of the two optional coreceptors, CCR5 or CXCR4, the virus in any given patient uses. A new predictive tropism test that forms the basis for therapy decisions for a totally new class of inhibitors, the coreceptor antagnonists, is urgently needed. And I regard it a central task of research to contribute validated, technically feasible solutions addressing this concrete clinical need for new diagnostic tools. During the reporting period my research group had invested in the assessment of phenotypic and genotype-based methods in order to identify and develop the most predictive, reliable test principle.
This will, in addition, also be suitable for the assessment of tretment failures due to the development of a viral resistance emerging against the respective drug class. Th ultimate aim is therefore to support the clinical management of HIV disease by identifying optimal remaining drug condidates for modern combination therapy.

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- Weiser, B., Philpott, S., Klimkait, T., Burger, H., Kitchen, C., Burgisser, P., Gorgievski, M., Perrin, L., Piffaretti, J. C., and Ledergerber, B. (2008). HIV-1 coreceptor usage and CXCR4-specific viral load predict clinical disease progression during combination antiretroviral therapy. Aids 22, 469-479.
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Atherosclerosis

Inflammation

Lipid retention

Diabetic nephropathy

Podocytes

Apoptosis

Molecular Nephrology

Prof. Dr. Barbara Biedermann*

Dr. Andreas Jehle

Department of Biomedicine
Medizinische Universitätsklinik Kantonsspital Bruderholz

Group Members
Dr. Daniela Thommen (MD PhD student)
Kapil dev Kampe (PhD student)
Jonas Sieber (PhD student)
Denise Dubler (technician)

* left during report period

Cytotoxic T cell-mediated vascular injury/ Cell biology of Diabetic Nephropathy

Group Biedermann (Vascular medicine): Our major research interest is to understand how vascular endothelium located strategically at the blood-tissue interface fulfills its role as a checkpoint for and avoids to be a target of an immune response. The interaction between vascular cells and antigen-specific lymphocytes is critically important to understand the pathogenesis of vascular diseases such as transplant-associated vasculopathy (Haeusermann et al., 2009), common atherosclerosis and vasculitis. Applying the arterial tissue microarray technique, we found that intramural, intimal cytotoxic T lymphocytes (CTL) distinguish patients with symptomatic atherosclerosis and individuals free of cardiovascular events. We characterized molecular requirements for CTL immigration into the human arterial intima using a modified Vogelsang-Santos assay (Gewaltig et al., 2008). We detected and reported for the first time intramural differentiated CTL in situ in a patient with CMV-associated venous thrombosis adding this viral disease to the candidate vascular disorders mediated by peptide-specific CTL (Jeanneret et al., 2008). We continued the quest for molecular features of active, symptomatic atherosclerosis. The unique advantages of the arterial tissue microarray approach are a) identical staining conditions for a large number (n=25-50) of tissue samples from donors suffering from various stages of the disease, b) confirmed success of staining reactions, assured by control tissues which are incorporated into each tissue array block and therefore are exposed to the identical reagents as the arteries, and c) known clinical history of the tissue donors and of the plaque type analyzed, allowing the unambiguous association between the molecular or structural feature with disease activity and disease stage, respectively. With this technique we quantified Lp(a) in the arterial wall and found it strongly correlated with disease stage. The apo(a) kringle IV-type 2 repeat number, a genotypical feature of its atherogenicity, was inversely correlated with the amount of intramural apo(a) deposits.

Group Jehle (Diabetic Nephropathy): Urinary loss of albumin and other proteins (= proteinuria) is an early characteristic of diabetic nephropathy. Proteinuria is presumed to result from increased passage of proteins through the glomerular filtration barrier as a consequence of raised transcapillary pressure as well as structural alterations. The glomerular filtration barrier consists of capillary endothelial cells, the glomerular basement membrane, and the so called podocytes (highly specialized epithelial cells). Importantly, morphological alterations of podocytes and finally podocyte loss resulting from apoptosis occur at the onset of diabetic nephropathy. Therefore, one main focus of our research group lies in the identification and molecular characterization of pro-apoptotic and anti-apoptotic factors determining podocyte survival. - Obesity and diabetes mellitus type 2 are associated with elevated long-chain fatty acids (FFAs) levels. Saturated FFAs such as palmitic acid are proapoptotic in other cell types including pancreatic β-cells. Recently we identified that palmitic acid increases podocyte cell death, both apoptosis and necrosis. Palmitic acid induces podocyte endoplasmic reticulum (ER) stress leading to an unfolded protein response (UPR) as reflected by the induction of the ER chaperon BiP and the proapoptotic transcription factor CHOP. Of note, we found that the monounsaturated palmitoleic and oleic acid can attenuate the palmitic acid-induced upregulation of BiP and CHOP, thereby completely preventing cell death. Similarly, we could demonstrate that gene silencing of CHOP protects against palmitic acid induced podocyte apoptosis. The clinical relevance of our results is underscored by the recently reported finding that CHOP-deficient mice are protected from diabetic nephropathy. Also in microdissected glomeruli from patients with diabetic nephropathy we observed that the gene expression of BiP is significantly upregulated further underscoring the relevance of ER-stress and UPR in the pathogenesis of diabetic nephropathy (Sieber et al., 2010).

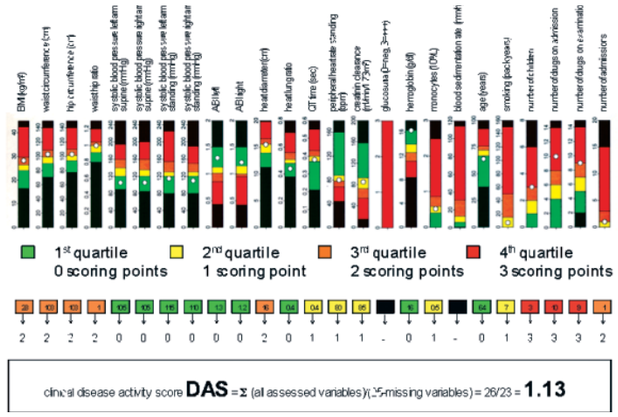

Fig. 1: The novel method for clinical phenotyping and the calculation of the clinical disease activity score (DAS).
The quartile distribution of 25 variables that were significantly different between patients with and without symptomatic atherosclerosis are shown as labeled color-coded columns. Each column visualizes the symptomatic patients' variables. Green, yellow, orange and red color represent the 1st, 2nd, 3rd and 4th quartile range and are quantitatively scored with 0, 1, 2 and 3 scoring points, respectively. Each individual patient's variable data are weighed according to the quartile color or score point. The clinical disease activity scores (DAS) is calculated as the average variable score determined by appropriate quartile allocation.

Connection to Clinical Practice

"Comprehensive bedside diagnosis system" – a novel approach to practice personalized medicine.

At the Bruderholzspital, we developed an IT-based approach to use available and affordable bedside information obtained directly from the patient for clinical disease phenotyping (COBEDIAS®). This method transforms clinical information into a disease activity score (DAS) following and applying the rules of differential display to data analysis. DAS was a good biomarker to distinguish patients with symptomatic, active atherosclerosis from asymptomatic patients free of cardiovascular events. We next tested whether gene variations would improve the discriminating power of DAS. Nine single nucleotide polymorphisms (SNPs) with reportedly proatherosclerotic impact were analyzed. We found only one of them (did further improve the discriminating power of DAS. Based on the five-year follow-up data of this cohort study, DAS is a remarkably strong predictor of mortality (Erzberger et al., 2010).

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Thymus
Development
Epithelial cells
Epigenetics
Aire
mTOR

Pediatric Immunology

Prof. Dr. Georg A. Holländer
Department of Biomedicine
University Children's Hospital Basel

Group Members
Dr. Thomas Barthlott (postdoctoral fellow)
Dr. Jason Gill (until April 2010)
Dr. Klaus Gossens (postdoctoral fellow)
Dr. Marcel Keller (postdoctoral fellow)*
Dr. Werner Krenger (postdoctoral fellow)
Dr. Sebastien Loeffler (postdoctoral fellow)
Dr. Silvia Naus (postdoctoral fellow)
Dr. Gretel Nusspaumer (postdoctoral fellow)
Dr. Noriko Shikama (postdoctoral fellow)
Dr. Gabor Szinnai (postdoctoral fellow)
Dr. Saule Zhanybekova (postdoctoral fellow)
Dr. Saulius Zuklys (postdoctoral fellow)
Caroline Berkemeier (MD/PhD student)
Angela Bosch (PhD student)
Simone Dertschnig (PhD student)
Kyung Na (PhD student)*
Carlos Mayer (Masters student)
Radhi Praba Velayutham (PhD student)*
Tatjana Zalac (PhD student)*
Elli Christen, Katrin Hafen, Annick Peter (technician)
Martha Gaio (administrative assistant)

* left during report period

The rules and regulation of thymus development and function

The thymus is a primary lymphoid organ where T cells are generated and selected to express an antigen receptor repertoire tolerant to harmless self-antigens but reactive to potentially injurious foreign antigens. Within the boundaries of the thymic stromal environment, immigrating T cell precursors develop in an ordered maturational process that eventually gives rise to functionally and phenotypically mature T cell populations. Separate anatomical compartments, which include the subcapsular area, the cortex, the cortical medullary junction and the medulla, comprise the thymic architecture, a structure and cellular composition well conserved throughout evolution. Thymic epithelial cells (TECs) constitute the major component of the stroma compartment and can be subdivided according to their functional, morphological and specific antigenic features into different subpopulations including the cortical (c) and medullary (m) TEC. The different TECs together with other stroma cells of haematopoietic (dendritic cells, macrophages, B cells) and non-haematopoietic origin (fibroblasts, endothelial cells and others) form a three dimensional meshwork. This stromal scaffold provides the specialized microenvironment for the life-long attraction of haematopoietic precursor cells, the signals to instruct early thymocyte differentiation, the factors to guide precursor cells to different anatomical compartments, the antigenic constraints for the selection of immature T cells and the molecules necessary for the functionally mature T cells to exit to the periphery. Though significant alterations in TEC differentiation and maintenance have been linked to debilitating states of immunodeficiency and autoimmunity, neither the molecular mechanisms responsible for regular thymus organogenesis and physiological senescence nor the pathomechanisms operational in congenital and acquired forms of thymus hypoplasia/aplasia have been completely elucidated.

The focus of the research of the Laboratory of Paediatric Immunology is to delineate the molecular and cellular pathways that govern regular thymus organogenesis and function. Specifically, the lab is interested (i) in the genetic control of the TEC differentiation and function, (ii) the phenotypic nature and developmental potential of fetal and adult TEC precursor cells, (iii) the molecular profile of mature cortical and Aire-expressing medullary TEC, and (iv) the functional potential of TEC to support the reconstitution of the T cell compartment following their exposure to chemo-radiotherapy and/or anti-host immunityin the context of hematopoietic stem cell transplantation.

Using gene targeting we have generated unique tools that allow compartment-specific, experimental gain- and loss-of-function models in mice to interrogate aspects of thymus development and function at the cellular and molecular level. A special interest of our research is focused on understanding the epigenetic "code" that defines the regulatory principles in gene expression in TECs and the programs that determine their cellular fate. Taking advantage of different molecular methods, we have begun to analyze the gene expression profile and the DNA methylation pattern of specific TEC subpopulations, demonstrating striking differences of the latter when comparing cortical with medullary epithelia. The importance of miRNA for the development and maintenance of epithelial stroma is being investigated in mice where Dicer was deleted in TEC. These mice reveal severe morphological changes in the composition and architecture of the thymic microenvironment leading to a reduced positive thymic selection and as a consequence to a T cell repertoire that elicits autoimmunity.

Differences in the size, stromal composition and function of the thymic microenvironment are observed in mice where signaling through the canonical Wnt pathway and via molecules of the TGF-b family is disturbed. Moreover, signaling involving the mTOR complex 1, Sox9 and Foxn1 has also been investigated and shown to play an important role in regular thymus organogenesis.

Based on our knowledge of TEC development, we are now investigating different therapeutic strategies to repair/replace damaged thymic stromal tissue.

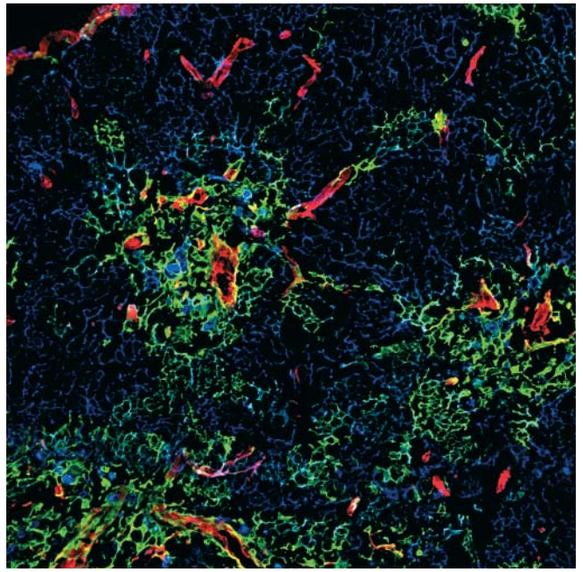

Fig. 1: Thymus section displaying the architectural organisation of thymic epithelial cells (medulla: cytokeratin 5: green; cortex: cytokeratin 8: blue) and mesenchymal cells (red)

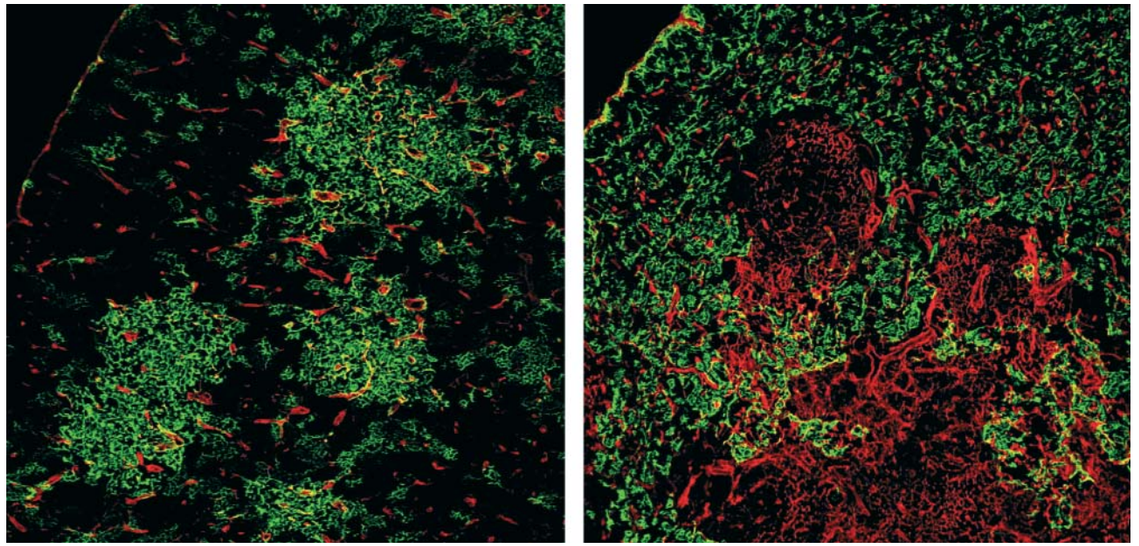

Fig. 2: Immunohistochemical analysis (epithelial marker for the medulla: cytokeratin 5: green; mesenchmal marker: ERTR7) of the thymic microenvironment of wild type mice (left panel) and mice deficient for the expression of Dicer in thymic epithelial cells.

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- Alimohammadi M., Björklund P., Hallgren A, Pöntynen N, Szinnai G, Shikama N, Keller P, Ekwall O, Kinkel SA, Husebye ES, Gustafsson J, Rorsman F, Peltonen L, Perheentupa J, Åkerström G, Westin G, Scott HS, Holländer GA, and Kämpe O. NALP5 is a major parathyroid antigen in autoimmune polyendocrine syndrome type 1. New England Journal of Medicine 2008, 358:1018-28.
- Kenins L, Gill JW, Boyd RL, Holländer GA*, Wodnar-Filipowicz A*. Intra-thymic expression of Flt3 ligand enhances thymic recovery following irradiation. Journal of Experimental Medicine 2008; 205:523-31; *=shared senior authorship.
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T cells
Tolerance
Autoimmunity
Regulatory T cells
TCR signaling

Transplantation Immunology and Nephrology

Prof. Dr. Ed Palmer
Department of Biomedicine
Clinic of Transplantation Immunology and Nephrology
University Hospital Basel

Group Members
Dr. Marina Hugot-Beaufils (postdoctoral fellow)
Dr. Dr. Simone Keck (postdoctoral fellow)
Dr. Carolyn King (postdoctoral fellow)
Dr. Michel Mallaun (postdoctoral fellow)
Dr. Dieter Naeher (postdoctoral fellow)
Sabrina Köhli (PhD student)
Martin Schaad (PhD student)
Barbara Hausmann (technician)
Virginie Galati (technician)
Rosmarie Lang (technician)
Regan Geissmann (administrative assistant)

Grasping the principles of naturally occurring T cell tolerance

One of the central mysteries of immunology is self-tolerance. How does the human body select ~10e12 T lymphocytes, that are reactive to foreign pathogens but tolerant to normal cellular constituents of the host? The work of our laboratory seeks to understand the general principles by which a healthy individual's immune system achieves a state of self-tolerance. We are particularly interested in how a tolerant T cell repertoire is selected during development and how it's maintained during adult life. The knowledge derived from our research may eventually impact organ transplantation and autoimmune diseases.

Over the last few years, we have focused on understanding how the body establishes a tolerant T cell repertoire. We demonstrated that the affinity threshold for negative selection is a constant for all thymocytes expressing MHC I restricted TCRs. This binding affinity threshold (K_D = 6 M; estimated $T_{½} \approx 2$ sec) is a fundamental biophysical parameter used by developing CD8 lineage cells to establish a tolerant T cell repertoire. We formulated a mechanism which explains how thymocytes undergoing selection can 'read' their TCR's affinity for an auto-antigen, which is based on the duration of TCR–ligand interactions and a 'zipper' mechanism that mediates the physical approximation of the TCR and co-receptor molecules to initiate negative-selection signaling. Recent experiments indicate that thymocytes destined to enter the CD4 lineage use an affinity threshold for negative selection that is 10-50 fold lower than that used for their CD8 lineage counterparts. Current experiments are underway to understand this difference.

Although ZAP-70 is required for T-cell development, it's unclear how this kinase controls both positive and negative selection. Peptide-MHC ligands promoting negative selection induce a discrete elevation of ZAP-70 recruitment, phosphorylation and enzymatic activity in the thymocyte:APC interface. The quantity of ZAP-70 kinase activity per cell is a key parameter controlling the fate of a developing thymocyte since partial inhibition of ZAP-70 kinase activity converted negative into positive selection. Surprisingly, the amount of ZAP-70 enzymatic activity observed during negative selection is not controlled by differential phosphorylation of the ZAP-70 protein but rather by the total amount of TCR and co-associated ZAP-70 recruited to the thymocyte:APC interface. These data provide evidence that a burst of ZAP-70 activity initiates the signaling pathways for negative selection.

Our work on TCR signaling has led to understand the requirements for generating a memory response. Following infection, naïve CD8+ T cells bearing pathogen-specific T cell receptors (TCRs) differentiate into a mixed population of short-lived effector and long-lived memory T cells to mediate an adaptive immune response. How the TCR regulates memory T cell development has remained elusive. Using a mutant TCR transgenic model, we found that point mutations in the TCR β transmembrane domain (βTMD) impair the development and function of CD8+ memory T cells without affecting primary effector T cell responses. Mutant T cells are deficient in polarizing the TCR and in organizing the nuclear factor kB signal at the immunological synapse. Thus, effector and memory states of CD8+ T cells seem to be separable fates, determined by differential TCR signaling.

Current projects include the following:

1. Extending our knowledge of the TCR / co-receptor zipper mechanism using molecular, cell biological and biochemical approaches.
2. Using a model of experimentally induced Type 1 autoimmune diabetes to understand
   a) how the affinity threshold for T cell tolerance, which is established during thymic development is enforced in the periphery and
   b) how T cell tolerance can be broken during the initiation of an autoimmune disease.
3. Studying how tolerance to self-antigens may limit immunotherapy to tumors.
4. Examining how oral tolerance is induced by feeding foreign antigens to mice. We specifically want to understand the role played by regulatory CD4+ T cells.
5. Understanding the differences in TCR signaling between regulatory and effector T cells.

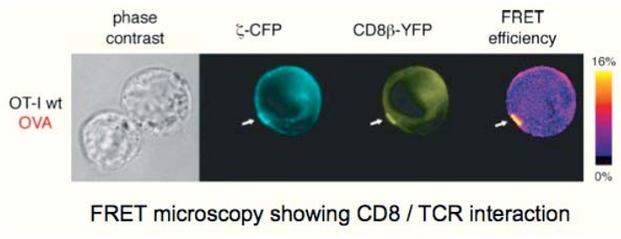

Fig. 1: FRET microscopy showing CD8/TCR interaction.

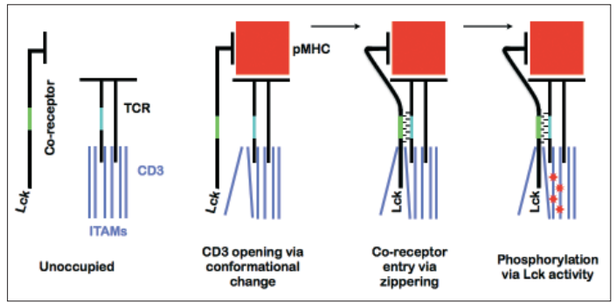

Fig. 2: TCR/co-receptor ZIPPER initiates negative selection.

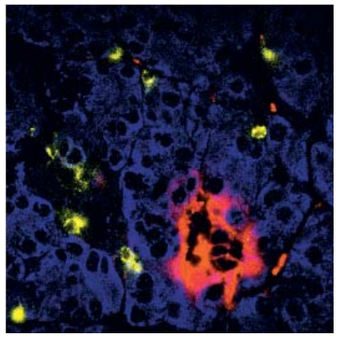

Fig. 3: Pancreatic islet destruction from infiltrating CD8 T cells.

Connection to Clinical Practice

Clinic Transplantation Immunology and Nephrology

Prof. Dr. Jürg Steiger heads the Clinic for Transplantation Immunology and Nephrology and leads a team of 4 clinical nephrologists and 5 fellows, which oversees 70 kidney transplantations, 600 transplanted patients, 17'000 dialyses and a general nephrology clinic each year. The team covers clinical and translational research spanning from pre-transplant risk stratification, transplantation in immunological high risk patients (i.e. ABO-incompatible transplants, transplantation across donor-specific HLA-antibodies), non-invasive post-transplant monitoring to side effects of immunosuppression. Michael Dickenmann has introduced ABO-incompatible living donor kidney transplantation in Basel. He investigates clinico-pathological short and long-term outcomes in these patients, and he is also interested to optimize assays measuring blood-group antibodies. Over the last few years the research group led by Stefan Schaub (Patrizia Amico, Patricia Hirt-Minkowski, and Gideon Hönger) has investigated the utility of highly sensitive HLA-antibodies analysis for pre-transplant risk assessment. Ongoing studies aim to uncover factors which predict the pathogenicity of donor-specific HLA-antibodies. In addition, two promising strategies to improve individualization of immunosuppression are currently explored: (i) urinary chemokine levels as a non-invasive biomarker for early, 'subclinical' renal allograft rejection, and (ii) determination of the immunogenicity of HLA-alloepitopes using the human pregnancy as a model.

Furthermore Prof. J. Steiger heads the Swiss Transplant Cohort Study (STCS). The STCS is a multicenter observational cohort study funded by the Swiss National Science foundation (SNF) and by the six Swiss transplantation hospitals that performs nationwide follow-up of all solid organ recipients in Switzerland. The objective of the STCS is to integrate and coordinate all information on transplant activities to provide a basis for high quality clinical research and will ultimately improve the management of transplanted patients in Switzerland. This is only possible with the help of the data center lead by Dr. M. Koller, who provides the necessary epidemiological backup.

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- Gil, D., Schrum, A. G., Daniels, M. A. & Palmer, E. (2008) A role for CD8 in the developmental tuning of antigen recognition and CD3 conformational change. *J Immunol*, 180(6), 3900-3909.
- Mallaun, M., Naeher, D., Daniels, M. A., Yachi, P. P., Hausmann, B., Luescher, I. F., Gascoigne, N. R. J. & Palmer, E. (2008) The T cell receptor's α-chain connecting peptide motif promotes close approximation of the CD8 co-receptor allowing efficient signal initiation. *J Immunol*, 180(12), 8211-8221.
- Palmer, E. & Naeher, D. (2009) Affinity threshold for thymic selection through a T-cell receptor-co-receptor zipper. *Nat Rev Immunol*, 9(3), 207-213.
- Teixeiro, E., Daniels, M. A., Hamilton, S. E., Schrum, A. G., Bragado, R., Jameson, S. C. & Palmer, E. (2009) Different T cell receptor signals determine CD8+ memory versus effector development. *Science*, 323(5913), 502-505.

Virus
Immunodeficiency
Transplantation
Polyoma
Respiratory
Herpes

Clinical and Transplantation Virology

Prof. Dr. Hans H. Hirsch
Department of Biomedicine
Institute for Medical Microbiology
University of Basel

Group Members
PD Dr. Rainer Gosert (postdoctoral fellow)
Dr. Alexis Dumoulin (postdoctoral fellow)
Dr. Gunhild Unterstab (postdoctoral fellow)
Michela Cioni (PhD student)
Piotr Kardas (PhD student)
Simone Neu (Master student)
Julia Manzetti (Master student)
Marion Wernli (technician)
Jacqueline Samarides (technician)
Min Lu (technician)
Andrea Glaser (technician)

Transplantation Virology: Elucidation of virological, immunological, and clinical determinants of disease

Virus infections are more severe when the immune system of the infected host is either "naive" or compromised in its response. Besides HIV-AIDS, the number of immunocompromized patients is rising due to successful solid organ transplantation (SOT), hematopoietic stem cell transplantation (HSCT), modern chemotherapies for cancer and new immunosuppressive biologicals for autoimmune diseases including inflammatory bowel, multiple sclerosis and rheumatoid arthritis.
We are characterizing virological, immunological and clinical factors defining the virus-host balance and its outcome. By improving diagnostic tools in the clinical virology laboratory, a better identification of viral pathogens becomes possible as well as elucidation of the specific opportunities created in the affected patient by the interplay of the underlying pathology and the respective immunosuppressive treatment.

Respiratory viruses

We established a multiplex PCR to identify 16 respiratory pathogens including Influenza A and B, new A/H1N1v ("swine flu"), respiratory syncytial- (RSV), human metapneumo- (hMPV), parainfluenz (PIV1-4), corona-, adeno, and rhinoviruses. Knowledge of pathogens and hosts prioritizes rationales for exploring new antiviral therapies.

Herpes viruses

Cytomegalovirus (CMV) and Epstein-Barr virus are significant pathogens in all transplant patients causing organ-invasive and post-transplant lymphoproliferative diseases. We found that low CMV-specific T-cells are a significant risk factor for CMV replication and the emergence of drug resistance. Adequate antiviral dosing and improving CMV-specific immunity without triggering transplant rejection are key objectives.

Polyomaviruses

BK virus (BKV) is linked to polyomavirus-associated nephropathy after kidney transplantation and hemorrhagic cystitis after HSCT. In an international randomized-controlled study comprising 682 de novo kidney transplant recipients, we found that BKV viremia is more frequent and higher in patients receiving tacrolimus compared to cyclosporine. The non-coding control region of BKV is altered in kidney transplant patients with persistent BKV viremia and associated with higher plasma loads and more advanced disease. One of the regulators of polyomavirus replication appears to reside in a late virus gene called agnoprotein which may be critical in virus release and immune recognition.
JC virus (JCV) is linked to progressive multifocal leukoencephalopathy (PML) seen in HIV-AIDS, but also in patients treated with lymphocyte-targeting biologicals for autoimmune disorders. In HIV-AIDS patients, we found that survival of PML patients is linked to mounting of humoral and cellular immune responses after initiating antiretroviral therapy. Rearrangements are also found in the JCV genome of PML patients which accelerate JCV replication rate in primary glia cells. Thus, profound immunodeficiency is a significant risk factor not only for the occurence of polyomavirus disease, but also for accelerated virus pathology and poor outcome.

Fig. 1: Comprehensive multiplex PCR for diagnosis of respiratory pathogens in patients with suspected swine Influenza A/H1N1v in the first phase of the pandemic 2009 (Dumoulin et al. 2009 Transplant Infectious Diseases 11: 287–289).

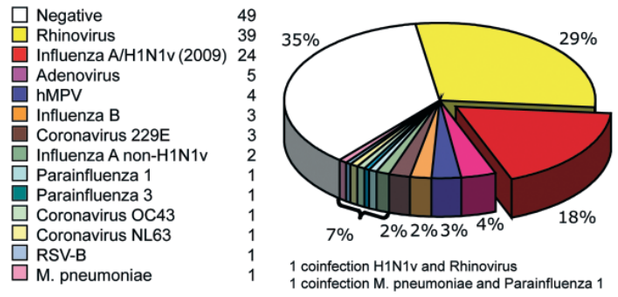


Fig. 2: JC virus with rearranged non-coding control region *(rr*-NCCR) found in the CSF and plasma of patients with progressive multifokal leukoencephalopathy increase early gene expression and accelerate JCV replication compared to the non-rearranged archetype *(at)*-NCCR JCV found in urine (Gosert et al. 2010, J Virology, 84: 10448-10456).

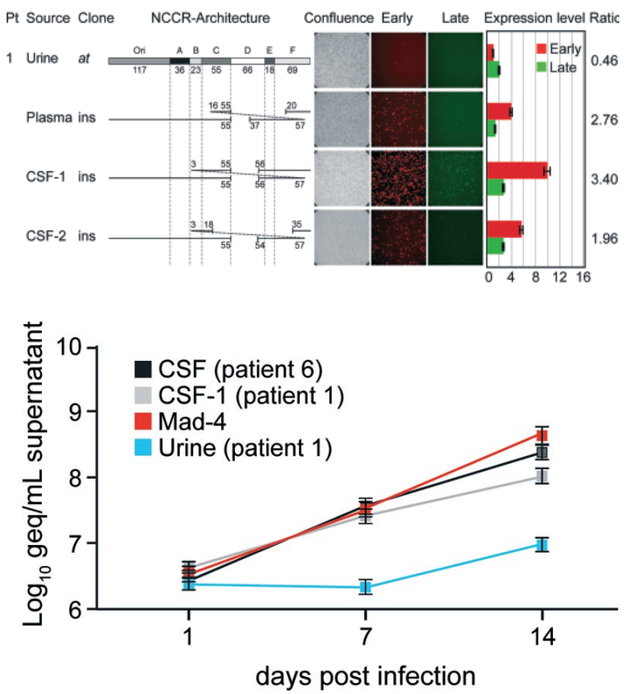
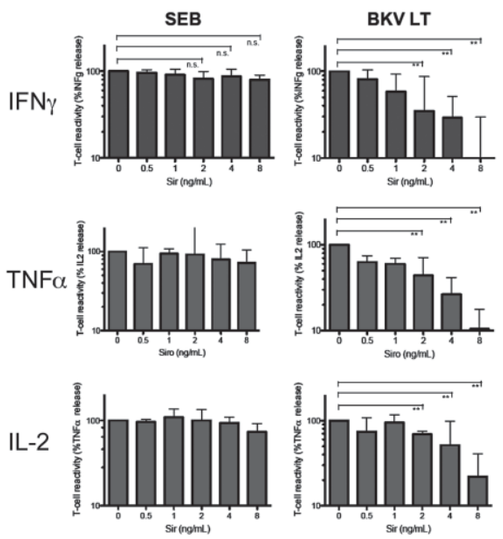


Fig. 3: Rapamycin inhibits BK virus antigen-specific T-cell proliferation, but not expression of Interferon-γ (IFN γ), Tumor necrosis factor-α (TNFα), and Interleukin-2 (IL-2) (Egli et al. 2009, Transplantation 88: 1161–1168).



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- Egli, A., Binet, I., Binggeli, S., Jaeger, C., Schaub, S., Steiger, J., Sester, U., Sester, M., and Hirsch, H. H. (2008). Cytomegalovirus-specific T-cell responses and viral replication in kidney transplant recipients. J Transl Med 6, 29.
- Gosert, R., Rinaldo, C. H., Funk, G. A., Egli, A., Ramos, E., Drachenberg, C. B., and Hirsch, H. H. (2008). Polyomavirus BK with rearranged noncoding control region emerge in vivo in renal transplant patients and increase viral replication and cytopathology. J Exp Med 208, 841-852.
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- Khanna, N., Wolbers, M., Mueller, N. J., Garzoni, C., Du Pasquier, R. A., Fux, C. A., Vernazza, P., Bernasconi, E., Viscidi, R., Battegay, M., and Hirsch, H. H. (2009). JC virus-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal leukoencephalopathy. J Virol 83, 4404-4411.
- Unterstab, G., Gosert, R., Leuenberger, D., Lorentz, P., Rinaldo, C. H., and Hirsch, H. H. (2010). The polyomavirus BK agnoprotein co-localizes with lipid droplets. Virology 399, 322-331.

Feral Pigeon *Columba livia*
Epidemiology
Wild Boar *Sus scrofa*
deterrent systems

Integrative Biology

Prof. Dr. Daniel Haag-Wackernagel
Department of Biomedicine
Institute of Anatomy
University of Basel

Group Members
Ila Geigenfeind (PhD student)
Adrian Schlageter (PhD student)
Andreas Ochsenbein (technician)

Problem animals – feral pigeons and wild boars

A. Transmission of *Chlamydophila psittaci* from feral pigeons to humans in the urban environment

Feral pigeons *(Columba livia)* are known to be chronically infected with the obligate intracellular bacterium *Chlamydophila (C.) psittaci*, the pathogenic agent of avian chlamydiosis and human ornithosis/psittacosis. The infectious chlamydial elementary bodies are shed either by respiratory or ocular secretions or by faeces if intestinal organs are involved. Up to the present, more than a hundred cases of transmission of *C. psittaci* from feral pigeons to humans have been published. We suppose that additionally a high number of *C. psittaci* infections have either been misdiagnosed due to general influenza-like symptoms, remained unreported, or feral pigeons have not been recognized as a source of infection.

We are assessing the zoonotic risk posed by *C. psittaci* in the public area of Basel by repeatedly analyzing pharyngeal- and cloacal swab samples from the feral pigeons in our lofts as well as faecal samples taken in public areas. Swabs and faecal samples are tested using a well-established species-specific nested-PCR assay targeting the *ompA*-gene of *C. psittaci*. Up to now, our results are consistent with previous publications (Magnino et al., 2009) and show that about 2.5% of the feral pigeons in our lofts are shedding *C. psittaci* into the environment. It could also be demonstrated, that chlamydial shedding occurs in fact intermittently, since some of the affected individual birds could be tested on multiple occasions with varying results. With our study we contribute to a risk assessment for human *C. psittaci* infections by feral pigeons in the urban environment.

B. Population dynamics of the feral pigeon *(Columba livia)* and management implications

In our public feral pigeon lofts we have the unique opportunity to study the population dynamics of feral pigeons under natural conditions. We are collecting relevant data in a long-term study, which gives us insight into seasonal variations in breeding activity and breeding success. Thus, we can correlate the breeding activity to seasonal influences, the occurrence of diseases and parasites, other factors and special events. Additionally, we are able to gain insight into the dynamics of parasite infestations, and we have direct access to parasites that can also infest humans. The aim of our study is to obtain more knowledge about the feral pigeon population dynamics and thus to contribute to an improvement of feral pigeon management strategies.

C. Investigation of the effectiveness of deterrent systems against wild boars *(Sus scrofa)*

During the last two decades wild boar populations have grown rapidly and the range of the species has increased steadily, covering almost the whole European continent today. Wild boars cause considerable damage to fields and grassland, but also pose a potentially high threat to livestock, as carriers of the pathogen of the classical swine fever, which may be transmitted to domestic pigs and can cause huge losses (Fig. 2). Together with the regulation of the populations by means of hunting, the protection of fields and livestock is therefore crucial for preventing major economic losses. Field protection is normally achieved by putting up electric fences. However, these are expensive and require regular maintenance to provide for functioning, which is time-intensive. Alternatively, several deterrent systems basing on optic-, acoustic-, olfactory-, and gustative effects are available, most of which are lacking scientific proof of efficacy. In our study we investigate the effectiveness and the sustainability of several deterrent systems in field experiments with free ranging wild boars. Deterrents investigated were solar blinkers, an odor repellent imitating a mixture of stenches of several predators, and a gustative repellent that claims to deter wild boars by its acetous taste. Preliminary results suggest that wild boars behave very cautiously concerning changes in their natural habitat. After a short period of neophobic effect, deterrent systems lose their effectiveness and wild boars surmount the optic, olfactory, and gustative barriers regularly. At the moment, we are investigating a self-constructed deterrent system that combines acoustic and optic effects. Our first results in the field are satisfying, however, it remains to be seen, whether the deterrent effect is sustainable. Our results contribute to an assessment of legal foundations and common practice of hunting, field protection, and compensation payments by cantonal veterinary- and game authorities.

Fig. 1: Feral pigeons pose a considerable health risk to the human population. Till today seven pathogenic agents and seven species of ectoparasites have been transmitted from feral pigeons to humans.

Fig. 2: Wild boars cause considerable damage to fields and grassland, but also pose a hygienic threat to livestock, e.g. the transmission of swine fever to domestic pigs.

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calcium homeostasis

Neuromuscular disorders

TIRF

Calcium channels

Excitation-contraction coupling

Perioperative Patient Safety

PD Dr. Susan Treves **PD Dr. Thierry Girard**

Department of Biomedicine and Division of Anesthesia
University Hospital Basel

Group Members

Dr. Mirko Vukcevic (postdoctoral fellow)
Dr. Marcin Maj (postdoctoral fellow)
Dr Soledad Levano (postdoctoral fellow)
Raphael Thurnheer (PhD student)
Anne-Sylvie Monnet (technician)
Marine Singer (technician)
Esther Schmidt (technician)
Antoni Teixeira (technician)
Prof. Francesco Zorzato (group leader)
Prof. Albert Urwyler

Calcium homeostasis under normal and pathological conditions

Changes in the intracellular free calcium concentration underlie a variety of biological phenomenon, such as neuronal excitability, muscle contraction, gene expression and metabolism. Under resting conditions, eukaryotic cells maintain the cytoplasmic calcium concentration ([Ca2+]) at very low levels (about 100 nM), but upon stimulation its concentration raises dramatically (more than 10000-fold) in just a few milliseconds; these changes are sensed by specialized proteins, resulting in a cellular response. Because of the importance of Ca2+ in cell physiology, eukaryotic cells have developed specialized organelles (or subregions of organelles) to finely control the cellular [Ca2+] and many proteins (from channels on the plasma membrane which allow Ca2+ ions to flux into the cytoplasm from the extracellular milieu, to intracellular calcium storing proteins, intracellular calcium channels and Ca2+ pumps or CaATPases), are devoted to calcium homeostasis. The most specialized organelle involved in Ca2+ regulation is the skeletal muscle sarcoplasmic reticulum; this organelle has a finely structured architecture. In fact the protein(s) sensing the action potential generated by the nerve impulse on one subspecialized membrane (the transverse tubular membrane), can physically interact with the calcium release channel (also known as the ryanodine receptor, RyR1) present on another specialized membrane, the terminal cisternae. The importance of the fine regulation of [Ca2+] is illustrated by several groups of neuromuscular diseases, which are linked to mutations in the ryanodine receptor calcium channel, namely malignant hyperthermia (MH), central core disease (CCD), multi-minicore disease MmD abd Centronuclear myopathy (CNM). To date more than 100 missense mutations in the RYR1 gene have been identified in patients and associated and linked to the CCD, MmD, CNM and/or MHS phenotype.

Our research focuses on several aspects of intracellular calcium homeostasis and how its dysregulation may bring about pathological phenotypes. During the past few years our studies have concentrated on two main aspects of how mutations in the RYR1 affect calcium homeostasis in human myotubes, namely "global" release from intracellular stores and influx from the extracellular environment. Abnormal Ca2+-release from intracellular stores is now known to be one of the underlying causes of the "weak muscle" phenotypes of patients with Core myopathies. On the other hand, abnormal Ca2+ entry through channels present on the plasma membrane may have important downstream effects, particularly affecting the activity of Ca2+-sensitive enzymes present on the plasma membrane as well as the subcellular distribution of Ca2+--sensitive transcription factors such as NFAT.

Our research also focuses on the role of ryanodine receptors in immune cells, with particular emphasis on dendritic cells and B-lymphocytes, two types of immune cells which are involved in antigen presentation and cytokine production. The latter point is important because it may indicate a link between muscle function and some aspects of immune response. Finally we are pursuing a proteomic approach of the endo(sarco)plasmic reticulum, the organelle responsible for calcium homeostasis in muscle and non-muscle cells. This has allowed us to characterize at the molecular and functional level a number of proteins (junctate, JP-45, SRP-35. SRP-27); for one of these proteins (JP-45) we have made a knock-out animal model which is yielding important information on the fine regulation of skeletal muscle excitation-contraction coupling.

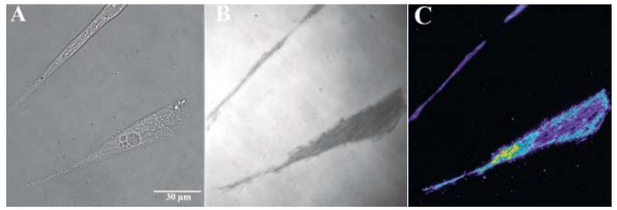

Fig. 1: Human myotubes viewed by brightfield microscopy (A), with a surface reflection interference contrast filter (SRIC) to visualize the contact site of the cell on the glass coverslip (B) and after fluo-4 loading with a 60x TIRF objective, to measure calcium influx after stimulation with 100 mM KCl (C). Blue pseudocolour indicates low levels of Ca^{2+}, yellow and red levels where the [Ca^{2+}] is higher, indicating that Ca^{2+} influx is occurring. Bar indicates 30 m.

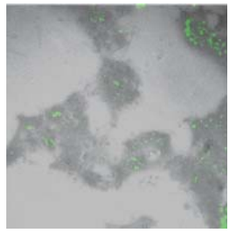

Fig. 2: HEK cell clones expressing GFP-tagged junctate. Cells were imaged by TIRF microscopy to localize the zone on or within 100 nm of the plasma membrane, expressing junctate. Photomicrograph shows a SRIC image (grey) overlayed with an image obtained by TIRF microscopy (100x objective) showing the distribution of GFP-junctate in microdomains on the plasma membrane.

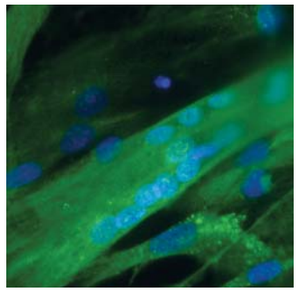

Fig. 3: Cultured human myotubes were stained with anti-NFATc1 (green) and DAPI (dark blue) to visualize the nuclei. Light blue nuclei indicate nuclear translocation of NFATc1.

Connection to Clinical Practice

Personalized anaesthesia?

Pharmacogenetics are playing an increasing role in clinical anaesthesia and for two diseases anaesthesia is getting very close to "personalized medicine":
Mutations in the butyrylcholinesterase gene (BCHE) lead to prolonged duration of action of neuromuscular blocking drugs. The patient is paralyzed for hours instead of minutes and has to be ventilated. We are investigating BCHE for such mutations and correlate specific mutations with the increase in duration of action. The patient's family is also tested and genetically counselled.
Another important pharmacogenetic disease is malignant hyperthermia (MH). In contrast to the variants in BCHE, MH is rare. It is the potential fatality, which renders MH important for clinical anesthesia. Predisposed individuals develop a hypermetabolic reaction in response some anaesthetics. This hypermetabolic reaction originates from skeletal muscle and leads to muscular breakdown, elevated oxygen consumption, potentially culminating in severe metabolic acidosis, hyperthermia and electrolyte disturbances, eventually leading to death.
The gold-standard to test for MH susceptibility is the in-vitro contracture test. Muscle specimen from an open muscle biopsy are challenged with caffeine and halothane and tested for their contractile response.
We and others have identified and characterized several mutations in gene encoding the skeletal muscle type ryanodine receptor (RYR1). Our ongoing research for yet unknown proteins in excitation-contraction coupling aims at identification of further proteins involved in MH susceptibility.

Selected Publications

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Alzheimer's disease
Amyloid-beta
Tau-protein
Mitochondria
Biomarker
Psychiatric disorders
Neurodegeneration

Brain Aging & Mental Health

Research Group associated with the DBM

Prof. Dr. Anne Eckert
Psychiatric University Clinics Basel

Group Members
Dr. Virginie Rhein (postdoctoral fellow)*
Lucia Pagani (PhD student)
Maria Giese (PhD student)
Karen Schmitt (PhD student)
Kathrin Schulz (PhD student)*
Amandine Grimm (PhD student)
Irene Krucker (Master student)
Brigitte Lamontagne (Master student)*
Stefania Rao (Master student)*
Tania Tripodi (Master student)*
Fides Meier (technician)
Ginette Baysang (technician)

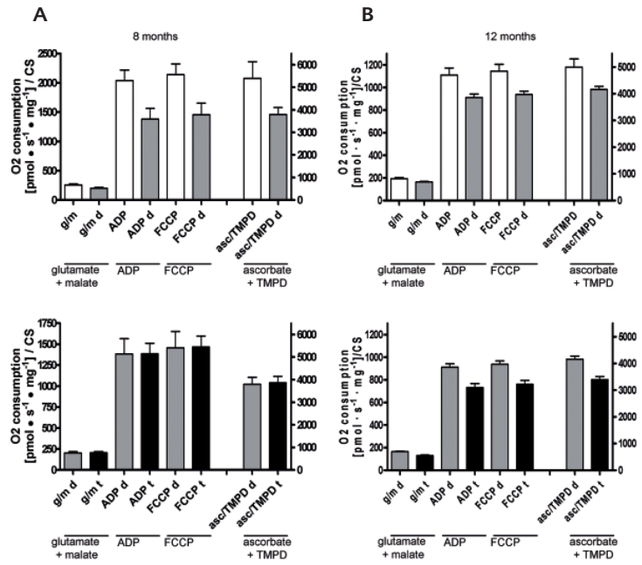
* left during report period

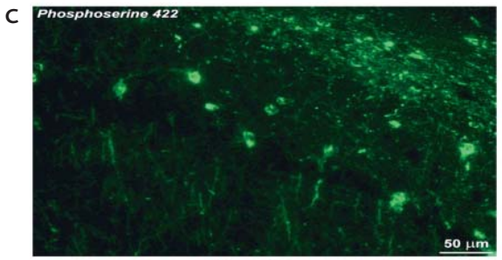
Role of Alzheimer's amyloid-beta and tau protein in neurodegeneration

Subproject 1
Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice
Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ)-containing plaques, neurofibrillary tangles, as well as neuron and synapse loss. Tangle formation has been reproduced in P301L tau transgenic pR5 mice while APPswPS2N141I double-transgenic APP152 mice develop Aβ plaques. Cross-breeding generates triple transgenic (tripleAD) mice that combine both pathologies in one model (fig. C and D). To determine functional consequences of the combined Aβ and tau pathologies, we performed a proteomic analysis followed by functional validation. Specifically, we obtained vesicular preparations from tripleAD mice, the parental strains and non-transgenic mice, followed by the quantitative mass-tag labelling proteomic technique, iTRAQ, and mass spectrometry. Within 1275 quantified proteins, we found a massive deregulation of 24 proteins of which one third were mitochondrial proteins mainly related to complexes I and IV of the oxidative phosphorylation system (OXPHOS). Notably, deregulation of complex I was tau-dependent, while deregulation of complex IV was Aβ-dependent, both at the protein and activity levels. Synergistic effects of Aβ and tau were evident in 8-month-old tripleAD mice as only they showed a reduction of the mitochondrial membrane potential at this early age. At the age of 12 months, the strongest defects on OXPHOS (fig. A and B), synthesis of ATP and reactive oxygen species were exhibited in the tripleAD mice, again emphasizing synergistic, age-associated effects of Aβ and tau in perishing mitochondria. Our study establishes a molecular link between Aβ and tau protein in AD pathology in vivo illustrating the potential of quantitative proteomics. (SNF grant # 310000-108223/1 to AE, Rhein et al., PNAS 2009).

Subproject 2
Tau-dependent uncoupling of NMDA receptors from PSD-95 ameliorates excitotoxicity in Alzheimer's disease mouse models
β-Amyloid (Aβ) and the microtubule-associated protein tau form aggregates in Alzheimer's disease (AD) brains. Tau pathology in AD models is augmented by Aβ but Aβ toxicity is also tau-dependent. Here, we show that not only reduction of tau, but also expression of truncated tau (Δtau) reduces premature lethality and susceptibility to excitotoxic seizures in Aβ-forming APPswe mutant APP23 mice. The post-synaptic localization of the tau-interacting N-methyl-D-aspartic acid (NMDA) receptor (NR) kinaseFyn emerged to be tau-dependent.Fynfailed to localize to dendrites in both tau-deficient and Δtau neurons, resulting in impaired interaction of NR with post-synaptic density (PSD) proteins, and excitotoxic signalling. We also show that uncoupling of the NR/PSD interaction with peptides protects primary cortical neurons from Aβ toxicity. Our data suggest that reduction of tau and expression of Δtau both ameliorate excitotoxicity by uncoupling NR, with implications for AD therapy. (Ittner et al., CELL 2010)

Subproject 3
Survival, neuron-like differentiation and functionality of mesenchymal stem cells in neurotoxic environment: the critical role of erythropoietin
Mesenchymal stem cells (MSC) have been shown to ameliorate symptoms in several neurodegenerative diseases. However, toxic environment in degenerated CNS consisting of hypoxia, glutamate (Glu)-excess and Amyloid-beta (Aβ) pathology may be an obviating factor affecting the survival and regenerative/replacing capacities of engrafted stem cells. Indeed, human MSC exposed to hypoxia were disabled in 1) their functionality of muscarinic receptors (mAChRs) to respond to acetylcholine (ACh) with transient increase of intracellular Ca2+, 2) their capacity to metabolize Glu reflected by glutamine synthetase activity and 3) their survival upon exposure to Glu. Our data show that neuron-like/cholinergic differentiation, functionality and resistance to deleterious neurotoxic environment of MSC is regulated and can be improved by EPO highlighting it`s potential for optimizing cellular therapies of the CNS. (Danielyan et al., Cell Death Diff 2009)





12 months

18 months

Connection to Clinical Practice

Identification of biomarkers for psychiatric disorders

Vulnerability and resilience factors of schizophrenia: An approach combining neuroimaging, neuropsychological and neurobiological methods
It is being increasingly recognized that schizophrenia is a pleiotropic disorder. The past decade has witnessed an abundance of studies focussing on the broad spectrum of different psychopathology, abnormalities in mitochondrial function and oxidative stress levels as well as brain structure and function. The discrepancies in published data might be the result of investigating different tissues and/or different patient populations by using different methods. Although different schizophrenia types are similar in symptom presentation and many neurobiological aspects, there is evidence on different disease variations with diverse etiology and pathomechanisms as articulated in the endophenotype concept of schizophrenia. Furthermore, there is evidence that a more favourite outcome is associated, among others, with less vulnerability and greater resilience. In many cases investigated patient groups are not well defined with regard to e.g. type of schizophrenia, course of illness and medication, age of onset, impact of gender, and neurobiology. Therefore, the present project is designed with specific regard to cope with these limitations. We will include well defined and highly specific patient groups to study the broad range in course of illness of schizophrenia. This allows for the first time a direct comparison between distinct patients groups usually merged under the term "schizophrenia". (SNF grant #320030_127323, Eckert, Dittmann, Riecher, Borgwardt)

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- Eckert A, Hauptmann S, Scherping I, Meinhardt J, Rhein V, Dröse S, Brandt U, Fändrich M, Müller WE, Götz J. Oligomeric and fibrillar species of β-amyloid (Aβ42) both impair mitochondrial function in P301L tau transgenic mice. J Mol Medicine, 86(11):1255-67, 2008. [Epub 2008 Aug 16].
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Atherosclerosis

Nanomedicine

"Targeted therapy"

"Polymer nanocarriers"

"Artificial organelles"

Microfluidics

Nanomedicine Research

Research Group associated with the DBM

Prof. Dr. Patrick Hunziker
Rheumatologische Universitätsklinik Basel
University of Basel

Group Members

Dr. chem. Philippe Polleux
Dr. med. & phil Xueya Wang
Dr. med. Kai Tisljar
Dr. med. Marc Wolf
PD Dr. L. Hunziker
dipl.Ing. Alexey Morozov (PhD student)
Kei Mikami, MA (PhD student)
Damian Clamer (MD student)

Nanomedicine Research

The group's scientific goal is to translate novel development in nanoscience towards preclinical and future clinical application, in particular for patient groups regularly seen in the intensive care unit, by a collaborative effort of researchers with an interdisciplinary background (medicine, biomedical research, nanoscience, mathematics/computing). Funding of the research was/is achieved through an own SNF NFP62 project, the NCCR nanoscience, a CTI project, and other sources.
A main scientific endeavour of our group is the work on polymeric delivery systems for therapy, for molecular imaging, for theragnostics, and, in particular for advanced functionality: one development goal are artificial nanosize organelles (defined as nanocarriers with the ability to deploy complex functionality intracellularly) for medical applications based on a proof of concept published by us in NanoLetters recently.
First steps in this direction were a) the development of a nanosize artificial organelle equipped with a light-switchable cytotoxic functionality intended for cancer therapy, which was designed, successfully tested in vitro and then applied to cultured cancer cells: we found an increase in anti-cancer efficacy of the organelle compared to a non-nano approach of more than an order of magnitude, while at the same time reducing toxicity on bystander - non-cancer cells, raising the expectation that this might develop into an important contribution for future cancer treatment. We are currently setting up in vivo experiments in mouse models of cancer to advance in this application.
A second step towards artificial nanotech based organelles was done in a prevalent metabolic disease: here, we are testing our hypothesis that artificial organelles may be inserted into cells and organs, where they have the potential to deploy long-term metabolic functionality deficient or absent in the diseased cells. Here, we have achieved solid in vitro and preliminary cell culture results supporting that claim. We are currently in a modified cell culture experiment and plan in vivo experiments this summer.
In a third line of development, we were testing in vivo behaviour of injected nanocarriers in wildtype and transgenic mice. We have produced pharmacokinetic data, organ distribution information and toxicology data based on serum chemistry, fluorometric quantification, histologic toxicity assessment (figure) magnetic resonance imaging (figure) and fluorescence microscopy tissue section of our functionalized block-copolymer nanocarriers, information which is fundamentally important for the experimental line mentioned above.
A further innovation is the application of TOF-SIMS (time-of-flight secondary ion mass spectroscopy) for nano-resolved metabolic imaging and detection of polymer nanoobjects in biological tissue, filling a gap in current detection methods in biology, achieved in a collaboration of our group with EMPA Dübendorf (figure).

Bringing together and shaping the nanomedical community is of major importance to facilitate clinical application of nanomedicine. Together with the CLINAM Foundation for Clinical Nanomedicine, we have therefore organized the 1st (2008) and second (2009) and third (2010) European Congress for Clinical Nanomedicine (see www.clinam.org), which has evolved into a prime interdisciplinary event in clinical-nanoscientific interaction, as acknowledged by the relevant EU bodies, a large number of testimonials from participants and the active participation of several presidents of large european medical societies, officials from the European Commission and the Swiss Government. Furthermore, we have established the new European Journal for Nanomedicine in 2008, which is developing according to plan. Scientific visibility of the project is also evident in the significant number of international invited talks in 2008, 2009 and 2010.

Selected Publications

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- Pavel Broz, Nadav Ben-Haim, Mariusz Grzelakowski, Stephan Marsch, Wolfgang Meier, Patrick Hunziker. Inhibition of Macrophage Phagocytotic Activity by a Receptor-targeted Polymer Vesicle-based Drug Delivery Formulation of Pravastatin. J Cardiovasc Pharmacol. 2008 Mar ;51 (3):246-252 DOI: 10.1021/nl0619305
- Nadav Ben-Haim, Pavel Broz, Stephan Marsch, Wolfgang Meier, Patrick Hunziker. Cell-Specific Integration of Artificial Organelles Based on Functionalized Polymer Vesicles. Nano Lett. 2008 Apr 30 DOI: 10.1021/nl080105g
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- Martin Zimmermann, Patrick Hunziker, Emmanuel Delamarche, Autonomous capillary system for one-step immunoassays. Biomedical Microdevices 2009; 11: 1-8

Radiopharmaceuticals
Molecular Imaging
Radiotherapy
Receptor-Mediated Tumour Targeting
Click Chemistry

Radiological Chemistry

Research Group associated with the DBM

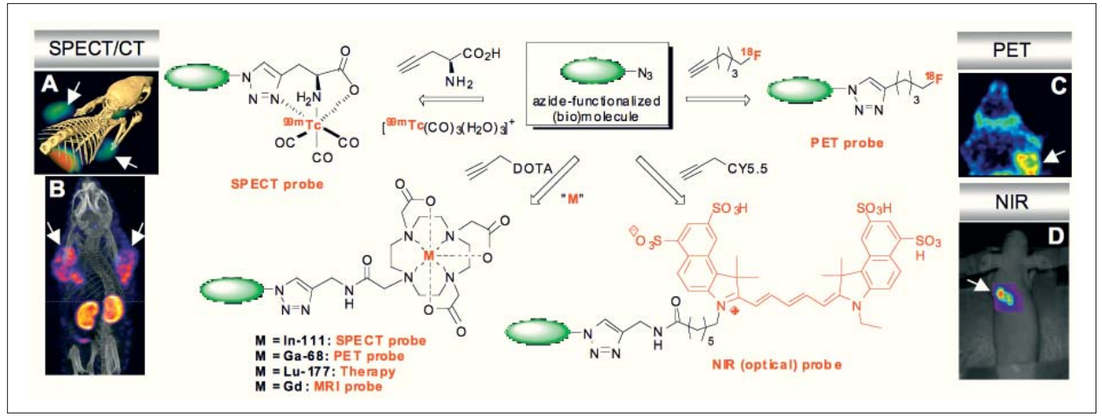
Prof. Dr. Thomas L. Mindt
Radiology and Nuclear Medicine
University Hospital Basel

Group Members
Dr. Andreas Bauman (postdoctoral fellow)
Dr. Ibai Valverde (postdoctoral fellow)
Christiane Kluba (PhD student)

Development of Targeted Radiotracers for Molecular Imaging and Radiotherapy

Radiopharmaceutical sciences is engaged in the development of radioactive labelled (bio)molecules for medical applications as diagnostic imaging probes (employing γ- and β^+-emitting isotopes) or radiotherapeutics (using α- and β^--particle emitters). In comparison to other imaging modalities used for the non-invasive (pre-)clinical assessment of drug candidates *in vivo*, Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) are distinguished techniques in terms of their outstanding sensitivity (detection of femtomoles). As such, they have become an indispensable tool for modern drug development. Many isotopes with decay properties suitable for diagnosis and particularly therapy are transition metal elements or possess a metallic character. Thus, to label molecules of biological interest with such radioisotopes, they have to be functionalized with a so-called bifunctional chelating agent (BFCA) capable of the stable complexation of the metal and its attachment to the vector. Thereby, the biological activity and affinity of the biologically active molecule should not be compromised or altered. This is a challenging endeavor and a number of chemical, physical and pharmacological parameters have to be carefully evaluated and optimized during preclinical development.

A crucial step in the development of imaging agents is the selective conjugation of the probe to the targeted (bio)molecule (vector). This step can be complicated by cross reactivity issues due to the multifunctional character of the components. As a result, indirect approaches are often applied (e.g. protective group strategies) which results in multistep procedures of low overall efficiency. The Cu(I)-catalyzed cycloaddition of azides and alkynes (CuAAC) forming 1,4-disubstituted 1,2,3-triazoles, a transformation termed a "click reaction", provides a solution because of its extraordinary selectivity and efficiency. Reaction of azide-functionalized vectors with alkyne derivatives of probes or precursors thereof respectively, provides directly imaging agents for different modalities in one step. There is no need of protective groups and the mild (aqueous) reaction conditions are well suited for the functionalization of delicate biomolecules. In the case of BFCAs, employment of particle-emitting metal isotopes yields radioconjugates for therapeutic applications. The "click strategy" has been exemplified for different imaging probes as well as various molecules of biological importance including peptides, vitamins, carbohydrates, nucleotides, and phospholipids. A number of these conjugates have been successfully used for the imaging of tumours in xenografted mice. Because the azide functionality can be introduced into molecules by either synthetic chemistry or bioengineering, the click chemistry approach represents a platform technology for the development of imaging probes (and therapeutic agents) based on virtually any (bio) molecule of interest.



Connection to Clinical Practice

PD Dr. Dr. Flavio Forrer
University Hospital Basel, Radiology and Nuclear Medicine

Targeted Imaging and Therapy with Radiopharmaceuticals

The radiolabelled somatostatin analogue DOTATOC was developed to a great deal by the Division of Radiological Chemistry and it was first used in patients in 1996. Since then more than 1500 patients with metastatic neuroendocrine tumors have been treated with ^{90}Y or ^{177}Lu labelled DOTATOC. Lately ^{68}Ga labelled DOTATOC has been introduced into the clinic which allows pre-therapeutic diagnostics and follow up using PET/CT. This results in much more accurate diagnostics for these patients suffering from a relatively rare disease.

This success story serves as a basic principle for the development of new radiopharmaceuticals for diagnosis and therapy. In particular regulatory peptides are ideal vectors for targeting a variety of receptors which are over-expressed on certain tumors. Recently radiolabelled substance P for targeting of the NK-1 receptor, exendin-4 for the GLP-1 receptor and bombesin for the GRP receptor has been brought to the clinic. Additionally it was shown that radiolabelled receptor antagonists feature suitable characteristics for imaging and therapy using radiopeptides and they seem to be superior to the respective agonists. However, not only peptides but e.g. radiolabelled antibodies such as ^{177}Lu-DOTA-Rituximab have been proven to be effective in the therapy of patients with malignant tumors. A close collaboration with the Division of Radiological Chemistry is needed to continue the successful track to help patients with new radiopharmaceuticals. At the same time the optimisation with regard to efficacy and reduced toxicity of the existing compounds continues to be a major challenge of our field of activity.

Selected Publications

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- Mindt Thomas L., Müller Cristina, Melis Marleen, de Jong Marion, Schibli Roger. "Click-to-Chelate: In Vitro and In Vivo Comparison of a 99mTc(CO)3-Labeled N(τ)-Histidine Folate Derivative with Its Isostructural, Clicked 1,2,3-Triazole Analogue" Bioconjugate Chemistry 2008, 19, 1689.
- Mindt Thomas L., Jungi Vera, Wyss Sara, Friedli Alexandra, Pla Gloria, Novak-Hofer Ilse, Grünberg Jürgen, Schibli Roger. "Modification of Different IgG1 Antibodies via Glutamine and Lysine using Bacterial and Human Tissue Transglutaminase" Bioconjugate Chemistry 2008, 19, 271.

Mesenchymal stem cell

Autoimmune disease

Transplantation

Rheumatology

Research Group associated with the DBM

Prof. Dr. Alan Tyndall
Rheumatologische Universitätsklinik Basel
University of Basel

Senior Scientist
Dr. Chiara Bocelli-Tyndall (PhD)

Properties and potential application of mesenchymal stem cells in autoimmune diseases

Mesenchymal stem cells (MSC) , more correctly called multipotent mesenchymal stromal cells, are increasingly being studied and applied therapeutically in various clinical settings including acute graft versus host disease (GvHD), acute ischemia e.g. myocardial infarct and renal tubular necrosis as well as inflammatory autoimmune diseases such as Crohns disease and SLE. Despite the many positive preclinical animal model study results, few clinical data in humans have been published. In addition, questions remain concerning ideal expansion conditions especially regarding growth factors, MSC source and whether allogeneic or autologous MSC would be most suitable for human trials.

We had shown for the first time that MSC derived from patients with active autoimmune disease demonstrated equal anti proliferative properties in an autologous setting as those of healthy allogeneic MSC. In addition, when cultured in the presence of the common gamma chain cytokines found in inflammatory lesions (IL-2, 7 and 15), MSC demonstrated a dichotomous effect on responding lymphocytes i.e. enhancement of poorly proliferating and inhibition of actively proliferating lymphocytes(Fig. 1).

In addition, when cultured in FGF, MSC showed a proliferation dependent expression of MHC class II, which was abrogated by thze presence of TGF-b or dexamethasone (Fig. 2). This may impact on their performance in vivo. One clinical trial in France in GvHD has been suspended pending further examination of the observed aneuploidy in MSC expanded in FGF containing medium. The potential antigen presenting ability of the MHC class II expression is currently under study by us (Arthritis Rheumatism, manuscript under revision).

Fig. 1

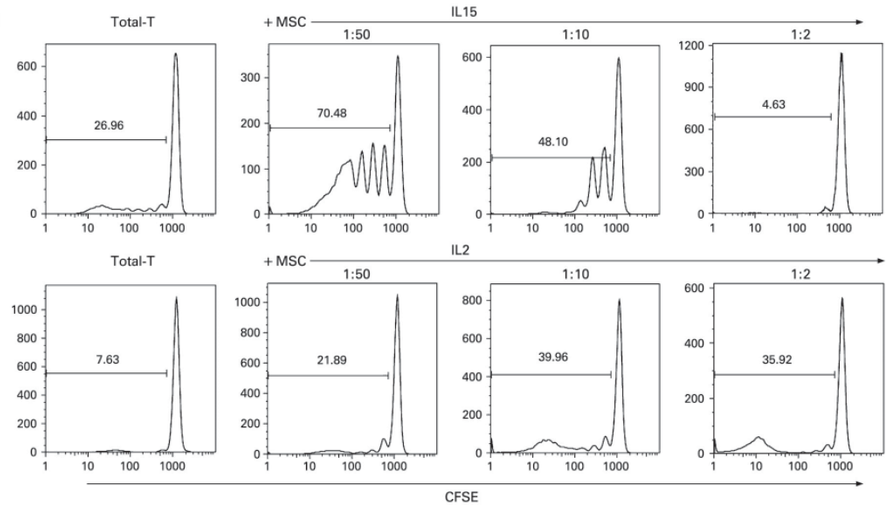
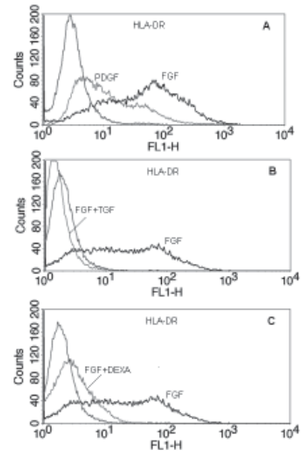


Fig. 2



Connection to Clinical Practice

The use of mesenchymal stem cells in the treatment of autoimmune diseases

The European League Against Rheumatism (EULAR) created a Stromal Cell Translational Group (chair; A Tyndall) which met to develop a strategic plan for the use of MSC immunomodulation in autoimmune rheumatic diseases. Type IV lupus nephritis was selected as an ideal first proof of principle clinical target and a randomised trial is being developed.

Selected Publications

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