DKBW 2000–2004

Departement Klinisch-
Biologische Wissenschaften
Universität Basel

Department
Clinical-Biological Sciences
University of Basel

www.dkbw.ch

Inhaltsverzeichnis

Impressum

Konzept:
DKBW, Advolis Life Science Concepts GmbH, 4057 Basel
Koordination: Advolis
Redaktion: Advolis, DKBW
Übersetzungen: Advolis, DKBW

Gestaltung:
VischerVettiger, Kommunikation und Design AG, Basel
Fotos:
Ralf Steininger D-79713 Bad Säckingen,
Verena Jäggin DF DKBW, z.Vfg.
Druck: Isenegger AG, 4313 Möhlin

www.dkbw.ch

Vorwort

Das Departement für Klinisch-Biologische Wissenschaften hat 2000-2004 eine sehr positive Startphase hinter sich gebracht. Zahlreiche Ordinarien und Extraordinarien wurden berufen, international renommierte, wissenschaftliche Persönlichkeiten konnten nach Basel gewonnen werden.

Die vielen Gespräche mit den «Neuen» zeigen ein einheitliches Bild. Grund für den Wechsel nach Basel und Einzug ins DKBW ist das Grundkonzept dieses Departements: enge Zusammenarbeit zwischen Grundlagenexperten und Klinikern, kurze Wege zwischen «bench» und bedside», gemeinsame Interessen und Projekte.

Das DKBW Fundament steht. Es braucht nun etwas Zeit und auch Geld, um den Ruf zu festigen. Die Basler Universität und Medizinische Fakultät sind international gesehen klein. Das DKBW hat deren Vorteile erfasst.
Die Bedingungen für eine erfolgreiche Zukunft sind jedoch gelegt, die «human ressources» sind gesichert. Die Fakultät freut sich, die weitere positive Entwicklung des Departements zu verfolgen und unterstützen.

André P. Perruchoud
Dekan Medizinische Fakultät,
Präsident des DKBW-Rats

Als das DKBW von den drei Vertragspartnern Universität, Sanitätsdepartement und Universitätskinderspital beider Basel vor 4 Jahren gegründet wurde, waren unter den vertraglichen festgesetzten Zielsetzungen: «*…die intensive Vernetzung und Förderung der klinischen mit der vorklinisch-naturwissenschaftlichen Forschung; …die Schwerpunktbildung*», sowie «*…den Standort Basel für Spitzenkräfte der medizinischen Forschung und für Sponsoren aufzuwerten*». Das Departement ist in den vier Jahren diesen Zielen erfreulich näher gekommen, was in der vorliegenden Schrift dokumentiert sei.

Die Forschung formierte sich neu in vier Schwerpunkten von zentraler wissenschaftlicher und klinischer Bedeutung: Neurobiologie (S. 16), Zellplastizität und Gewebereparatur (Regenerative Medizin) (S. 36), Onkologie (Krebsforschung) (S. 78) und Immunologie (S. 92).

Das neue Konzept erlaubte eine erfolgreiche Serie neuer Berufungen von Professorinnen und Professoren, die auf S. 14 kurz vorgestellt werden.
Die Berufbarkeit von Spitzenkräften ist bekanntlich ein valabler Gradmesser der Qualität einer Universität!

Für die Entwicklung eines Departements ist auch die bauliche Erneuerung ein wichtiger Schrittmacher. Das Kernstück der baulichen Entwicklung bildete ein von Novartis an die Universität geschenktes Gebäude, wo neu das «Zentrum für Biomedizin» entstand (S. 12). Am 3. November 2004 soll es offiziell eingeweiht werden. Ein über 4 Jahre dauernder Planungs-, Finanzierungs- und Bauprozess findet somit einen erfreulichen Abschluss.

Die Kurzberichte der über 50 Forschungs-Gruppen, finden sich nach den vier Schwerpunkten gegliedert, sind englisch verfasst mit einer auch für den Laien lesbaren deutschen Zusammenfassung. Die Beiträge dokumentieren die zunehmende Bedeutung der DKBW-Forschung für das Life Science Konzept der Universität Basel wie für den Pharmaforschungsplatz Basel.
Die in der Schrift aufgelisteten über 1200 Publikation geben ein erfreuliches Bild der wissenschaftlichen Kapazität des DKBW.

Ich danke im Namen der Departementsleitung allen, die zum Erreichen der Ziele beigetragen haben. Mein besonderer Dank an Rektor Gäbler als ersten Präsidenten des Departementsrates und an die weiteren Mitglieder des Departementsrates. Unser Dank schliesslich allen, die zu diesem Bericht beigetragen haben und sich auch in Zukunft für das DKBW in Lehre und Forschung einsetzen.

Christoph Moroni
Vorsitzender der Departementsleitung

Die Organe des Departements Klinisch-Biologische Wissenschaften

Departementsrat

Vertreter der Universität:
Prof. Dr. A. P. Perruchoud,
Dekan Medizinische Fakultät, Präsidium
Prof. Dr. U. Gäbler, Rektor der Universität,
Präsidium 2000–2003
Prof. em. Dr. Werner Arber
Dr. Kurt Altermatt,
Verwaltungsdirektor
Prof. Dr. Walter E. Haefeli,
Universität Heidelberg

Vertreter des Sanitätsdepartements:
Frau lic. oec. Rita Ziegler,
Spitaldirektorin USB
Herr lic. iur A. Faller,
Leiter Spitalplanung im Sanitätsdepartement

Vertreter des Universitäts-Kinderspitals Beider Basel:
Dr. Hanspeter Meister
Mitglied UKBB-Rat

Departementsleitung

Prof. Dr. med. Christoph Moroni, Vorsitz

Prof. Dr. rer. nat. Gerhard Christofori

Prof. Dr. med. Georg A. Hollaender

Prof. Dr. med. Radek Skoda

Jean-Jacques Jobin, Geschäftsführer

Kennzahlen des DKBW

Forschungsgruppen
50

Dienstleistungsgruppen
5

Vollamtliche Professuren
26

Beim DKBW beschäftigte Personen
527 (voll- und teilzeitlich)

Budget
Das Globalbudget beträgt insgesamt CHF 31,174 Mio und gliedert sich auf in:

Personalkosten	CHF 21,149 Mio
Sachkosten	4,203
	25,352
Erträge	- 3,502
	21,850
Overheadkosten	9,324
Total	CHF 31,174 Mio

Investitionen
CHF 7,8 Mio in den Jahren 2000–2003

Eingeworbene Drittmittel
CHF 52 Mio

Zur Verfügung stehende Gesamtfläche
11 315 m^2

Organisation des Departements Klinisch-Biologische Wissenschaften

Übersicht über die Institute und Forschungsgruppen

Institut für Anatomie
Prof. Rolf Zeller

Pestalozzistrasse 20, 4056 Basel
www.unibas.ch/anatomie

- Functional Neuroanatomy
  Prof. C. Nitsch
- Developmental Neurobiology and Regeneration
  Prof. J. Kapfhammer
- Cytomorphology
  Prof. L. Landmann
- Developmental Genetics
  Prof. R. Zeller
- Integrative Biology
  Prof. D. Haag
- Electron Microscopy
  Prof. U. Spornitz
- Histology
  Prof. K. Beier
- Anatomisches Museum
  Dr. h.c. H. Kurz

Institut für Biochemie und Genetik
Prof. Gerhard Christofori

Mattenstrasse 28, 4058 Basel
www.unibas.ch/dbmw/biochemie, www.unibas.ch/genetik

- Tumor-Stroma Interactions
  Dr. G. Orend
- Molecular Genetics
  Prof. P. Schär
- Tumor Biology
  Prof. G. Christofori
- Cancer- and Immunobiology
  Prof. M. Wymann
- Human Genetics
  Prof. Hj. Müller
- Genetic Counselling and Diagnostics
  Prof. Hj. Müller
  Prof. P. Miny

Institut für Physiologie
Prof. Bernhard Bettler

Klingelbergstrasse 50/70, 4056 Basel (Pharmazentrum) und Vesalgasse 1, 4051 Basel (Vesalianum): www.unibas.ch/dbmw/physiologie

- Molecular Neurobiology
  Synaptic Plasticity
  Prof. B. Bettler
- Molecular Neurobiology
  Synapse Formation
  Prof. HR. Brenner
- Molecular Neurobiology
  Neural-Immune Interactions
  Prof. U. Otten

Institut für Medizinische Mikrobiologie
Prof. Christoph Moroni

Petersplatz 10, 4003 Basel
www.unibas.ch/imm

- Transplantation Virology
  Prof. H. H. Hirsch
- Molecular Diagnostics
  PD Dr. T. Klimkait
- Experimental Immunology
  Prof. P. Erb
  PD Dr. U. Günthert
- Experimental Oncology
  Prof. Ch. Moroni
- Abteilung für Diagnostik
  Prof. P. Erb
  Prof. H. H. Hirsch
  PD Dr. T. Klimkait

Departement Forschung des Universitätsspitals Basel
Prof. Radek Skoda

Hebelstrasse 20, 4031 Basel
www.dfbs.ch

- Pediatric Immunology
  Prof. G. A. Holländer
- Immunonephrology
  Prof. J. A. Schifferli
- Experimental Critical Care Medicine
  Prof. U. Eriksson
- Neurosurgery
  Prof. O. Gratzl
- Neuro-Oncology
  Prof. A. Merlo
- Signal Transduction
  Prof. Th. J. Resink
  Prof. P. Erne
- Tissue Engineering
  Dr. I. Martin
  Prof. M. Heberer
- Experimental Hematology
  Prof. R. Skoda
  Prof. A. Wodnar-Filipowicz
- Gynaecological Endocrinology
  Prof. Ch. DeGeyter
- Endocrinology
  Prof. A. N. Eberle
- Perioperative Patient Safety
  Dr. S. Treves
  Dr. T. Girard
- Diabetology
  PD Dr. U. Zumsteg
- Infectious Diseases
  Prof. R. Landmann
  Prof. M. Battegay
- Molecular Nephrology
  PD Dr. B. Biedermann
  Prof. R. Krapf
- Neurobiology
  PD Dr. N. Schaeren-Wiemers
  Prof. A. J. Steck
- Oncology Surgery
  Prof. G. C. Spagnoli
  Prof. M. Heberer
- Vascular Biology
  Prof. E. J. Battegay
- Cardiobiology
  Prof. M. Brink
  Prof. P. Buser
- Pneumology
  PD Dr. M. Roth
  Prof. M. Tamm
- Dermatology
  Dr. M. Bigliardi-Qi
  Prof. Th. Rufli
- Hepatology
  Prof. M. H. Heim
- Experimental Immunology
  Prof. G. De Libero
- Transplantation Immunology and Nephrology
  Prof. E. Palmer
  Prof. J. Steiger
- Immunobiology
  Dr. C. Hess
- Clinical Neuroimmunology
  Prof. D. Leppert
  Prof. L. Kappos
- Medical Oncology
  Prof. Ch. Rochlitz
  Dr. M. Pless
- Metabolism
  Prof. U. O. Keller
  PD Dr. B. Müller
- Cardiothoracic Surgical Research
  Prof. H.-R. Zerkowski
- Clinical Pharmacology
  Prof. J. Drewe
  Prof. St. Krähenbühl
- Gastroenterology
  Prof. Ch. Beglinger
- Prenatal Medicine
  PD Dr. S. Hahn
  Prof. W. Holzgreve

Roche Professur SNF Professur

Mattenstrasse 28, 4058 Basel

- Developmental and Molecular Immunology
  Prof. A. Rolink
- Developmental Immunology
  Prof. D. Finke

Legende

Schwerpunkte:

- Immunologie
- Neurobiologie
- Onkologie
- Zellplastizität und Gewebereparatur

- Spezialitäten
- Dienstleistungen

- UKBB-Gruppen
- Externe DF-Gruppe
- Externe Physiologie-Gruppe

Die Gebäude des Departements Klinisch-Biologische Wissenschaften

1 **Institut für Anatomie**
Pestalozzistrasse 20, 4056 Basel

2 **Zentrum für Lehre und Forschung (ZLF)**
Hebelstrasse 20, 4031 Basel

3 **Pharmazentrum (7. Stock)**
Klingelbergstrasse 50/70, 4056 Basel

4 **Zentrum für Biomedizin**
Mattenstrasse 28, 4058 Basel

5 **Vesalianum**
Vesalgasse 1, 4051 Basel

6 **Institut für Medizinische Mikrobiologie**
Petersplatz 10, 4003 Basel


2

3


4


5

1

1


6

Ein neues «Zentrum für Biomedizin»

Das neue DKBW Gebäude ist ein Geschenk der Novartis an die Universität Basel, die es dem DKBW zugeteilt hat. Die Architekten Wirth & Wirth, Gewinner des hierfür ausgeschriebenen Architekturwettbewerbs planten und leiteten Umbau und Anpassung des Gebäudes.
Das DKBW Gebäude an der Mattenstrasse soll im November 2004 feierlich eingeweiht werden. Es beherbergt rund zehn Forschungsgruppen aus drei Schwerpunkten.

Architektonischer Baubeschrieb

Gebäudehülle
Das Gebäude an der Mattenstrasse ist ein lang gezogener, fünfgeschossiger Bau mit einem Attikageschoss (und Untergeschossen), Er präsentiert sich nach aussen als Skelettkonstruktion mit sichtbaren, gestrichenen Stirnen von Betonpfeilern und -decken, dazu abgesetzt Wandausfachungen aus rotem Sichtbackstein. Fenster und Lamellenstoren wurden saniert, haben aber die optische Erscheinung nicht verändert.
Neu dagegen ist der öffentliche Eingang an der Mattenstrasse. Er war notwendig geworden, da Areal und Gebäude aus dem Syngenta-Areal ausgegliedert wurden. Ein Vordach bietet Wetter- und Sonnenschutz für den Eingangsbereich und grosszügige, neue Fenster erhellen die angegliederte Cafeteria. Die ehemaligen, rückwärtigen Zugänge dienen neu zur Anlieferung.
Das sanierte Dach ist mit einer Extensivbegrünung und für die begehbaren Bereiche mit Zementplatten gestaltet worden.

Allgemeine Gebäudestruktur und Nutzung
Das Innere des Gebäudes wird längs von der Gangzone in einen breiteren, zum Innenhof orientierten Bereich und eine schmälere, auf die Strasse gerichtete Zone geteilt. An beiden Enden des Gebäudes befinden sich Treppenhäuser und Personenliftanlage.
Der Besucher findet im Eingangsbereich den Empfang und die kleine, helle Cafeteria zur Selbstbedienung. In der rückwärtigen Zone des Erdgeschosses sind ein grosser Seminarraum sowie kleinere Besprechungsräume und eine kleine Bibliothek untergebracht.
In den oberen Etagen wurden die Labor- und Büroräumlichkeiten des DKBW eingerichtet und gegen die Strasse weitere Büros und Nebenräume.
Im 1.Untergeschoss sind die Tier- mit dazugehörigen Arbeits-, Lager- und Reinigungsräumen untergebracht und im 2.Untergeschoss befinden sich die Energiezentrale sowie verschiedene Lagerräume für die Labors.

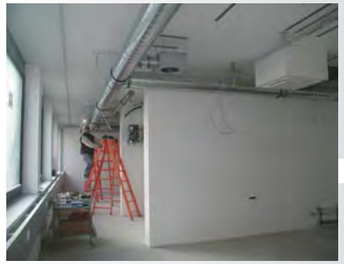
Christian Schmid, Direktor Wirth & Wirth AG

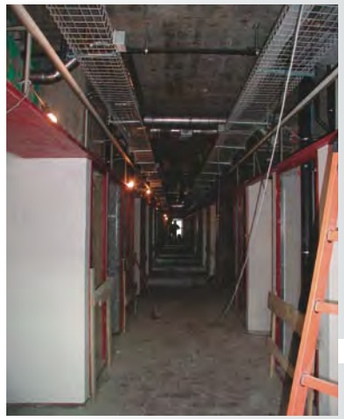
Wir danken folgenden Firmen, die am Umbau beteiligt waren, und die uns für die vorliegende Schrift grosszügig unterstützt haben:

indulab® ag

WIRTH + WIRTH ARCHITEKTEN

Vosseler
Innenausbau
Laboreinrichtungen
Trennwandsysteme





Newly Appointed Professors 2002–2004

Prof. Dr. Bernhard Bettler, born 1957 in Baden, Switzerland, studied microbiology at the University of Zürich where he obtained his PhD in 1986. Between 1989 and 1997 he worked in the biotechnology department at CIBA-Geigy in Basel, at the Salk Institute for Biological Sciences in San Diego, California in Neurobiology, and at the CIBA-Geigy Pharma division in Basel. From 1998, he has been group leader in neurobiology research at Novartis in Basel. In 2001, Prof. Bettler was been appointed Professor of Physiology and heads the Institute of Physiology. His work focuses on the role of GABA receptors in the brain.

Prof. Dr. Marijke Brink, born in 1959 in Bussum, NL, studied biology and biochemistry at the Rijksuniversiteit in Leiden. In 1989, she obtained her PhD in Biochemisty at the Max Planck Institut in Martinsried/München and was a postdoctoral fellow at the University of Amsterdam (until 1992), in Ciba-Geigy Basel (until 1994) and at the Emory University in Atlanta, USA (until 1996). She habilitated at the University Hospital in Geneva in 1997. She has been appointed Professor of Physiology in 2004. Her work focuses on the role of growth factors in cardiology and she is an expert in clinical research in the domains of cardio-vascular biology and endocrinology.

Prof. Dr. Gerhard M. Christofori, born in 1957 in Pforzheim, Germany, studied biology at the University of Heidelberg where he obtained his PhD in molecular biology in 1988. He worked at the Krebsforschungszentrum in Heidelberg and at the Biozentrum in Basel as postdoctoral fellow. From 1989 to 1994, he stayed at the Hormone Research Institute in the Department of Biochemistry and Biophysics of the University of California, San Francisco. In 1994, he became group leader at the Research Institute for Molecular Pathology (IMP) in Vienna and habilitated in 2001. He was appointed Professor for Biochemistry in 2001 and heads the Institute for Biochemistry and Genetics. His work focuses on the identification and characterization of genes and factors involved in carcinogenesis and metastasis.

Prof. Dr. Urs Eriksson, born in 1964 in studied chemistry at the ETH in Zürich and medicine at the University of Zürich. In addition to his clinical training at the University Hospitals of Zürich and Basel, he was a research fellow from 2001–2003 at the Departments of Medical Biophysics and Immunology, Princess Margaret Hospital, at the University of Toronto, Canada. In 2004 he obtained a professorship from the Swiss National Science Foundation and joined the Department of Research at the University Hospital Basel. His work focuses on inflammation of the cardiac muscle, on the frequent causes of heart failures of young persons and on clarifying the mechanisms leading to inflammatory heart disease.

Prof. Dr. Daniela Finke, born in 1964, studied medicine in Freiburg i.B. where she graduated 1994. After two clinical years, she moved to Lausanne where she trained in immunology at the Ludwig Institute, for Cancer Research, at the Swiss Institute for Experimental Cancer Research, and at the Institute of Biochemistry of the University of Lausanne. She works on developmental aspects of immunology, on the formation of lymphatic tissue that is important in the immune defense. Since 2003 she holds a professorship from the Swiss National Science Foundation and chose the DKBW as host insitution.

Prof. Dr. Hans H. Hirsch, born in 1958 in Flensburg, Germany, studied medicine in Freiburg i. Br. and biochemistry at the University of Oregon State in Corvallis, USA. In 1986, he joined the Biotechnology Department of Ciba-Geigy in Basel. From 1989, he was at the Institute for Medical Microbiology at the University of Basel where he habilitated in 1997. After clinical training in internal medicine and infectiology in the University Clinics of Basel, he was appointed Professor of Medical Microbiology in 2004 with a joint appointment at the DKBW (Institute of Medical Microbiology) and the Department of Infectious Diseases of the University Hospital. His work focuses on viral infections of immuno-compromised patients.

Prof. Dr. Ed Palmer, born in 1952 in Oceanside, New York, USA, obtained a PhD in microbiology and a MD, both obtained at the Rochester University in 1980. After a postdoctoral fellowship at the Salk Institute in La Jolla, California he became assistant professor at the University of Colorado in Denver in 1984. He is specialist in transplantation immunology and his work focuses on the domains of T-cells and T-cell receptors. In 2001, he joined the Department of Transplantation Immunology and Nephrology of the University Hospital Basel and became 2003 full Professor of Transplantation Immunology at the DKBW.

Prof. Dr. Antonius Rolink, born 1953 in the Netherlands, studied Molecular Sciences at Agricultural School in Wageningen, Netherlands. He obtained his PhD at the Red Cross blood transfusion center of the University of Amsterdam in 1982. He moved to Basel in 1983, where he joined the Basel Institute for Immunology. He habilitated in 1997 at the University of Basel and was appointed 2001 Roche Professor for Immunology, a professorship financed by Roche. His work focuses on hematopoietic stem cells and the development of the immune system.

Prof. Dr. Primo Schär, born 1961 in Willisau-Stadt, Switzerland, studied biology at the University of Bern and obtained his PhD in 1991 at the Institut für Zellbiologie. From 1993 to 1997, he was a postdoctoral fellow at the Imperial Cancer Research Fund in London thereafter as researcher and teacher at the Institut für Medizinische Radiobiologie of the University of Zürich. Appointed Professor of Medical Genetics at the DKBW in 2003, his research focuses on the molecular mechanisms involved in DNA repair using genetic and biochemical approaches.

Prof. Dr. Radek Skoda, born 1956 in Bratislava, Slovakia, studied medicine at the University of Zürich. After research activities at the Biozentrum in Basel, training in internal medicine at the Basler Kantonsspital and a fellowship at the National Cancer Institute in Bethesda, USA, he was from 1989 to 1993 in the Department of Genetics of the Harvard Medical School in Boston, USA. Back in Switzerland, he was a recipient of a SCORE-A fellowship by the Swiss National Science Foundation and specialized in internal medicine. He habilitated in 1998 at the University of Basel and became Assistant Professor at the Biozentrum. From 2000 on, he was at the Deutsche Krebsforschungszentrum in Heidelberg, Germany. In 2001 he has returned to Basel and was appointed Professor of Molecular Medicine and head of the Department of Research at the University Hospital Basel.

Prof. Dr. Matthias Wymann, born 1960 in Solothurn, Switzerland, studied biochemistry at the ETH Zürich and obtained his PhD in 1988 at the Theodor Kocher Institut of the University of Bern. After research activities at the Department of Medical Microbiology of the University of Linköping, Sweden, he came back to Switzerland in 1991 and habilitated in cell biology and biochemistry at the University of Fribourg (CH) in 1997. His projects are dealing with the role of lipid kinases in the cellular processes underlying tumor inception and inflammation. He was appointed Professor of Biochemistry in 2004.

Prof. Dr. Rolf Zeller, born in 1957 in Basel, Switzerland, studied molecular biology at the Biozentrum, Basel. After his PhD in 1984, he was a postdoctoral fellow from 1985 to 1989 in the Department of Genetics at the Harvard Medical School in Boston, USA. He became group leader at the European Molecular Biology Laboratory in Heidelberg, then head of the Department of Developmental Biology at the University of Utrecht (NL), and was appointed Professor of Anatomy and Embryology at the DKBW in 2002. He is the head of the Institute of Anatomy. His research focuses on the molecular and genetic analysis of cell to cell communication during growth and morphogenesis.

DKBW Schwerpunkt Neurobiologie

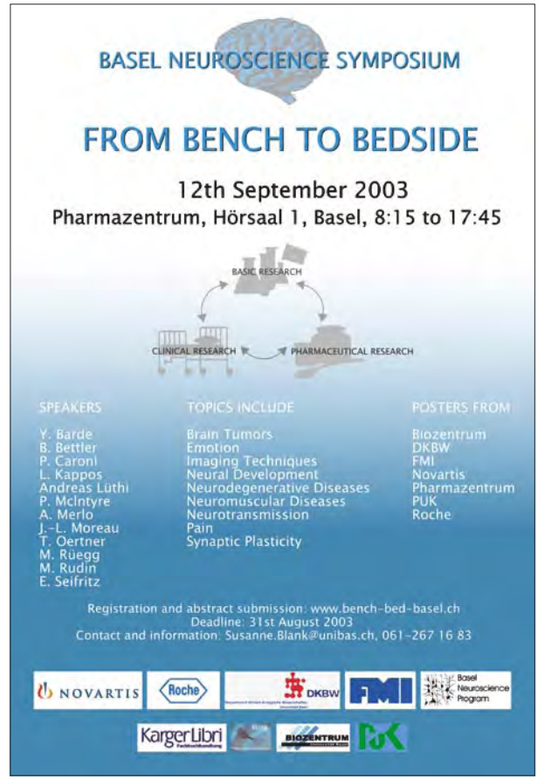
Professor B. Bettler
Institut für Physiologie
Universität Basel

Professor A. J. Steck
Neurologische Klinik
Universitätsspital Basel

Der DKBW-Schwerpunkt Neurowissenschaften wurde ins Leben gerufen, weil die Aufklärung der Erkrankungen des Nervensystems mit zu den grössten Herausforderungen der biomedizinischen Forschung gehört. Der DKBW-Schwerpunkt ergänzt die Neurobiologie-Schwerpunkte des Biozentrums und des Friedrich-Miescher-Instituts und ist Teil des fakultätsübergreifenden «Basel Neuroscience Programs» (BNP, http://www.biozentrum.unibas.ch/neuro). Das BNP vereint mehr als 400 Basler Neurowissenschaftler aus 40 verschiedenen Laboratorien der Universität und pharmazeutischen Industrie. Im Rahmen des BNP finden wöchentliche interdisziplinäre Veranstaltungen, wie beispielsweise die «Thursday Seminars in Neurobiology» oder die «Basel Neurobiology Lectures», statt. Diese bieten eine ideale Plattform für einen regen Austausch zwischen Grundlagenforschern und klinischen Forschern. Zusätzlich koordiniert Neurex (http://www.neurex.org/), ein tri-nationaler Zusammenschluss des BNP mit den Neuro-Netzwerken der Universität Freiburg (NeurAG, http://www.neurag.uni-freiburg.de) und der Universität Strassburg/Rouffach (IFR 37, http://neurochem.u-strasbg.fr), regelmässig Workshops im Dreiländereck. Neurex verleiht zudem überregionale Forschungsstipendien, von denen auch DKBW-Neurowissenschaftler profitieren.

Der DKBW-Schwerpunkt hat sich zum Ziel gesetzt, die in der Region Basel aussergewöhnlich starke Ballung von neurowissenschaftlicher Expertise zu nutzen, um Erkrankungen von grosser medizinischer und gesellschaftlicher Relevanz zu untersuchen. Aufgrund dieser Initiative sind die ersten gemeinsamen Forschungsprojekte von Biologen und Medizinern des DKBW beim Schweizerischen Nationalfonds eingereicht worden. Die vorliegenden Beiträge illustrieren die laufenden DKBW-Forschungsprojekte, welche sich insbesondere auf die Erforschung neuroinflammatorischer, neurodegenerativer, psychiatrischer, neuro-onkologischer und neuromuskulärer Erkrankungen konzentrieren.

Eine vordringliche Aufgabe ist, wissenschaftliche Erkenntnisse so rasch wie möglich in den Dienst des Patienten überzuführen. Unser Schwerpunkt hat deshalb – zusammen mit dem BNP – im September 2003 zum ersten Mal das Basel Neuroscience Symposium: «From Bench-to-Bedside» durchgeführt. Das Treffen hat 150 Basler Neurowissenschaftler aus den Forschungslabors von Novartis, Roche, dem Friedrich-Miescher Institut, der Universität sowie dem Universitätsspital zusammengeführt. Der Erfolg des Symposiums hat uns darin bestärkt, das Symposium jährlich durchzuführen und damit den Basler Neurowissenschaftlern ein Forum für neue medizinische Konzepte und Ideen zu bieten (http://www.bench-bed-basel.ch).



Neuronal plasticity
Brain lesions
Stroke
Language learning
Bilingualism

Functional Neuroanatomy

Prof. Dr. Cordula Nitsch
Institut für Anatomie

Group Members
Dr. I.-Piotr Maly
Dr. Florence Vollenweider
Dr. Kerstin Bendfeldt
Anelis Kaiser Lic. phil. psychol.
Olga Bollag (technician)
Gabriela Kalt (technician)
Esther Künzli (MD student)
Constantine Bloch (MD student)

The Role of Calcium-binding Proteins in Stroke-related Neurodegeneration

The causes and consequences of neurodegeneration, this is the central topic of our research. How does the brain react to an insult and why are certain nerve cells and brain areas more resistant than others against identical noxious interventions? Are there endogenous mechanisms protecting against nerve cell loss which could be exploited therapeutically? Mediators of local cerebral inflammation could influence stroke-related neurodegeneration (1). Presently, we focus on the role of cytosolic calcium-binding proteins, parvalbumin and calbindin-D28K in particular, which help to control intracellular calcium concentrations and which are differentially distributed in defined nerve cell populations.
Calcium is one of the most important intracellular second messengers and a key element in neuronal excitation and neurodegeneration. Chronically elevated intracellular calcium levels have serious consequences: induction of apoptotic signalling cascades, stimulation of catabolic enzymes and a collapse of mitochondrial membrane potential, all leading towards nerve cell death. Thus, overload with calcium can have a deleterious effect on neurons. Calcium levels are therefore tightly controlled via calcium pumps, calcium storing organelles as mitochondria e.g., and calcium-binding proteins. Deficiency in the calcium-binding protein parvalbumin in certain inhibitory neurons is correlated with spontaneous epileptiform seizures (2), while neurons expressing parvalbumin (3) or other cytosolic calcium binding proteins survive an excitotoxic or ischemic episode.
The pathophysiological processes resulting in stroke-related (ischemic) nerve cell death involve the excessive release of the excitatory neurotransmitter glutamate. This causes an overstimulation of target neurons with depolarisation and increased calcium influx and ultimately neurodegeneration. Therefore, wouldn't it be advantageous if all neurons in the brain expressed cytosolic calcium binding proteins? Transgenic mice expressing parvalbumin in all neurons (via the THY1-promoter, in cooperation with Beat Schwaller, Inst. of Histology, Univ. Fribourg) could provide some answers. In an in vivo model of transient global ischemia we observed that, in sharp contrast to the widely held assumption, parvalbumin-overexpressing mice are highly vulnerable against ischemia. Also, intracerebral injections of excitotoxic glutamate agonists result in significantly larger lesions in the parvalbumin-overexpressing mice than in controls. From this it can be concluded that presence of cytosolic calcium-buffering capacity per se is not neuroprotective and further, that an increase in cytosolic calcium buffering impairs other mechanism of calcium sequestration. In fact, in neurons ectopically expressing parvalbumin, the mitochondrial volume is decreased to 50 % of control and the mitochondrial marker enzyme COXI is reduced (4). Mice devoid of parvalbumin and/or calbindin-D28K (PV-KO and PVxCB-KO) were, on the other hand, more resistant against transient global ischemia as their wild-type counterparts (Fig. 1), in part possibly because their mitochondrial pool is enlarged. In addition, improved survival was seen also intraoperatively, where they tolerated vagal stimulation. This observation initiated an ongoing study on the role of parvalbumin and calbindin-D28K in the control of respiratory reflexes (Fig. 2).
Our present studies show that ectopic presence of calcium-binding proteins is deleterious, while absence of these calcium-binding proteins is protective. This demonstrates first that global alterations in the expression of key proteins as provided by the transgenic technologies are a superior tool to test hypotheses, and second that interference with the expression of key molecules of neuronal homeostasis can induce compensation mechanisms which might even result in an opposite effect.

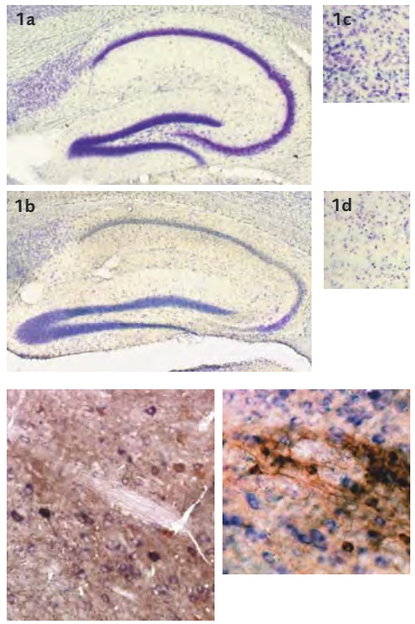


Fig. 1: Neurodegeneration after global transient ischemia. (A) The hippocampus of a PVxCB-KO mouse is well preserved. (B) Severe damage in the hippocampus of a wild type mouse. (C) The striatum of a PVxCB-KO mouse is well preserved. (D) Marked nerve cell loss in the striatum of a wild type mouse.

Fig. 2: GABAergic neurons in the respiratory centre of the nc. tractus solitarius are labelled in blue and contrasted with calcium-binding proteins, labelled in brown. (A) Distinct calbindin-D28K containing neurons do not colocalize with GADm-RNA. (B) A subgroup of GABAergic neurons colocalizes with parvalbumin.

Transdisciplinary project
Prof. Dr. phil. Rita Franceschini, Institut für Romanistik, Universität Saarland, D
Prof. Dr. phil. Georges Lüdi, Romanisches Seminar, Universität Basel
Prof. Dr. med. Ernst Wilhelm Radü, Departement Radiologie, Universitätsspital Basel

The Multilingual Brain

More than half of mankind is multilingual or lives in a multilingual environment. Languages are learnt at different ages and in different settings and up to different levels of competence. Nevertheless, there is a prevalent prejudice: monolingualism is considered the norm, monolingual upbringing necessary for high proficiency in the "native tongue", and it is believed that there are innate constraints in learning second and third languages. In the multilingual brain project, researchers from linguistics and from neurosciences join to address different features of multilingualism with the common goal to gain new insights into the use and processing of multiple languages in the individual, in his/her brain and in society. The investigations are carried out in students proficient in at least 3 languages. Their language biographies are recorded and analyzed with respect to age and form of language acquisition, attitudes towards language learning, use etc. The proficiency is controlled in language competence tests. Using functional Magnetic Resonance Imaging (fMRI) the regional cerebral activation during processing of the three single languages is studied. Results suggest that presence of two languages in the early childhood results in differences in language processing in the first language indicating that the age of second language learning influences the construction of multilingual repertoires in the brain. Also, language learning (rule-based and structured i.e. explicit; or focused on meaning and communication i.e. implicit) influences the representation of languages in the brain (Fig. 3). Questions currently pursued are the presence/absence of a critical time window for native-like learning of languages and the influence of early second language acquisition on third language learning. Further we address the issue of the construction of boundaries between languages. What are the conditions under which the brain deals with a related language as an independent entity or as a variety? (E.g.: Is Swiss German a language or a dialect in this respect?)

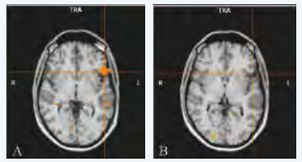


Fig. 3: Regional cerebral activation during processing of the third language, learned during early adulthood (data analysis by Brain Voyager, random effect, p (uncorr.) < 0.05). (A) Strong activation of Broca's area in *explicit learners* (n=9). (B) No activation in Broca's area in *implicit learners* (n=11).

Kalzium-Puffer sind neuroprotektiv – aber nicht ausschliesslich

Kalzium (Ca) ist ein bedeutender zellulärer Signalstoff, der die Erregungseigenschaften und die Überlebensfähigkeit von Nervenzellen massgeblich beeinflusst. Seine intrazelluläre Konzentration wird durch mehrere Mechanismen kontrolliert: Ca-Pumpen, Ca-Speicher – in Nervenzellen sind dies insbesondere die Mitochondrien – und Ca-bindende Proteine, die als Puffer wirken können. Chronisch gesteigerte Ca Konzentrationen, wie sie bei verschiedenen neurodegenerativen Erkrankungen, insbesondere beim Schlaganfall auftreten, führen meist zum Nervenzelltod. Nervenzellen, die konstitutiv zytosolische Ca-bindende Proteine besitzen, wie z.B. Parvalbumin oder Calbindin-D28K, scheinen gegen diese Art des Nervenzelltods geschützt zu sein.
Wir haben bei transgenen Mäusen untersucht, ob die An- oder Abwesenheit dieser Kalziumpuffer in Modellen für Schlaganfall tatschlich neuroprotektive Wirkungen hat. Mäuse, die in allen Nervenzellen Parvalbumin enthalten, sind jedoch viel anfälliger auf transiente Unterbrechung der Durchblutung und zeigen grössere Ausfälle nach Applikation von Neurotoxinen. Ist hingegen die Expression von Parvalbumin und/oder Calbindin-D28K ausgeschaltet, so wird eine Unterbrechung der Durchblutung länger toleriert und die Ausfälle sind geringer. Mangel an Calbindin-D28K und Parvalbumin ist also neuroprotektiv, während die Expression von Parvalbumin in Neuronen, die dieses Protein normalerweise nicht enthalten, zu gesteigerter Anfälligkeit führt. Die einfache Beziehung, mehr Ca-Puffer gleich mehr Neuroprotektion, stimmt also nicht. Darüber hinaus zeigt diese Untersuchung, dass sich bei transgenen Tieren Kompensationsprozesse entwickeln können. Dies ist wohl insbesondere bei Interaktionen mit Schlüsselsubstanzen der Fall, die durch verschiedene parallele Mechanismen konstant gehalten werden – wie hier dem Kalzium. So ist das Volumen an Mitochondrien in den Neuronen, die ektopisch Parvalbumin exprimieren, um 50% reduziert. Die Kompensation ist demnach überschiessend und kann so die Anfälligkeit der Nervenzellen steigern.

Selected Publications

- Vollenweider F, Herrmann M, Otten U, Nitsch C (2003) Interleukin-6 receptor expression and cellular localization after transient global ischemia in gerbil hippocampus. Neurosci. Lett. 341: 49-52
- Scotti AL, Bollag O, Kalt G, Nitsch C (1997) Loss of perikaryal parvalbumin immunoreactivity from surviving GABAergic neurons in the CA1 field of epileptic gerbils. Hippocampus 7: 524-535
- Nitsch C et al. (1989) GABAergic hippocampal neurons resistant to ischemia-induced neuronal death contain the Ca2+-binding protein parvalbumin. Neurosci. Lett. 105: 263-268
- Maetzler W, Nitsch C, Bendfeldt K, Racay P, Vollenweider F, Schwaller B. (2004) Ectopic parvalbumin expression in mouse forebrain neurons increases susceptibility to excitotoxic injury provoked by ibotenic acid injection into the striatum. Exp. Neurol. 186: 78-88
- Franceschini R, Zappatore D, Nitsch C (2003) Lexicon in the brain: What neurobiology has to say about languages. In: "The Multilingual Lexicon" Kluver, Amsterdam, pp.153-166

Axonal regeneration
Organotypic slice cultures
Dendritic development
Protein kinase C
Neural repair
Neuronal plasticity

Developmental Neurobiology and Regeneration

Prof. Dr. Josef Kapfhammer
Institut für Anatomie

Group Members
Dr. Vesna Radojevic
Markus Saxer (technician)
Brenda Bonnici (PhD student)
Alexandra Zelenskaya (PhD student)

The Regulation of Axonal and Dendritic Growth

Axonal projections build the neuronal connections within the CNS. They can be destroyed by traumatic lesions (e.g. spinal or head injury), but also by vascular insults and neurodegenerative diseases. During embryonic development the connections between neurons are generated by the directed growth of axons towards their target regions, followed by synapse formation with the appropriate target neurons. This axonal growth program cannot be easily recalled in the adult CNS. After lesions, severed axons cannot regrow and the disconnected neurons remain permanently dysfunctional. In the moment several experimental strategies are being explored by many laboratories worldwide with the goal to eventually be able to offer therapeutic options to patients suffering from axonal damage. In our laboratory we are focusing on the entorhino-hippocampal projection. This axonal projection can be studied in a tissue culture setup, so-called organotypic slice cultures. The entorhino-hippocampal projection develops in these cultures and mechanical lesions of the axons can be made. This tissue culture approach, therefore, allows the study of axonal regeneration avoiding or reducing the need for in vivo experiments. We have studied the potential for axonal regeneration in entorhino-hippocampal slice cultures during maturation, i.e. when the axons loose growth potential present during embryonic development. We could show that there is a sharp decline in the regeneration of this projection between day 4 and day 6 of postnatal development. We have then tested whether the regeneration of the lesioned fibers could be stimulated by pharmacological intervention (Fig. 1). These experiments demonstrated that some growth factors, for example neurotrophin 4 (=NT4) and glial cell line – derived neurotrophic factor (GDNF), could promote axonal regeneration. Similarly, interference with the protein kinase C signaling pathway with the drug GF 109203X or of G-protein signaling with pertussis toxin (PTX) promoted axonal regeneration. In ongoing experiments we now explore the ability of transplanted immature neural cells ("stem cells") to rebuild this specific axonal projection after lesion or degeneration of the original axons.

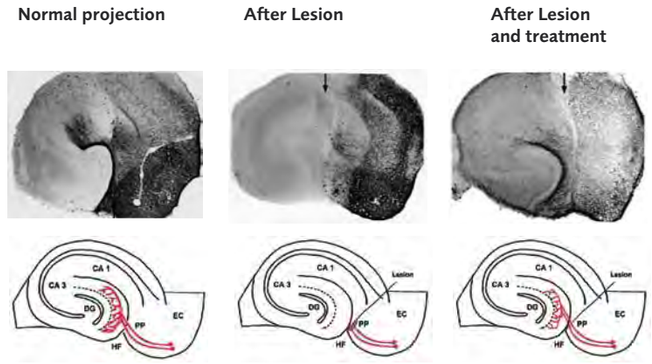


Fig. 1: Schematic representation (lower row) and experimental data (upper row) for the regeneration of the entorhino-hippocampal projection in culture. Without lesion (left images) entorhinal axons (red in schematic drawings) grow into the hippocampus and terminate in the outer molecular layer (OML) of the dentate gyrus (DG).
After a lesion (middle images) the axons stop at the lesion site (arrow). After pharmacological stimulation the axons re-grow, cross the lesion site (arrow) and rebuild the typical projection to the OML (right images).

In a second area of research we study the development of dendritic trees. The outgrowth of dendritic trees is an important step in the differentiation of neurons. Most types of neurons can actually be identified by the morphology and the shape of their dendritic tree. Because the dendritic tree harbors most of the synaptic input of a neuron its growth and shape will determine the synaptic connectivity of the cell. We have shown that the activity of Protein Kinase C (PKC) is an important regulator of the dendritic growth of Purkinje cells, a major neuron of the cerebellum with a large dendritic tree. Stimulation of PKC activity inhibits Purkinje cell dendritic growth and branching. In contrast, inhibition of PKC activity thus stimulates Purkinje cell dendritic growth and branching (Fig. 2). PKC is a signaling molecule, which was shown before to determine synaptic function of Purkinje cells, raising the possibility that similar signalling mechanisms are involved in the regulation of synaptic plasticity and dendritic growth. By using different mouse strains deficient for specific isoforms of the Protein kinase C proteins we could attribute the function on dendritic development to the alpha- and gamma-Isoforms of the protein. In ongoing experiments we explore the role of activity and neurotransmitter receptors for the development of Purkinje cell dendritic trees.

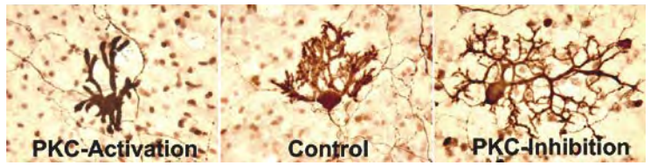


Fig. 2: Cerebellar Purkinje cells develop a typical dendritic tree in organotyic slice cultures (middle, Control). After activation of Protein Kinase C (PKC) the dendritic tree shrinks and loses side-branches (left, PKC-Activation).
In contrast, stimulation of PKC inhibition leads to increased growth and branching of the Purkinje cell dendrites (right, PKC-Inhibition)

Die Regulation des Wachstums von Axonen und Dendriten

Axonale Projektionen bilden gerichtete neuronale Verbindungen im Zentralnervensystem, die entscheidende Bedeutung für die Funktion des Nervensystems haben. Traumatische Verletzungen, Durchblutungsstörungen oder neurodegenerative Krankheiten können diese Verbindungen zerstören. Durch Läsionen unterbrochene Axone wachsen nicht nach und die Funktion der betroffenen Systeme ist verloren. In unserem Labor untersuchen wir die axonale Verbindung zwischen zwei Hirngebieten, dem entorhinalem Cortex und dem Hippokampus. Diese Verbindung kann in Zellkultur in sogenannten organotypischen Schnittkulturen untersucht werden. Wir zeigten, dass Schnittkulturen von Mäusen die Fähigkeit zur Reparatur dieser Verbindung 4-6 Tage nach der Geburt abrupt verlieren. Durch pharmakologische Behandlung mit neurotrophen Faktoren sowie Inhibitoren der Signalmoleküle Protein Kinase C (PKC) und Pertussistoxin konnte die Regeneration verbessert werden. In weiteren Versuchen prüfen wir die Fähigkeit implantierter neuronaler Stammzellen, spezifisch die geschädigte axonale Projektion zu ersetzen.
Ein zweites Arbeitsgebiet unserer Gruppe ist die Entwicklung des Dendritenbaums einer Nervenzelle. Die Form des Dendritenbaums ist ein typisches Merkmal jeder Nervenzelle und von grosser Bedeutung für ihre Funktion. Das Signalmolekül PKC ist hier ein wichtiger Regulator der Dendritenbildung. Stimulierung von PKC hemmt die Ausbildung der Dendriten von Purkinjezellen (den grössten Zellen des Kleinhirns), während eine Hemmung von PKC die Ausbildung des Dendritenbaums fördert. Mit Hilfe von verschiedenen Mausmodellen, denen jeweils ein bestimmter Subtyp des PKC-Moleküls fehlt, konnten wir die Rolle für zwei PKC-Subtypen in der Ausbildung der Dendriten von Purkinjezellen charakterisieren. In weiteren Experimenten untersuchen wir die Rolle von neuronaler Aktivität und der Aktivierung von Neurotransmitterrezeptoren für die Ausbildung des Dendritenbaums von Purkinjezellen.

Selected Publications

- Metzger, F., and Kapfhammer, J.P. (2000) Protein kinase C activity modulates dendritic differentiation of rat Purkinje cells in cerebellar slice cultures. Eur. J. Neurosci., 12, 1993-2005.
- Prang, P., Del Turco, D., Kapfhammer, J.P. (2001) Regeneration of entorhinal fibers in mouse slice cultures is age dependent and can be stimulated by NT-4, GDNF and modulators of G-proteins and protein kinase C. Exp. Neurol., 169, 135-147.
- Schrenk, K., Kapfhammer, J.P., Metzger, F. (2002) Altered dendritic development of cerebellar Purkinje cells in slice cultures from protein kinase Cgamma-deficient mice. Neuroscience, 110, 675-689.
- Radojevic, V., Kapfhammer, J.P. (2004) Repair of the entorhino-hippocampal projection in vitro. Exp. Neurol. 188, 11-19.
- Adcock, K. H., Metzger, F., Kapfhammer, J.P. (2004) Purkinje cell dendritic tree development in the absence of excitatory neurotransmission and of brain-derived neurotrophic factor in organotypic slice cultures. Neuroscience, 127, 137-145.

Mental Health
Brain tumors
GABA
Notch
Neurotransmitter
Knock-out

Synaptic Plasticity

Prof. Dr. Bernhard Bettler
Institut für Physiologie

Group Members
Dr. Martin Gassmann
Dr. Samuel Barbieri
Dr. Emilio Casanova
Dr. Claire-Marie Vacher
Dr. Rejan Vigot
Corinne Haller (technician)
Barbara Biermann (PhD student)
Nicole Guetg (PhD student)

$GABA_B$ Receptor Subtypes as Drug Targets for the Treatment of Anxiety and Depression

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and as such plays a key role in controlling neuronal activity. GABA mediates its action via two receptor systems, the $GABA_A$ and $GABA_B$ receptors. Unlike $GABA_A$ receptors that are ion channels, $GABA_B$ receptors are G-protein coupled receptors (GPCRs) and signal through second messenger systems. Dysfunction of GABA-mediated synaptic transmission in the brain is a cause or a consequence of various neurological and psychiatric disorders. For example, a hypoactivity of the GABA system was proposed to underlie epilepsy, spasticity, anxiety, stress, sleep disorders, depression, addiction and pain. In contrast, a hyperactivity of the GABA system was associated with schizophrenia. The pharmaceutical industry successfully exploited the GABA system and introduced a variety of drugs, such as e.g. the benzodiazepines and barbiturates, to the clinic. Most of these drugs target the $GABA_A$ system, while progress in developing $GABA_B$ drugs was slow. Baclofen (Lioresal®), the only $GABA_B$ drug on the market, is used as a muscle-relaxant to treat spasticity. Baclofen showed therapeutic potential in mental health indications. However, its main therapeutic effect, muscle relaxation, is a severe side-effect when it comes to psychiatric indications. All attempts to develop $GABA_B$ drugs without muscle-relaxant activity failed, which prohibited a more widespread use of $GABA_B$ drugs in man.
To reduce side-effects, a goal in pharmaceutical research is to target drugs selectively to structurally distinct receptor subtypes. The shortage of clinically successful $GABA_B$ drugs was attributed to this lack of subtype-selectivity. In 1997, our laboratory succeeded in cloning the first $GABA_B$ receptors. Revealing a new principle for GPCRs, we showed that $GABA_B$ receptors are not monomeric proteins but instead consist of two distinct subunits. Dimerization between $GABA_{B(1a)}$, $GABA_{B(1b)}$ and $GABA_{B(2)}$ subunits generates two pharmacologically indistinguishable receptor subtypes in the brain, $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$. These subtypes represent the only means for directing the search for novel $GABA_B$ drugs towards molecularly distinct receptor populations. We have started to address the individual functions of $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors by generating knock-out mice that selectively express one, but not the other subtype. Preliminary experiments indicate that these mice exhibit a subset of the phenotypes, i.e. epilepsy, impaired memory, hyperactivity, hyperalgesia and anxiety that we observed in mice expressing no $GABA_B$ receptors at all. Most importantly, we found that the muscle-relaxant effect of baclofen is mediated by only one of the two $GABA_B$ subtypes. This now allows designing $GABA_B$ drugs that dissociate the unwanted side-effects from the therapeutic effects. This will expand the scope of medical applications to hopefully include anxiety and depression. This project is carried out in collaboration with Novartis.

Fig. 1: Co-localization of $GABA_{B(1a)}$ and $GABA_{B(1b)}$ (1a+1b) with $GABA_{B(2)}$ (2) mRNA in rat brain. This highlights that both a $GABA_{B(1)}$ and $GABA_{B(2)}$ subunit is necessary to form a functional receptor.

Notch2 as a Drug Target for the Treatment of Malignant Brain Tumors

Malignant astrocytomas are among the most aggressive brain tumors in man. Screening for genetic alterations in astrocytomas revealed frequent amplifications at the *Notch2* locus. *Notch2* has been linked to cancer before, but never in the etiology of brain tumors. We currently carry out transgenic experiments to clarify whether expression of *Notch2* in mature astrocytes, which normally do not express this protein, causes malignant astrocytomas. Our experiments will reveal whether blocking *Notch2* function represents a valid treatment for this most devastating human disease.

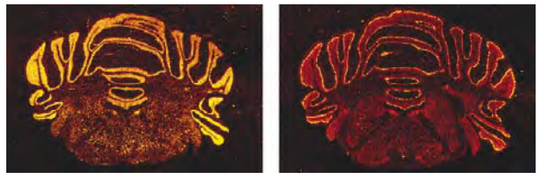


Fig. 2: Differential localization of $GABA_{B(1a)}$ and $GABA_{B(1b)}$ mRNA in the rat cerebellum, indicating that these two subunits fulfill distinct physiological roles.

Tumor Suppressors and Oncogenes Operative in Human Brain Tumors

The research of the Molecular Neuro-Oncology Laboratory is focusing on the genetics of malignant brain tumors of glial origin (gliomas). We conducted several studies about the mutational frequencies in gliomas at the INK4A/ARF locus and of the PTEN gene. These are two critical tumor suppressor loci that are frequently altered during gliomagenesis. In addition, we have identified focal adhesion kinase (FAK) to be overexpressed in invasive malignant gliomas and showed that dominant negative FAK impairs invasion and survival of glioblastoma cells. Moreover, we performed a somatic mapping study on the 10q arm which points to the 10q25-26 region and identified GPR26 as a candidate gene, a novel member of the amine-like receptor subgroup of G protein-coupled receptors, for which no cognate ligand has been identified so far. This gene is inactivated by epigenetic silencing in 50% of GBMs. Furthermore, we performed a somatic mapping study of the 1p arm in different types of gliomas and found that, in oligodendrogliomas, the deletion breakpoint targets the Notch2 gene. The Notch2 protein is not detectable in oligodendrogliomas by immunohistochemistry. In contrast, Notch2 is highly expressed in astrocytoma cell lines and primary malignant astrocytomas. Moreover, the genetic status of the Notch2 alleles appears to allow the prediction of patient survival.

Prof. Dr. Adrian Merlo
Neurochirurgische Klinik
Universitätsspital Basel

Die Rolle verschiedener $GABA_B$ Rezeptoren bei Angst und Depression

Gamma Amino-Buttersäure (γ-aminobutyric acid, GABA) ist der wichtigste hemmende Neurotransmitter (Botenstoff) im Gehirn. Er vermittelt seine Aktivität auf die Nervenzellen über $GABA_A$ und $GABA_B$ Rezeptoren. Störungen des GABA Systems können sowohl Ursache als auch Folge von neurologischen und psychiatrischen Erkrankungen, wie beispielsweise Epilepsie, Spastizität, Angstzustände, Schlaflosigkeit, Depression, Sucht, Schmerz und Schizophrenie sein. Einige bekannte Produkte der Pharmaindustrie zur Behandlung dieser Erkrankungen, wie etwa die Barbiturate und Benzodiazepine, greifen an den $GABA_A$ Rezeptoren an. Baclofen ist zurzeit das einzige Medikament welches über $GABA_B$ Rezeptoren wirkt. Baclofen wird vor allem bei der Therapie von Muskel-Spasmen verwendet. Baclofen kann leider nicht zur Behandlung von psychiatrischen Erkrankungen eingesetzt werden, da Muskelrelaxation für diese Indikationen eine unerwünschte Nebenwirkung darstellt. Bisher ist es leider nicht gelungen, $GABA_B$-Medikamente ohne muskelrelaxierende Wirkungen zu entwickeln. Wir haben 1997/98 die ersten $GABA_B$ Rezeptoren kloniert und konnten zeigen, dass das Gehirn zwei verschiedene Rezeptoren exprimiert. In Zusammenarbeit mit Novartis haben wir Knock-out Mäuse hergestellt, welche die zwei $GABA_B$ Rezeptoren in Abwesenheit des jeweils anderen Rezeptors exprimieren. In einer der beiden Maus-Linien behält Baclofen seine therapeutischen psychiatrischen Wirkungen, praktisch ohne dass dabei Muskelrelaxation eintritt. Damit bietet sich nun ein molekular Ansatz für die Entwicklung von spezifischeren $GABA_B$-Pharmaka, welche auch bei psychiatrischen Erkrankungen eingesetzt werden können.

Selected Publications

- Kaupmann, K., Huggel, H., Heid, J., Flor, P. J., Bischoff, S., Mickel, S. J., McMaster, G., Angst, C., Bittiger, H., Froestl, W. and Bettler, B. (1997) Expression cloning of $GABA_B$ receptors uncovers similarity to metabotropic glutamate receptors. Nature 386, 239-246.
- Kaupmann, K., Malitschek, B, Schuler, V., Heid, J., Froestl, W., Beck, P., Mosbacher, J., Bischoff, S., Kulik, A., Shigemoto, R., Karschin, A. and Bettler, B. (1998) $GABA_B$ receptor subtypes assemble into functional heteromeric complexes. Nature 396, 683-687.
- Schuler, V., Lüscher C., Blanchet, C, Klix, N., Sansig, G., Klebs, K., Schmutz, M,. Heid, J., Gentry, C., Urban, L., Fox, A., Spooren, W., Jaton, A.-L., Vigouret, J.-M., Pozza, M., Kelly, P.H., Mosbacher, J., Fröstl, W., Käslin, E., Korn, R., Bischoff, S., Kaupmann, K., Van der Putten, H. and Bettler, B. (2001) Epilepsy, hyperalgesia, impaired memory and loss of pre- and postsynaptic $GABA_B$ responses in mice lacking $GABA_{B(1)}$. Neuron 31, 47-58.
- Kaupmann, K., Cryan, J.F., Wellendorph, P., Mombereau, C., Sansig, G., Klebs, K., Schmutz, M., Froestl, W., Van der Putten, H., Mosbacher, J., Bräuner-Osborne, H., Waldmeier, P. and Bettler, B. (2003) Specific γ-hydroxybutyrate-binding sites but loss of pharmacological effects of γ-hydroxybutyrate (GHB) in $GABA_{B(1)}$-deficient mice. Eur. J. Neurosci. 18, 2722-2730.
- Bettler, B., Kaupmann, K., Mosbacher, J and Gassmann M. (2004) Structure and function of $GABA_B$ receptors. Physiol. Rev. 84, 835-867.

Brain Tumors
Glioblastoma
Somatic deletion mapping
GPR26
Notch2
PKI inhibitors

Neuro-Oncology

Prof. Dr. Adrian Merlo
Neurochirurgische Klinik
Universitätsspital Basel

Group Members
Dr. Jean-Louis Boulay
Dr. Roland Imber
Dr. Mihai Ionescu
Françoise David (technician)
Beatrice Dolder (technician)
Dr. Elisabeth Taylor (technician)
Balasubramanian Sivasankaran (PhD student)
Viviane Egler (PhD student)
Mike Failly (PhD student)

Human Brain Tumors: From Genetic Alterations to Therapeutic Interventions

On the role of the INK4A/ARF and PTEN locus in human gliomas
Our research laboratory is focusing on the molecular genetics of malignant brain tumors of glial origin (gliomas). During clonal expansion, stochastic selection of growth and survival promoting mutations leads to the outgrowth of ever more malignant clonal tumor cell populations. The consequence of these progressive genetic changes is gain or loss of function, also classified as alterations in oncogenes and/or tumor suppressor genes. Our focus is to identify critical genes and pathways involved in brain tumorigenesis.
We conducted a genetic study about the frequency of homozygous deletions at the INK4A/ARF locus on chromosome 9p21. We compared real-time PCR with microsatellite mapping and fluorescence-in situ-hybridisation (FISH). Homozygous deletions were discovered in nearly half of all glioblastomas. Thus, the INK4A/ARF locus is an important mutational target during gliomagenesis (Fig. 1). Interestingly, this deletion was found to be associated with poor survival in elderly glioblastoma patients. We also analyzed the mutational frequency of PTEN in gliomas and studied the role of PTEN in invasion, using the two highly infiltrative glioma cell lines U87MG (which lacks functional PTEN) and LN229 (wild-type PTEN). Constitutive expression of wild-type PTEN reduced phosphorylation on Ser-473 of PKB/Akt in U87MG cells (Fig. 2). Moreover, we showed that overexpression of PTEN is sufficient to reduce the invasive potential of glioma cells, independently of the phosphatase activity. In addition, we have identified focal adhesion kinase (FAK) to be overexpressed in invasive malignant gliomas and showed that dominant negative FAK impairs invasion and survival of glioblastoma cells.

Identification of *GPR26* and *Notch2* by somatic deletion mapping
A second tumor suppressor region involved in a number of human cancers has been identified on 10q25.3-26. Therefore, we performed a somatic mapping study on the 10q arm which points to the 10q25-26 region, an area that harbors the DMBT1 candidate tumor suppressor gene, which we could not ascertain as a glioma suppressor gene. Instead, we identified GPR26 as a candidate gene, a novel member of the amine-like receptor subgroup of G protein-coupled receptors, for which no cognate ligand has been identified so far. This gene is inactivated by epigenetic silencing in 50% of GBMs (Glioblastomas).

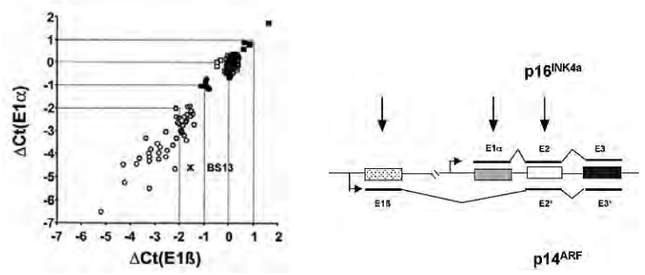


Fig. 1: 50% of glioblastomas display homozygous deletions at the INK4A/ARF locus on chromosome 9p21 as assessed by real time PCR. Exon 1a is plotted against exon1b. Hemizygous deletions cluster around -1, homozygous deletions around -2. The genetic structure of the INK4A/ARF locus is shown on the right. Two entirely different reading frames are transcribed from this complex locus, which are translated into the $p16^{INK4A}$ and $p14^{ARF}$ (in mice $p19^{ARF}$) proteins.

Clinical studies showed that anaplastic oligodendrogliomas clearly respond to conventional chemotherapy, while malignant astrocytomas are chemoresistant. A deletion on chromosome 1p was found to correlate with this characteristic. We performed a somatic mapping study of the 1p arm and found that, in oligodendrogliomas, the deletion breakpoint targets the *Notch2* gene. The *Notch2* protein is not detectable in oligodendrogliomas by immunohistochemistry. In contrast, *Notch2* is highly expressed in astrocytoma cell lines and primary malignant astrocytomas. Moreover, the genetic status of the *Notch2* alleles appears to allow the prediction of patient survival.

A combinatorial strategy against glioblastoma cells
With regard to novel therapeutics, we have set up an in vitro assay system to test single and combinatorial strategies for genetically well characterised glioblastoma cell lines. We test a new generation of protein kinase inhibitors (PKI) against EGFR, KDR, PDGFR and mTOR as well as a histone deacetylase inhibitor and new highly potent cytotoxic drugs (Novartis). The question is, whether biologically active drugs alone or in combination can induce cell death in glioblastoma cells, or whether an additional cytotoxic stimulus is required.

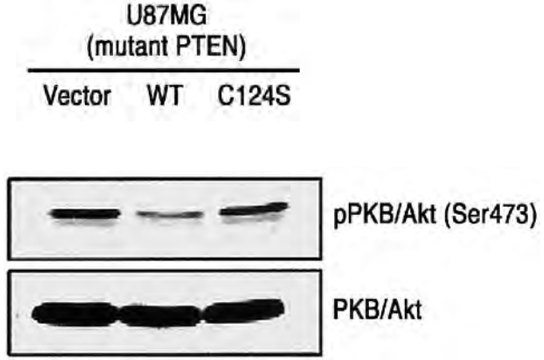


Fig. 2: Expression of wild-type PTEN protein in PTEN-deficient U87 glioblastoma cells dephosphorylates PKB/Akt (Ser-473), whereas expression of the $PTEN^{C124S}$ protein does not.

Genetik und Biologie von Hirntumoren

Im Gehirn können sich Nervenzellen und Stütz- oder Gliazellen nach der Geburt normalerweise nicht mehr teilen, mit Ausnahme von neuralen Vorläuferzellen, die in Verdacht stehen, auch zu Tumoren führen zu können. Tumorzellen unterscheiden sich aber durch eine Reihe von erworbenen genetischen Veränderungen von diesen Vorläuferzellen. Unsere Gruppe befasst sich mit der Identifikation von Genen und deren Signaltransduktionsregelkreise, welche bei der Bildung von Gehirntumoren eine entscheidende Rolle spielen. Auf dem Chromosom 9p21 befindet sich ein für die Krebsentstehung wichtiger Genlokus, der zwei Genprodukte – INK4 und ARF – codiert. Wir fanden in Glioblastomen eine Mutationsrate von etwa 50%. Weiter untersuchten wir die Rolle von PTEN (Phosphatase and Tensin Homolog). PTEN ist ein Protein, das Phosphatgruppen von anderen Proteinen abspaltet und damit deren Aktivität reguliert. PTEN ist häufig in invasiven Glioblastomen durch erworbene Mutationen ausgeschaltet. Dies führt dann z.B. zur Ueberaktivierung der Proteinkinase B (Akt). Neben PTEN spielt auch FAK (focal adhesion kinase) eine wichtige Rolle in der Tumorzellmigration, welches in Glioblastomen überexprimiert wird. Im Rahmen einer strukturellen Analyse von weiteren häufigen Bruchstellen im Genom von Hirntumoren haben wir GPR26 identifiziert, ein G Protein gekoppelter Rezeptor, dessen Ligand noch nicht identifiziert ist. Daneben stiessen wir auf Notch2 auf Chromosom 1p11, welches in Oligodendrogliomen ab-, in Glioblastomen aber angeschaltet ist. Die Analyse dieser Gendefekte hilft neue Regelkreise zu charakterisieren, welche wiederum Ansätze für innovative therapeutische Interventionen liefern können.

Selected Publications

- Merlo A., Bettler B. (2004) Glioblastoma on the move. Science STKE. 229: p 18-19
- Jones G., Machado J., Tolnay M., Merlo A. (2001) PTEN-independent induction of caspase-mediated cell death and reduced invasion by the focal adhesion targeting domain (FAT) in human astrocytic brain tumors which highly express FAK. Cancer Res. 61, 5688-5691.
- Maier D., Jones G., Li X., Schönthal A., Gratzl O., Van Meir E.G., Merlo A. (1999) The PTEN lipid phosphatase domain is not required to inhibit invasion of glioma cells. Cancer Res. 59: 5479-5482.
- Maier D., Zhang Z., Taylor E., Hamou M.F., Gratzl O., van Meir E., Scott R.J., Merlo A. (1998) Somatic deletion mapping on chromosome 10 and sequence analysis of *PTEN/MMAC1* point to the 10q25-26 region as the primary target in low-grade and high-grade gliomas. Oncogene 16, 3331-3335.
- Merlo A., Herman J.G., Mao L., Lee D.J., Gabrielson E., Burger P.C., Baylin S.B., Sidransky D. (1995) 5' CpG island methylation is associated with transcriptional silencing of the tumour suppressor CDKN2/p16 in human cancers. Nature Med., 1: 686-693, 1995.

Neurobiology
Development
Neuromuscular Junction
Muscle
Agrin

Synapse Formation

Prof. Dr. Hans Rudolf Brenner
Institut für Physiologie

Group members
Dr. Alex Blindenbacher
Dr. Pascal Escher
Dr. Eric Lacazette
Dr. Agnieszka Sadowska
Michèle Courtet (technician)
Soizic Carnejac (PhD student)

Signaling Mechanisms Regulating the Formation of the Neuromuscular Junction

Congenital myasthenic syndromes are diseases of the neuromuscular junction (NMJ), the synapse that motor neurons form on skeletal muscle fibers. They cause severe muscle weakness, and some are ultimately lethal. In recent years, an increasing number of these diseases have been linked to various mutations of genes encoding components of the neuromuscular junction. Nevertheless, the molecular events regulating the formation of synapses are only poorly understood.

The billions of synapses formed during development of the nervous system function, in principle, in a similar way as the NMJ. Consensus is that their formation share common mechanisms. Detailed investigation of NMJ formation at the molecular level will thus contribute to understanding not only the etiology of congenital myasthenic syndromes, but will also yield insights into how synapses in the brain are formed. This will be important to understand CNS disorders which are thought to be related to malfunctioning of central synapses. The NMJ is particularly well suited for studies of synapse formation because of its easy experimental accessibility compared to synapses in the brain.

Aim of our research project is to understand the signals exchanged between motor neurons and skeletal muscle fibers and leading to the formation of the neuromuscular junction. Specifically, we investigate the molecular mechanisms by which motor neurons are made to contact muscle fibers, how through this contact they induce the muscle fiber to form a subsynaptic apparatus and how the fiber reciprocates to induce the differentiation of the motor nerve terminal (see Figures).

Two molecules required for NMJ formation are Agrin, a heparansulfate proteoglycan secreted from nerve terminals, and its receptor MuSK expressed by the muscle. We found that Agrin/MuSK are sufficient for the induction of a postsynaptic muscle membrane, including the localized expression of the musk gene by a subset of nuclei located in the synaptic region of the muscle fiber. This involves a novel signaling loop that can maintain MuSK levels at the synapse, a condition for the maintenance of neuromuscular function throughout life (for details, see Fig. 2). The same path can also regulate synaptic acetylcholine receptors (AChR) whose malfunctioning causes different forms of myasthenic syndromes. In fact, this pathway appears more important for the expression of synaptic AChR than a classical path generally thought to regulate AChRs (via neuregulin/ErbB). Our models are currently tested in mouse mutants that we are generating by gene targeting. Motor neurons made to secrete Agrin and muscle fibers overexpressing MuSK are not sufficient for synapse formation, however. Rather, the formation of a neuromuscular contact requires additional muscle factors that are expressed when muscles become electrically inactive, e.g. by denervation. To identify such factors we compare the proteomes of normally innervated and of denervated muscle fibers.

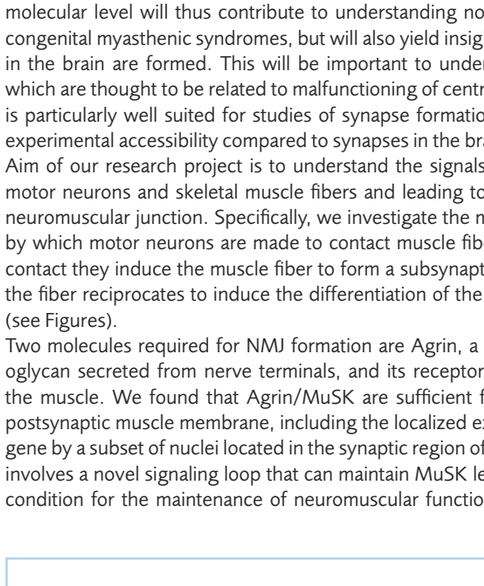


Fig. 1: Top. Schematic of neuromuscular junction. Synaptic (dark coloured) and extrasynaptic nuclei (light coloured) express different sets of genes under neural control. Subsynaptic apparatus including membrane folds is induced by recombinant Agrin.
Bottom: Longitudinal section through skeletal muscle fiber after detection of acetylcholine receptor e-subunit mRNA (arrow: accumulation of silver grains).

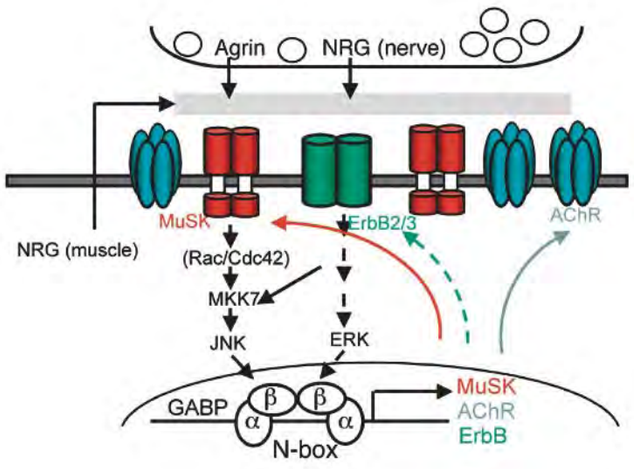


Fig. 2: Model for synapse-specific gene expression under control by the nerve terminal.

Bildung und Erhaltung der neuromuskulären Synapsen

Neuromuskuläre Synapsen (motorische Endplatten) sind die Strukturen, an denen Nerven-Impulse auf die Skelettmuskeln übertragen und damit Muskelbewegungen der Steuerung durch das Gehirn unterstellt werden. Bei neuromuskulären Erkrankungen ist die Impuls-Uebertragung gestört. Solche Defekte verursachen schwere Muskelschwächen, die tödlich sein können. Obschon die genetischen Defekte bei einer Vielzahl dieser Erkrankungen identifiziert wurden, ist über die molekularen Mechanismen der Synapsenbildung noch wenig bekannt. Ihre Untersuchung ist daher für das Verständnis von Uebertragungsstörungen und die Entwicklung neuer Therapieansätze von zentraler Bedeutung. Wegen vermuteter Gemeinsamkeiten zwischen den neuromuskulären und zentralen Synapsen im Gehirn können sie aber auch für das Verständnis von Störungen des Zentralnervensystems relevant sein. Wir untersuchen den Austausch der Signale zwischen Motoneuronen und Skelettmuskelfasern, die zur Bildung von neuromuskulären Synapsen führen, insbesondere die molekularen Mechanismen, welche die Neuronen dazu bringen, mit Muskelfasern in Kontakt zu kommen und wie durch diesen Kontakt die Muskelfasern einen subsynaptischen Apparat und die Motoaxone Nervenendigungen ausbilden. Zwei für die Endplattenbildung unerlässliche Signalmoleküle sind das von Nervenzellen gebildete Agrin und dessen Rezeptor MuSK in den Muskelzellen. Wir zeigten, dass Agrin/MuSK ausreichen, um im Muskel die Expression des musk Gens sowie weiterer Gene zu induzieren, die für die Bildung der Endplatte notwendig sind. Ueber einen Signalrückkoppelungs-Mechanismus wird dabei die ausreichende Expression von MuSK und Acetycholin-Rezeptoren und damit die Funktionstüchtigkeit der Endplatte auf Lebzeiten gesichert. Die Kontaktaufnahme zwischen Motoneuron und Muskelfaser selber erfordert aber noch weitere Signale, die v.a. von inaktiven Muskeln gebildet werden. Um diese zu identifizieren, vergleichen wir das Proteinmuster (Proteom) von aktiven mit demjenigen von gelähmten Muskelfasern.

Selected Publications

- Jones, G., Meier, T., Lichtsteiner, M., Witzemann, V., Sakmann, B. and Brenner, H.R. (1997) Induction by agrin of ectopic and functional postsynaptic-like membrane in innervated muscle. Proc.Natl.Acad.Sci. USA 94, 2654-2659.
- Meier, T., Masciulli, F., Moore, C., Schoumacher, F. , Eppenberger, U., Denzer, A.J., Jones, G. and Brenner, H.R. (1998) Agrin can mediate AChR gene expression in muscle by aggregation of muscle-derived neuregulins. J. Cell Biol. 141, 715-726.
- Moore, C., Leu, M., Müller, U. and Brenner, H.R. (2001) Induction of multiple signalling loops by agrin during neuromuscular synapse formation. Proc.Natl.Acad.Sci. USA 98, 14655-14660.
- Naguib, M.B., Flood, P., McArdle, J.J. and Brenner, H.R. (2002) Advances in the neurobiology of the neuromuscular junction-implications for the anesthesiologist. Anesthesiology 96, 202-231.
- Lacazette, E., Le Calvez, S., Gajendran, N. and Brenner, H.R. (2003) A novel pathway for MuSK to induce key genes in neuromuscular synapse formation. J. Cell Biol. 161, 727-736.

Interleukin-6
Neuroprotection
Neurodegeneration
Signaling
Transgenic animals

Molecular Neurobiology Neural-Immune Interactions

Prof. Dr. Uwe Otten
Institut für Physiologie

Group Members
PD Dr. Dieter Kunz
Dr. Pia März
Martine Schwager (technician)
Béatrice Dimitriades-Schmutz (technician)
Daniela Thommen (PhD student)
Christelle Augé (PhD student)

The Role of Interleukin-6 (IL-6) in Neuroprotection and Neurodegeneration

Interleukin-6 (IL-6) and related cytokines play a key role in inflammation and immune responses. In addition, IL-6 exerts specific effects in the central nervous system (CNS). Transcripts for IL-6 and its receptor have been detected in various brain regions.
IL-6 can have completely opposite activities on neurons promoting either neuronal survival or contributing to neurotoxicity. Many of these effects can be explained by the unique feature of the IL-6 receptor complex.
IL-6 actions are mediated by cellular receptors, which upon dimerization and interaction with the signal transducing component gp130 induce signal transduction through the JAK/STAT pathway. IL-6 also binds to a soluble form of the IL-6 receptor (s-IL-6 R) which can transfer IL-6 responsiveness to cells which are devoid of membrane-bound receptor. This new signaling principle called "trans-signaling" is characteristic for neurons and glial cells.
At present, we know little about IL-6-regulated genes/gene products and the mechanisms contributing to the physiological or pathophysiological functions of IL-6- type cytokines in the CNS.
Our research is directed towards elucidation of the mechanisms involved in IL-6-mediated events.

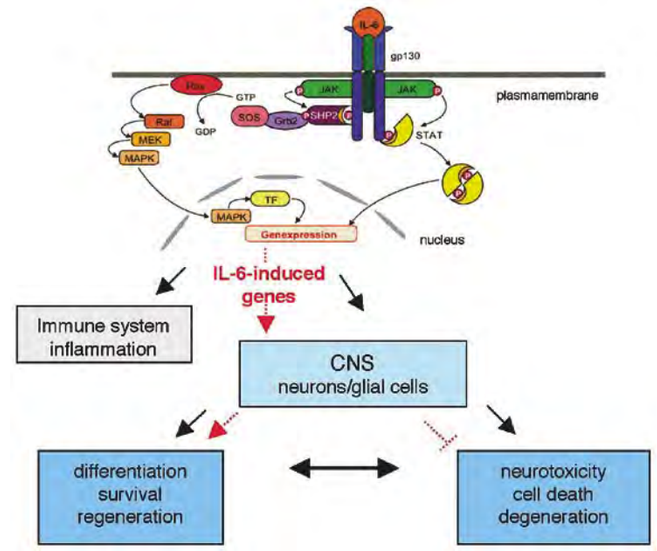
a) neuroprotection
b) neurodegeneration in chronic inflammatory disorders including Alzheimer's disease (AD)

ad a) Using genechip technology induction of gene expression in neuronal targets by IL-6/s IL-6 R was monitored. Promising IL-6-induced candidate genes have been identified. Strategies are being developed to define the cellular origin and function of these gene products. Elucidation of the molecular mechanisms involved in neuronal differentiation and plasticity should help to develop new therapeutic concepts (see Fig.).

ad b) Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder affecting the elderly population. A hallmark of this disorder is the accumulation of amyloid-β protein in the brains of diseased patients resulting in an inflammatory response leading to neuronal dysfunction and death. IL-6 has been implicated in the cascade of events leading to Alzheimer's dementia. In order to unravel the role of IL-6 in AD pathogenesis it is necessary to generate a transgenic animal model of AD which overexpresses h-amyloid-β precursor protein (APP) + human presenilin-2 with deficiency in IL-6. These animals should help to answer the following key questions:

1) does IL-6 deficiency alter the formation of amyloid plaques in the CNS?
2) is the time-course of plaque formation altered by lack of IL-6?
3) is glial activation, notably microglial activation, significantly affected by IL-6?
4) does IL-6 deficiency affect death or survival of neuronal subpopulations in brain?

Our research is performed in collaboration with the groups of:
Proff. Dr. R. Nitsch/Dr. C. Hock, Division of Psychiatric Research, University of Zürich
Prof. Dr. F. Müller-Spahn, Psychiatrische Universitätsklinik, Universität Basel
Prof. Dr. S. Rose-John, Dept. of Biochemistry, University of Kiel
Prof. Dr. M. Jucker, Institut für Pathologie, Universität Basel
Prof. Dr. C. Nitsch, Anatomisches Institut, Universität Basel
Prof. Dr. I. Campbell, Mol. Biol. School of Molecular and Microbial Biosciences, University of Sidney
PD Dr. H. Langen, Roche Center for Medical Genomics, Basel
Dr. M. Staufenbiel, Novartis Neuroscience, Basel



Investigation of IL-6-mediated mechanisms of neuroprotection: Analysis of IL-6-induced genes
Interleukin-6 (IL-6) binds to its specific receptor leading to dimerisation of gp130 molecules and intracellularly to activation of different tyrosine kinases (JAK- and MAP-kinases), resulting in phosphorylation of transcription factors (TF) of the STAT-family. In the CNS, IL-6 elicits both neuroprotective and neurotoxic effects. It is not clear, which target genes are involved in the neuron-specific actions of IL-6.

Funktionelle Bedeutung neuer Interleukin-6 (IL-6)–induzierter Gene/Genprodukte für Neuroprotektion und Neurodegeneration

IL-6 artige Zytokine mediieren sowohl neuroprotektive als auch neurotoxische Effekte im Zentralnervensystem (ZNS). Obwohl die intrazellulären IL-6 Signaltransduktionswege detailliert untersucht sind, ist bisher unverstanden, welche Zielgene die neuron-spezifischen Wirkungen von Zytokinen wie IL-6 vermitteln.
Mittels moderner "gene chip array" Technologie haben wir verschiedene "candidate genes" wie pancreatitis-associated protein-1 (PAP1) und Ataxin 10 identifiziert, die mit neurodegenerativen Erkrankungen wie M. Alzheimer und Spinozerebellärer Ataxie Typ 10 assoziiert sein könnten.
Ziel unseres Forschungsvorhabens ist es, mit Hilfe neuester molekularer und zellbiologischer Methoden wie z.B. der small interfering RNA (siRNA)-Technologie und definierten Zellkultursystemen für ZNS Neurone und Gliazellen sowie IL-6 transgenen Tiermodellen für neurodegenerative Erkrankungen die spezifische funktionelle Bedeutung IL-6-induzierter Gene/Genprodukte für Neurone des ZNS aufzuklären.
Erforschung der molekularen Mechanismen, die den neuroprotektiven und neurotoxischen Wirkungen von IL-6 induzierten Genen im ZNS zugrunde liegen, könnte die Basis für neue therapeutische Ansätze bei neurodegenerativen Erkrankungen sein.

Selected Publications

- März, P., Chen, J., Gadient, R.A., Patterson, P., Stoyan, T., Otten, U., Rose-John, S. (1998) Sympathetic neurons can produce and respond to interleukin-6. Proc. Natl. Acad. Sci (USA) 95: 3551-3556.
- Hock, C.,Heese, K., Müller-Spahn, F., Huber, P., Riesen, W., Nitsch, R.M. and Otten, U. (2000) Increased CSF levels of nerve growth factor in patients with Alzheimer's disease. Neurology 54: 2009-2011.
- Otten, U., März, P., Heese, K., Hock, C., Kunz, D. and Rose-John, S. (2001). Signals regulating neurotrophin expression in glial cells. Prog. Brain Res. 132: 545-554.
- März, P., Oezbek, S., Fischer, M., Voltz, N., Otten, U. and Rose-John, S. (2002). Differential response of neuronal cells to a fusion protein of ciliary neurotrophic factor/soluble CNTF-receptor and leukemia inhibitory factor. Eur. J. Biochem. 269: 3023-3031.
- März, P., Probst, A., Lang, S., Schwager, M., Rose-John, S., Otten U. and Özbek, S. (2004) Ataxin-10, the SCA 10 neurodegenerative disorder protein, is essential for survival of cerebellar neurons. J. Biol. Chem. 279: 35542-35550.

Cerebral Ischemia
Neuroprotection
17-estradiol
Red Wine Polyphenols
Brain Injury
Hypothermia

Neurosurgery

Prof. Dr. Otmar Gratzl
Neurochirurgische Klinik
Universitätsspital Basel

Group members:
Dr. Marie-Françoise Ritz
Petra Schmidt (technician)
Yann Curin (PhD student)

The Neuroprotective Effects of 17-Estradiol and Red Wine Polyphenols against Stroke Induced Damage in a Model of Transient Ischemia in Rats.

Focal decrease of cerebral blood flow during stroke produces rapid brain cell death induced by a complex neurotoxic cascade of events. In developed countries, stroke is one of the leading causes of death and neurological impairment and its number is growing rapidly, due to ageing of the population. In subjects with established cardiovascular disease, consideration is now given to a range of secondary preventive steps with proven success. These include the administration of antihypertensive drugs, anticoagulants (aspirin), diuretics and a series of lifestyle adaptations. An important challenge, however, will be to find ways to reduce the damaging effects of stroke once it has occurred in order to minimize pain and disability of patients. Despite the completion of a number of clinical trials investigating neuroprotective agents with various mechanisms of action, as yet no truly effective agent has been identified, probably because the neuroprotective agents studied so far target only a single specific pathway of the complex ischemic cascade.
During ischemia, the cascade of biochemical events is initiated by the reduction of blood flow and leads to an increase in extracellular excitatory amino acid concentration (excitotoxicity), to the formation of free radicals and nitric oxide, to the activation of proteases, and finally to mitochondrial dysfunction and apoptosis.
Recent evidence suggests that estrogens and polyphenols are important neuroprotective players in the cerebrovascular pathophysiologic context, therefore, therapeutical approaches using these agents in the acute stage of stroke are of great interest.
Using intracerebral microdialysis monitoring, we showed that 17-estradiol injection at the onset of the middle cerebral artery occlusion in male rats (the clinically relevant model for human stroke) is able to significantly reduce the efflux of the excitotoxic amino acids glutamate and aspartate (Figure 1). This effect allows cellular survival and a tremendous reduction of the cerebral infarct (Figure 2). 17-estradiol also possesses antioxidative, anti-apoptotic and anti-inflammatory properties that may contribute to its brain-protective role in the context of ischemia. Both prolonged and short-term administration of polyphenols extracted from red wine to rats with cerebral ischemia protects brain cells mainly by vasodilatatory effects. We showed that chronic treatment induced a general enlargement of the arteries in rats, therefore reducing the risk of an occlusion of the small cerebral vessels (Figure 3). A beneficial effect on the efflux of amino acids is also observed after acute treatment with polyphenols.

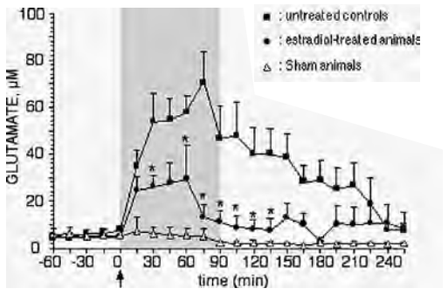


Fig. 1: One single injection of 17 -estradiol in rats (depicted by the arrow) during the occlusion of the middle cerebral artery (gray bar) reduces the efflux of glutamate in the extracellular fluid. *: p 0.05 compared with operated but untreated controls. Sham animals are controls in which the middle cerebral artery was not occluded.

Effects of 17-estradiol and polyphenols on brain energy metabolism, on their role in free radical scavenging and on changes in specific protein expression are also investigated in our laboratory. The molecular mechanisms involved are investigated with the help of transgenic mice (estrogen receptors knock-out mice).
A drug for the treatment or prevention of stroke-induced damage will only be beneficial if the therapeutic time-window for its application is sufficient to enable treatment of patients coming to the critical care unit. Estradiol may also exert its neuroprotective effect on cerebral metabolism after the onset of ischemia and during reperfusion. The therapeutic time window and the optimal doses of 17-estradiol and polyphenol for post-ischemia intervention are being determined in order to be able to significantly improve the recovery of patients in the future.

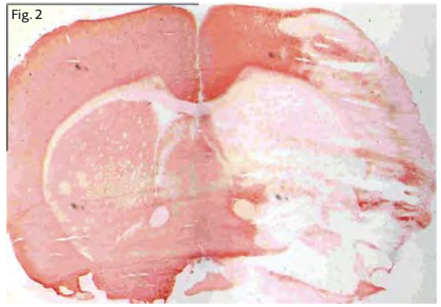


Fig. 2: The unstained brain region depicts the ischemic infarct, where all cells are damaged. Acute treatment with 17-estradiol reduces this area by 50%.

Fig. 3: Measurements of the internal diameters of the rat arteries (solidified by the injection of methyl-methacrylate) indicated that chronic polyphenol consumption for one week induces sustained vasodilation, hence diminishing the risk to have an occlusion.

Clinics

In patients with severe brain injury, the final outcome depends on both the extent of the original damage and on the later appearance of secondary lesions. Microdialysis is the only minimally invasive method currently available for continuous monitoring of metabolites in the brain extracellular fluid. Results of such a monitoring should cast light on the origin of the lesions and enable effective therapy. We have therefore developed a transcranial screw with four lumina, which enables multiparametric monitoring of the traumatized brain (Fig. 4).
In a current project we are investigating the neuroprotective effect of moderate hypothermia on cerebral metabolism and its relation with the outcome of severe head injured patients.

PD Dr. Aminadav Mendelowitsch
Departement Forschung
Universitätsspital Basel

Fig. 4: a. Instrumentation used for the 4-way screw, together with the screw. b: The four lumen screw with ICP catheterm microdialysis and paratrend sensors.

Oestrogene und Rotweinextrakte als neuroprotective Substanzen

In entwickelten Ländern gehört der Schlaganfall zu den häufigsten Todesursachen und zu den häufigsten Ursachen für Behinderungen neurologischer Art. Bei Patienten mit bekannten kardiovaskulären Krankheiten sind nun effiziente, sekundäre Präventivmassnahmen bekannt. Diese umfassen die medikamentöse Behandlung von Bluthochdruck, die Einnahme von Koagulationshemmern (Aspirin) und Diuretika, sowie eine Reihe von Massnahmen der Lebenshygiene. Dennoch lassen sich durch diese Massnahmen lange nicht alle Schlaganfälle verhindern. Es ist eine grosse Herausforderung, nun Behandlungsformen zu finden, mit denen sich die Folgen des Schlaganfalls, die Schmerzen und die Behinderungen abwenden oder zumindest begrenzen lassen. Der Schlaganfall ist ein lokalisierter Unterbruch der Gehirndurchblutung (Ischemie) der zum raschen Zelltod und so zum Verlust von Nervenzellen führt. Der Zelltod wird durch eine Kaskade von Reaktionen hervorgerufen. Es ist bisher nicht gelungen Medikamente zu finden, welche die Nerven vor der Zerstörung schützen können. Zu den durch Ischemie induzierten Reaktionen gehören die Ausschüttung der sog. exitatorischen Aminosäuren und die Bildung von freien Radikalen und von Stickoxid. Oestrogene und Polyphenole aus Rotwein sind potentiell neuroprotektive Substanzen. Wir haben festgestellt, dass sich die Ischämie-bedingte Ausschüttung der exitatorischen Aminosäuren, sowohl durch Oestrogen als auch durch Rotwein-Polyphenole vermindern lässt (Fig. 1). Mit Hilfe von Ratten, die einem künstlichen Schlaganfall unterworfen werden, erforschen wir die Effekte dieser Substanzen im Detail. Rotwein-Polyphenole schützen zudem vor Schlaganfällen durch eine allgemeine Gefässerweiterung (Fig. 3). Wir haben auch eine transcraniale Mikrodialysesonde entwickelt, mit der sich die verschiedenen Parameter der Veränderungen nach einem Schlaganfall oder nach einem Gehirntrauma verfolgen lassen. Damit konnten wir zeigen, dass sich die Veränderungen in diesen zwei Fällen deutlich unterscheiden.

Selected Publications

- Langemann H, Feuerstein T, Gratzl O, Mendelowitsch A. (2001) Microdialytic Monitoring of Uric and Ascorbic Acids in the Brains of Patients after Severe Brain Injury and during Neurovascular Surgery. J. Neurol. Neurosurg. Psychiatry 71: 169-174.
- Langemann H, Alessandri B, Mendelowitsch A, Feuerstein T, Landolt H, Gratzl O. (2001) Extracellular levels of Glucose and Lactate measured by quantitative Microdialysis in the Human Brain. Neurol. Res. 23: 531-536.
- Feuerstein TH, Langemann H, Gratzl O, Mendelowitsch A. (2000) A four lumen screwing device for multiparametric brain monitoring. Acta. Neurochir. (Wien)142, 909-12.
- Mendelowitsch, A., Ritz, M.F., Ros, J., Langemann, H. and Gratzl, O. (2001) 17beta-Estradiol reduces cortical lesion size in the glutamate excitotoxicity model by enhancing extracellular lactate: a new neuroprotective pathway. Brain Res. 901, 230-6.
- Ritz, M.F., Schmidt, P. and Mendelowitsch, A. (2002) 17beta-estradiol effect on the extracellular concentration of amino acids in the glutamate excitotoxicity model in the rat. Neurochem. Res. 27, 1677-83.

Myelin
Multiple Sclerosis
Peripheral Neuropathy
Membrane Domains
Autoimmune Disease
Neuroprotection

Neurobiology

PD Dr. Nicole Schaeren-Wiemers
Departement Forschung
Universitätsspital Basel

Group Members
Dr. Michael Erb
Dr. U. Graumann
Beat Erne (technician)
Frances Kern (technician)
Chantal Urdieux (technician)
Thomas Zeiss (PhD student)
Bettina Flück (PhD student)
Andres Buser (PhD student)

Molecular Mechanisms of Myelin 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 biochemically distinct way (Fig. 1). The focus of our research is the characterization of the molecular mechanisms of myelin formation and maintenance, and their regenerating capacity in major demyelinating diseases such as Multiple sclerosis (MS) and peripheral neuropathies.
We study the molecular and cellular mechanisms regulating the coordinated expression and translocation of myelin constituents to the different compartments during development and in the adult. The detergent-insoluble glycolipid-enriched microdomains, called rafts, are thought to serve as a platform for the polarized delivery of specialized plasma membrane structures in epithelial and also in myelinating cells. The "myelin and lymphocyte protein" (MAL) is a major player in polarized sorting mechanisms in epithelial cells. We have identified and characterized MAL in myelinating cells, and shown that MAL is exclusively localized in rafts of myelin membranes. Genetic ablation of mal in mice resulted in cytoplasmic inclusions within the compact myelin, in paranodal loops that were everted away from the axon and in disorganized transverse bands at the axon-glial junction in the adult CNS (Fig. 2). These structural changes were accompanied by a marked reduction of the paranodal proteins Caspr, Neurofascin 155 (NF155) and juxtaparanodal of potassium channel Kv1.2, while nodal clusters of sodium channels were unaltered. Developmental analysis revealed that initial node formation appeared normal in mal -/- Mice, but got altered at a stage, paralleling the onset of MAL expression in the controls. Biochemical analysis showed that MAG, MBP and NF155 protein levels were reduced in myelin and in myelin-derived rafts. These results demonstrate a critical role for MAL in the maintenance of the CNS axo-glial junction and the nodal environment, most likely by controlling the trafficking/sorting of NF155 and other membrane components in oligodendrocytes.
Parallel to these studies, we characterized the functional role of the two splicing variants of the myelin-associated glycoprotein (MAG), L- and S-MAG. For a better differentiation of the two isoforms, we generated a genomic construct in which the coding sequence for the green fluorescent protein (GFP) was introduced. Thereby, we could demonstrate the S-MAG expression was regulated by cAMP. A transgenic mouse line, which expresses the S-MAG isoform fused to GFP, allows us now to characterize the cellular and spatial regulation of both isoforms separately (Fig. 3).

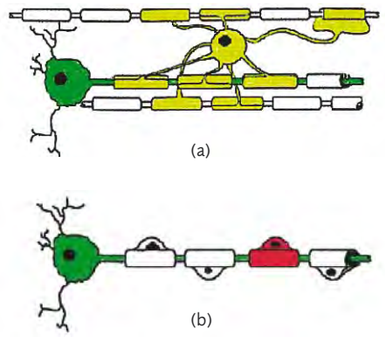


Fig. 1: Schematic drawing of (a) CNS and (b) PNS myelination. The neurons with their axons are shown in green. The oligodendrocytes (yellow) generate the myelin sheaths in the CNS and the Schwann cells (red) in the PNS.

Multiple sclerosis (MS) is a chronic demyelinating disease of the CNS. The molecular mechanisms of lesion formation is still unknown. We performed a microarray study in which we compared the expression pattern of normal apperaring subcortical white matter from MS and control patients. The genes that were upregulated in MS patients indicate the occurrence of oxidative stress, but also of many neuroprotective mechanisms. Our data introduce novel concepts of the molecular pathogenesis of MS with ischemic preconditioning as a major mechanism for neuroprotection. A deeper understanding of the underlying mechanisms is required for the development of new and more specific treatments to protect residing cells and thus minimize progressive oligodendrocyte and axonal loss.

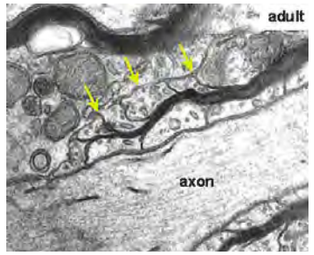


Fig. 2: Paranodal loops (arrows) that are everted away from the axon in MAL-deficient mice

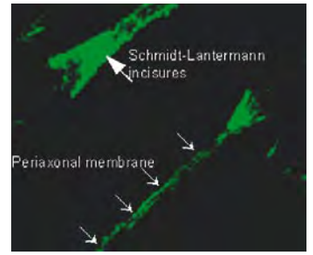


Fig. 3: GFP-Autofluorescence of S-MAG-GFP fusion protein specifically localized in Schmidt-Lantermann incisures and periaxonal membranes

Clinics

Primary demyelinating peripheral neuropathies can be inherited or the result of an autoimmune reaction to myelin components. Although the causes of these diseases are known and the pathophysiology well documented, the molecular mechanisms of the myelin disturbance is still poorly understood. One of the most common autoimmune mediated demyelinating neuropathies is the anti-MAG M-IgM polyneuropathy. We showed that the monoclonal IgM antibodies bind to specific myelin epitopes and that they can penetrate into the myelin sheath. Further, we have localized IgM antibodies on the basal membrane of peripheral nerve fibers. In a recent study, we investigated the presence of IgM deposits in dermal myelinated nerve fibers. Skin biopsies from 14 patients with anti-MAG neuropathy, 8 patients with CIDP (chronic immune demyelinating polyneuropathy), and 2 patients with IgM paraproteinemic neuropathy were compared. MAG positive fibers with IgM deposits were found in all anti-MAG neuropathy patients. IgM deposits were located throughout the length of the fibers as well as at the paranodal loops and on the basal membrane. CIDP and IgM paraproteinemic neuropathies did not show any myelinated fiber with IgM deposit. In summary, we demonstrated that in anti-MAG neuropathy, specific IgM deposits are also found in cutaneous myelinated sensory fibres. Therefore, skin biopsy provides a useful, minimally traumatic method for early diagnosis and, possibly, to monitor the follow-up in patients with an anti-MAG neuropathy.

Prof. Dr.
Andreas J. Steck
Departement Neurologie
Universitätsspital Basel

Myelin – der Schutz der Nervenfasern

Die Myelinscheide ist eine spezielle Membran, welche Nervenfasern im Gehirn und in der Peripherie umhüllt. Ihre isolierende Eigenschaft ermöglicht eine schnelle Leitgeschwindigkeit der elektrischen Nervensignale. Geschädigte Myelinscheiden kommen in der Multiplen Sklerose (MS) und in vielen peripheren Neuropathien vor. Die Bildung der Myelinscheide bedingt koordinierte Expression und korrekte Eingliederung von Myelin-Bestandteilen. Wir konnten nachweisen, dass das MAL-Protein im Nervensystem ausschliesslich in Myelinmembranen zu finden ist. Dort scheint dieses in speziellen zellulären Transportmechanismen von bestimmten Membrandomänen eine zentrale Rolle zu spielen. Mit transgenen Mäusen, welche kein MAL bilden können, zeigten wir, dass MAL die korrekte Eingliederung bestimmter Myelinbestandteilen kontrolliert und dadurch eine wichtige Rolle für die Erhaltung der Nervenfaser-Myelin Interaktion hat.
Die MS Erkrankung führt zu einem chronischen Zerfall des Myelins im Zentralnervensystem. Mit Gen-Chips untersuchten wir die molekularen Mechanismen in MS Hirngeweben, welche auch nach langer Krankheitsdauer nicht geschädigt waren. Wir zeigten, dass dort viele Gene angeschaltet wurden, die Hinweise darüber geben, dass einerseits krankheitsverursachende Abläufe stattfinden, andererseits auch viele nervenschützende Mechanismen angeschaltet wurden. Detailliertere Erkenntnisse über diese Vorgänge werden Ansätze für neue Therapieformen bringen, um den Verlust der Nervenfunktionen einzuschränken.
MAG ist ein weiteres Protein der Myelinscheide. Eine der häufigsten Myelinerkrankungen der Peripherie ist eine Autoimmunreaktion des Körpers gegen MAG. Immunglobuline des Typs IgM lagern sich dabei an die Myelinscheide. Wir konnten zeigen, dass sich IgM Moleküle, ausschliesslich bei dieser Erkrankung, auch in kleinen Nervenfasern in Biopsien der Haut nachweisen lassen. Dieser neuartige Nachweis ist relativ einfach, bedeutet für den Patienten nur einen kleinen Eingriff und erlaubt eine frühe Diagnose und die Beobachtung des Behandlungserfolges.

Selected Publications

– U. Graumann, R. Reynolds, A.J. Steck, N. Schaeren-Wiemers. (2003). Molecular changes in normal appearing white matter in Multiple Sclerosis are characteristic of neuroprotective mechanisms against hypoxic insult. Brain Patho.13:554-573, .
– M. Erb, A.J. Steck, K. A. Nave, N. Schaeren-Wiemers. (2003). Differential expression of L- and S-MAG upon cAMP stimulated differentiation in oligodendroglial cells. J Neurosci Res. 71: 326-337.
– M. Sollberger, B. Erne, S. Sansano, A.J. Steck, N. Schaeren-Wiemers. (2002). Characterization of human nerve basal lamina for their binding properties of anti-MAG antibodies. J Neurocytol. Jan;31(1):5-14.
– B. Erne, S. Sansano, M. Frank, N. Schaeren-Wiemers. (2002). Rafts in adult peripheral nerve myelin contain major structural myelin proteins and MAL and CD59 as specific markers. J Neurochem. 82: 550-562.
– Empl, M., Renaud, S., Erne, B., Fuhr, P., Straube, P., Schaeren-Wiemers, N., and Steck, A.J. (2001). TNF-alpha expression in painful and non-painful neuropathies. Neurology, 56, 1371-1377.

Multiple sclerosis
Expression profiling
Metabolomics
Antibodies
Matrix metalloproteinases

Clinical Neuro-immunology

Prof. Dr.
David Leppert
Departement Forschung
Universitätsspital Basel

Prof. Dr.
Ludwig Kappos
Abteilung Neurologie
Universitätsspital Basel

Group members
PD Dr. Raija LP Lindberg
Dr. Jens Kuhle
Francine Hoffmann (technician)

Molecular Analysis of Multiple Sclerosis

Gene expression profiling in Multiple Sclerosis and related animal model (DTH) with microarrays
The aim of this work is to define comprehensively altered physiologic pathways at various stages of development of multiple sclerosis (e.g. during the development of lesions, during relapses and remissions) in various tissue compartments. We approach this by studying the gene expression pattern in brain tissue, cerebrospinal fluid (CSF), and peripheral blood mononuclear cells (PBMC) from MS patients, and in brain tissue in the delayed-type hypersensitivity (DTH) model of MS. The goals are the following: 1) to define an array of genes that are related to susceptibility and the course of disease with the perspective for the use as diagnostic markers, and 2) to define MS differentially regulated genes, but not known to participate in its pathogenesis. We are also investigating the effects of current treatments of MS, e.g. IFN-β and Natalizumab, on gene expression profiles in blood to define markers for treatment efficacy in order to identify responders and non-responders.
In brain tissue from MS, inflammatory changes are not confined to plaques but appear as a continuum of cellular and humoral immune response between acute lesions and surrounding normal appearing white matter (NAWM). The two tissue compartments distinguish by a stronger up-regulation of genes related to cellular immune response in normal appearing white matter, while genes related to synthesis of immunoglobulins and regulation of B-cells were more prevalent in acute lesions. These results challenge the concept of MS as a focal disease. They are in line with recent MRI findings of generalized brain atrophy and extralesional changes in the normal appearing white matter indicating of neuronal loss and diffuse water accumulation. A group of genes has been found to be differentially expressed in PBMC of untreated MS patients in remission as compared to age and gender matched healthy volunteers.
Since the availability of early stage and longitudinal samples of MS tissue is scarce, we used an experimentally-induced, delayed-type-hypersensitivity (DTH) model of MS for gene expression profiling studies. We have examined the development of lesions at Day 0, 5, 12, and 31 after peripheral sensitization with BCG by gene expression profiling with microarrays, and compared it with that of tissue in the vicinity of the lesion, and in the opposite hemisphere. We found 48 genes upregulated, and 25 genes downregulated at a certain time point and tissue compartment. The most prominent feature is the increased expression of TNF-related receptors and FAS ligand, suggesting the importance of the TNF-pathway in the development of DTH lesions.

The pathogenetic role of matrix metalloproteinases and their regulators in multiple sclerosis (MS)
Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that act as effectors of parenchymal invasion by immune cells and tissue destruction during inflammation. Based on our previous work it is now accepted that the beneficial effect of IFN-β on the course of MS results from its downmodulatory effect on MMPs in T-cells. The study of the expression pattern of MMPs in cerebrospinal fluid and blood cells during different phases of MS will allow determining the disease relevant targets for future therapy with MMP-inhibitors. We have recently shown that some MMPs are constantly up-regulated in cerebrospinal fluid and in brain tissue of MS patients, irrespective of clinical disease activity. Furthermore, MMP-upregulation is present not only in MS plaques, but also in brain tissue that appears to be unaffected by conventional microscopic criteria. These findings also challenge the concept of MS as a focal disease and imply that constant suppression of MMP-activity may be required to ameliorate the course of disease. In collaboration with Drs. E. Waubant and D. Goodkin (UCSF), we have found that serum levels of MMP-9 are increased in secondary progressive MS. Moreover, MMP-9 and its physiologic inhibitor TIMP-1 are related to the occurrence of new gadolinium-enhancing lesions in secondary progressive MS. MxA is a type-I-IFN-induced protein. Although MxA seems not to be directly involved in the pathogenesis of MS, its concentration in serum, and the transcriptional expression in PBMC can be used as a functional marker of IFN-activity. Hence, measurement of MxA allows to monitor functionally the effects of neutralizing antibodies (NAB) against IFN-β, a method we believe being clinically more relevant than the measurement of neutralising antibodies per se, which is notoriously difficult and poorly standardizable.
As IFN treatment decreases MMP-9 and increases TIMP-1, we hypothesize that the decreased effect of IFN due to neutralizing antibodies does not only manifest by decreased serum concentrations of MxA, but also by a lack of, or reduced downregulation of MMP-9 and upregulation of TIMP-1. This has been confirmed as well as the increase of MMP-9 transcripts after the occurrence of NABs quantitatively correlated with the NAB titer (collaboration with Prof A. Bertolotto, Orbassano, Italy).

Metabolite pattern analysis and metabolite identification in CSF and serum of MS patients
Metabolomics is used to determine cellular and systemic biochemical profiles by comprehensive spectroscopic detection and identification of endogenous metabolites in biological samples, mainly body fluids, but also in tissue. The aim of such procedure is to extract latent biochemical information that is of diagnostic and prognostic value, and which reflects 'actual' biological events (real-world end points, biomarkers), as opposed to the potential for such events with measurements of DNA, and mRNA. We have started to use metabolomics technique (1H-NMR) to analyze human CSF samples with different clinical diagnosis, e.g. from MS, inflammatory CNS diseases of non-MS type, tumours, intracranial bleeding, and compared the metabolite profiles to that of control CSF-samples. Preliminary results indicate that the metabolite profile allows defining a specific pattern that distinguishes each disease group. This work aims at analyzing cohorts of MS patients homogeneous for extrinsic (type of therapy) and intrinsic (age, gender, disease state, clinically isolated syndrome (CIS), rrMS, spMS), actual disease activity (relapse, clinically stable) by 1H-NMR spectroscopy. Differential spectral patterns will be searched for specific metabolites differentially expressed, that may be determinants of disease processes in the respective groups.

Myelin oligodendrocyte glycoprotein (MOG) and Myelin basic protein (MBP) antibodies as prognostic markers for patients with Clinically Isolated Syndrome (CIS)
Most of MS patients initially present with a clinically isolated syndrome (CIS), which is caused by inflammatory, demyelinating lesions in the optic nerve, brain stem or spinal cord. Up to 80% of CIS cases progress to clinically definite MS (CDMS) by time. Prognostic indicators for the transition to clinically definite MS are still imprecise. Antibodies against myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) have been found in serum and active lesions of MS patients. We have set up Western blot analysis for MBP and MOG antibodies in serum and CSF (in collaboration with Dr. Markus Reindl, Innsbruck) and could show a high reproducibility of the method in the two labs. Our goal is to evaluate the importance of antiMBP and -MOG antibodies as a prognostic marker for disease activity and progression in well-defined patient cohorts. We are now offering MBP/MOG antibody test for Swiss physicians for clinical use as a lab test in CIS.

Molekulare Analyse der Multiplen Sklerose

Die Multiple Sklerose ist nebst der bakteriellen Meningitis einer unserer Forschungsschwerpunkte. Unser Ziel ist es, in Zusammenarbeit mit Forschern in Bern und Zürich, neue Ansätze für die Diagnostik und die Therapie dieser Krankheiten zu finden.
Wir möchten die veränderten physiologischen Abläufe während den verschiedenen Phasen der Multiplen Sklerose (MS) kennenlernen. Um dies zu erforschen untersuchen wir, welche Gene in verschiedenen Geweben von MS Patienten und MS Tiermodellen angeschaltet sind. Wir konzentrieren uns dabei auf zwei Gruppen von Genen. 1. Gene die wir mit der Pathogenese von MS in Zusammenhang bringen können und die daher für die Diagnostik von Bedeutung sein könnten 2. Gene die bei MS auffallend reguliert sind, von welchen aber ein Zusammenhang mit dem Krankheitsverlauf bislang nicht bekannt ist. Unter diesen könnten einige Ziele für neuartige Therapieansätze liefern.
Matrix-Metalloproteinasen (MMPs) sind Enzyme, die Proteine spalten. Diese spielen eine Rolle bei der Gewebezerstörung während Entzündungsreaktionen. Einige dieser MMPs sind im Gehirn von MS Patienten dauernd hochreguliert, unabhängig vom klinischen Zustand des Patienten und dies im ganzen Gehirn, d.h. auch in Regionen, welche frei von MS bedingten Plaques sind. Dieser Befund weist darauf hin, dass MS nicht eine Krankheit ist, deren Äusserung sich auf gewisse Regionen des Gehirns konzentriert. Eine konstante Unterdrückung der MMP Aktivität könnte sich positiv auf den Verlauf der Krankheit auswirken.
In einem weiteren Ansatz prüfen wir das metabolisch-biochemische Muster von z.B. MS Geweben im Vergleich zu gesunden Geweben. Dieser Ansatz, Metabolomics genannt, gibt Auskunft über den aktuellen Zustand des Gewebes. Mit diesen Informationen lassen sich Krankheitsverlauf und die Wirkung von Therapien verfolgen.

Selected Publications

- Leppert D, Lindberg RLP, Kappos L, Leib SL. (2001) Matrix metalloproteinases: multifunctional effectors of inflammation in bacterial meningitis and multiple sclerosis. Brain Res Rev 36, 249-257.
- Waubant E, Goodkin D, Bostrom A, Bacchetti P, Hietpas J, Lindberg R, Leppert D. (2003) IFN beta lowers MMP-9/TIMP-1 ratio which predicts of new gadolinium enhancing lesions in secondary progressive multiple sclerosis. Neurology 60, 52-57.
- Gilli F, Bertolotto A, Sala A, Hoffmann F,Capobianco M, Malucchi S, Glass T, Kappos L, Lindberg RLP, Leppert D. (2004) Neutralizing antibodies against IFN-beta in multiple sclerosis: antagonization of IFN-mediated suppression of MMPs. Brain 127, 259-268.
- Lindberg RLP, De Groot CJA, Certa U, Ravid R, Hoffmann F, Kappos L, Leppert D. (2004) Multiple sclerosis as a generalized CNS disease – comparative microarray analysis of normal appearing white matter (NAWM) and lesions in secondary progressive MS.J Neuroimmunol 152 154-167
- Leppert D, Martin R. (2004) A Plea for "Omics" Research in Complex Diseases such as Multiple Sclerosis – A Change of Mind is needed. J Neurol Sci 222, 3-5

DKBW Schwerpunkt Zellplastizität und Gewebereparatur

Professor R. Zeller
Institut für Anatomie

Professor A. Gratwohl
Abteilung Hämatologie
Universitätsspital Basel

Der Forschung an embryonalen und adulten Stammzellen wird zurzeit grosse Beachtung geschenkt. Dies vor allem wegen ihrer Eigenschaft sich in verschiedene, von einander unabhängige Zelltypen entwickeln zu können. Diese Vielfältigkeit lässt hoffen, dass therapeutische Anwendungen von Stammzellen neue Möglichkeiten in der Behandlung von kranken Geweben und Organen eröffnen werden.

Eine beachtliche Anzahl Forschungsgruppen des DKBW hat sich in den letzten Jahren mit der Erforschung von Grundlagen sowie klinisch relevanten Aspekten der Stammzellenbiologie und -therapie beschäftigt. Mehrere Gruppen untersuchen dabei hämatopoietische Stammzellen aus Menschen oder Mäusen im Hinblick auf ihr Differenzierungspotential und ihre Nützlichkeit in verschiedenen therapeutischen Anwendungen wie z.B. neue Ansätze der Therapie von Autoimmunkrankheiten.

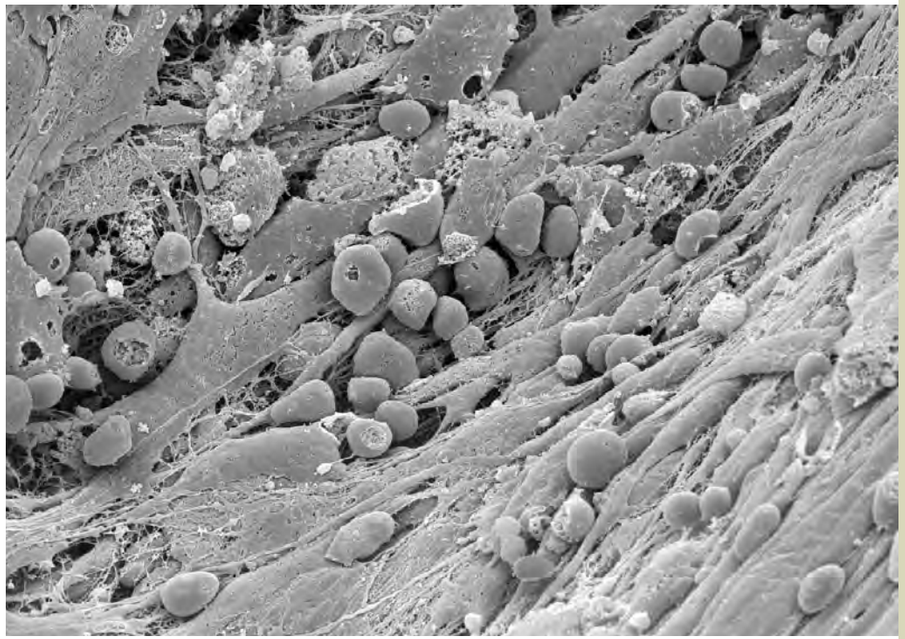
Ausserdem wurde in Basel eine Nabelschnurbank mit Stammzellen von Neugeborenen angelegt. Andere Forscher widmen sich der in vitro Züchtung von Gewebe für Knorpel- und Knochenersatz.

Trotz rascher Fortschritte werden Themen wie die gezielte Differenzierung von Zelltypen, die in vitro Züchtung von Gewebe und die therapeutische Anwendung von Stammzellen weiter intensiv untersucht und auch eingehend diskutiert.

Insbesondere ist es entscheidend herauszufinden, wie der Signalaustausch zwischen den Zellen funktioniert, welcher die Stammzellen dazu veranlasst, sich zu spezifischen Geweben zu differenzieren, wie dies während der Embryogenese und bei einer Geweberegeneration geschieht.

Der DKBW Forschungsschwerpunkt «Zellplastizität und Gewebereparatur» stellt sich die Aufgabe die Gundlagenforschung und die Klinik zusammenzubringen um gemeinsam die Lücke zwischen Labor und Krankenbett zu schliessen.

Ein kleiner aber wichtiger Schritt auf dem Weg zu diesem Netzwerk des Wissens ist der «Stammzellen-Club», der als Forum dazu dient, über Forschung zu diskutieren und die Zusammenarbeit voranzutreiben. In Kürze wird dieser neue Schwerpunkt seine Aktivitäten noch erweitern.



Cytokines
Growth Factors
Apoptosis
Cardiomyopathies
Cardiomyocytes
Myofibrillogenesis

Cardiobiology

Prof. Dr. Marijke Brink
Institut für Physiologie
Departement Forschung
Universitätsspital Basel

Group Members
PD Dr. Christian Zaugg
Dr. Dagmar Keller
Dr. Thomas Dieterle
Dr. Silvia Butz
Dr. Isabelle Plaisance
Dr. Vivian Suarez Domenech
Dietlinde John (technician)
Christian Morandi (technician)
Serguei Driamov (PhD student)
Claire Murigande (PhD student)

Effect of Cytokines and Growth Factors on Cardiomyocyte Architecture and Function

Much as skeletal muscle grows with progressive weight training, the myocardium responds to increased mechanical load by compensatory hypertrophy, i.e. increasing size and mass of its myocytes. Autocrine insulin-like growth factor (IGF)-I production contributes to hypertrophy in both muscle types, as it is required for protein synthesis and myofibril formation. In the heart, stress stimuli such as ischemia or hypertension cause the release of various other factors that on the short term preserve its function, but when acting for extended periods may lead to diminished cardiac output. Ultimately, when myocardial performance becomes insufficient to adequately supply blood to other organs, the disease is referred to as heart failure (HF).
We aim at understanding the mechanisms that cause the progressive change from cardiac hypertrophy to end-stage HF, and hope to contribute to new strategies to prevent or treat this disease. We use the following approaches:
(1) Myocyte cell culture models to analyze molecular mechanisms of cardomyocyte generation from stem cells and of cardiac remodelling, in particular mechanisms whereby cytokines, growth factors, and ion channels modulate contractile-protein turn-over, sarcomere-assembly, and apoptosis.
(2) Animal models of ischemia and heart failure to measure physiological parameters and identify new cardioprotective substances in and ex vivo.
(3) Human molecular genetics to analyze mutations in contractile and ion channel proteins and genotype/phenotype relationships of cardiomyopathies and arrhythmic syndromes.
Common features observed in cardiomyocytes of patients with HF of various etiology are myofibril disarray and apoptosis. Examples of factors that can adversely change cytoarchitecture are angiotensin II (ang II), endothelin-1, and cytokines such as tumor necrosis factor (TNF)-α. Using cardiomyocyte cultures, we analyzed how these factors change the protective activity of IGF-I. IGF's role in cardioprotection may be multiple, in that (1) it promotes protein synthesis and prevents protein degradation, each involving distinct mechanisms but together enhancing myofibril formation, (2) it protects against apoptosis, and (3) it prevents the shift of contractile proteins toward their fetal isoform, usually occuring in cardiac hypertrophy. TNF-α decreased IGFBP-4 mRNA, an inhibitor of IGF-I activity, whereas ang II had no effect, indicating that TNF-α potentiates IGF-I activity in the cardiomyocyte. In contrast, TNF-α blunted immediate IGF-induced Akt phosphorylation, decreased the anti-apoptotic protein Bcl-2 and increased bax, consistent with a pro-apoptotic function (Fig. 1). Thus, TNF-α appears to be a double-edged sword for the cardiomyocyte. Rodent models of heart failure will be used to analyze the role of IGF-I, TNF-α and the activation state of downstream-mediators such as Akt and NFκB, in cardiac remodeling. In addition, an isolated organ Langendorff set-up allows assessment of electro-physiological parameters. Our studies will be extended to analysis of novel potentially protective factors, such as NFκB inhibitors or urocortin II.

Fig. 1: (a) TNF-α decreases IGFBP-4 mRNA in cardiomyocytes isolated from adult rat heart, suggesting the induction of a protective mechanism. (b) TNF-α increases the pro-apoptotic protein bax and decreases the anti-apoptotic bcl-2 in cardiomyocytes.

Clinical relevance of our work in cell culture- and animal-models is assessed using samples from HF patients. In their plasma, significantly lower IGF-I levels were detected than in healthy controls. Stratification for the use of angiotensin converting enzyme (ACE) inhibitors by patients, combined with data from our experimental rat studies has established that low systemic IGF-I is related to increased ang II levels. In contrast, preliminary data shows high levels of IGF-I mRNA in cardiac specimens of HF patients, with IGF-I protein detectable in cardiomyocytes (Fig. 2). The proposed beneficial role of IGF-I to prevent apoptosis and enhance myofibrillogenesis, has led to clinical trials aimed at increasing IGF-I levels, e.g. achieved by growth hormone treatment. The effects of direct IGF-I treatment is analyzed in further clinical investigations.

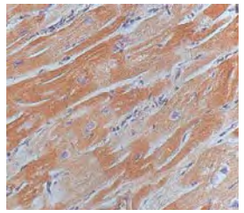


Fig. 2: Immunohistochemical detection of IGF-I in a cardiac specimen from a heart failure patient (brownish staining; cell nuclei are blue). IGF-I is produced in response to increased work load, and may enhance myofibrillogenesis or prevent apoptosis.

Prevention and Therapy of Heart Failure

As a consequence of improved survival of acute coronary disease, valvular and congenital heart disease and changing demographics, heart failure is the main epidemic of the next decades. Diabetes mellitus is the strongest single risk factor for the development of coronary artherosclerosis. Our clinical research aims at optimizing prevention and treatment of coronary artery disease, which accounts for 65 to 70 % of heart failure etiology. The TIME-DIA trial detects asymptomatic coronary artery disease in diabetics and tests if early treatment prevents ischemic events and heart failure. BASKET evaluates if drug eluting stents decrease the rate of ischemic events and repeat revascularization in a real world population with coronary artery disease. The TIME-CHF randomized multicenter trial checks if biomarker guided heart failure therapy in elderly patients improves quality of life and reduce hospitalization rates for decompensated heart failure. In patients with end stage heart failure, can IGF therapy and modulation of the RAAS have a favorable effect on hemodynamics and the sympathoadrenergic receptor expression on myocytes? An ongoing study will give insight into the role of neurohumoral modulation in end stage heart failure. Patients with severe asynchrony of the left ventricle may show dramatic symptom improvement with resynchronization therapy whereas biventricular, multi-site pacing devices are used to improve individual response. Moreover, heart failure with preserved left ventricular function has recently been identified as a major cause for hospitalization of elderly patients with pulmonary edema. To characterize this, echocardiographic, Doppler, Tissue Doppler and strain rate imaging are used as well as to study hemodynamic mechanisms and prevention of the high altitude pulmonary edema at an altitude of 4'500 m. In the Swiss Cardio-Gene Program between Universities of Basel and Lausanne, genetic analysis of the extremely heterogeneous phenotypes of familial hypotrophic cardiomyopathy will help to identify patients with an increased risk for sudden death. A genetic consulting will be institutionalized.

Prof. Dr. Peter Buser
Abteilung Kardiologie
Universitätsspital Basel

Die Wirkung von Wachstumsfaktoren auf den Herzmuskel

Mit progressivem Gewichtstraining lässt sich die Skelett-Muskelmasse vergrössern. Auch der Herzmuskel reagiert auf grössere Belastung mit einer kompensatorischen Hypertrophie, d.h. die Herzmuskelzellen (die Myofibrillen) gewinnen an Grösse und Masse. IGF-I (insulin-like growth factor), ein Wachstumsfaktor, ist in beiden Muskeltypen bei der Entstehung der Hypertrophie beteiligt. Im Herz führen Stressfaktoren wie Ischämie (unzureichende Durchblutung) und Bluthochdruck zur Ausschüttung weiterer Faktoren, welche über kurze Zeit die Funktion des Herzes gewährleisten. Lang andauernde Einwirkung dieser Faktoren führen jedoch zur Verminderung der Herzfunktion und schliesslich zum Herzversagen. Von Herzversagen spricht man dann, wenn das Herz die anderen Organe nur unzureichend mit Blut versorgen kann. Unser Ziel ist, die Mechanismen zu Verstehen, welche von einer Hypertrophie des Herzes schliesslich zum Herzversagen führen um Therapieansätze zu finden, wie man diese Entwicklung verhindern kann. Wir verwenden hierzu:
1. Myozyten Zellkulturen: Damit untersuchen wir die Wirkung von Wachstumsfaktoren auf die Differenzierung der Zellen, auf den Umsatz von Muskelproteinen und den programmierten Zelltod.
2. Tiermodelle und isolierte Organkulturen für Ischämie und Herzversagen um physiologische Parameter zu messen und neue schützende Substanzen zu finden.
3. Menschliche Molekulargenetik: Wir suchen nach unbekannten Mutationen welche Ionenkanäle oder Muskelproteine betreffen und etablieren die Relation zwischen der Genetik und den klinischen Befunden von Herzkrankheiten und Herz-Rhythmusstörungen.
Da Herzversagen zu den wichtigsten Krankheiten und Todesursachen gehört, verfolgen wir in der Klinik multizentrische Studien mit dem Ziel, Resistenz und Behandlung von Herzinfarkt und Rhythmusstörungen zu verbessern.

Selected Publications

- Brink M, Chrast J, Price SR, Mitch WE, Delafontaine P. (1999) Angiotensin II stimulates gene expression of cardiac insulin-like growth factor I and its receptor through effects on blood pressure and food intake. Hypertension. 34:1053-1059.
- Keller DI, Coirault C, Rau T, Cheav T, Weyand M, Amann K, Lecarpentier Y, Richard P, Eschenhagen T, Carrier L. (2004) Human homozygous R403W mutant cardiac myosin presents disproportionate enhancement of mechanical and enzymatic properties. J Mol Cell Cardiol. 36:355-362.
- Brink M, Price SR, Chrast J, Bailey JL, Anwar A, Mitch WE, Delafontaine P. (2001) Angiotensin II induces skeletal muscle wasting through enhanced protein degradation and down-regulates autocrine insulin-like growth factor I. Endocrinology. 142:1489-1496.
- Zhu P, Zaugg CE, Hornstein PS, Allegrini PR, Buser PT. (1999) Bradykinin-dependent cardioprotective effects of losartan against ischemia and reperfusion in rat hearts. J Cardiovasc Pharmacol. 33:785-790.
- Brink M, Anwar A, Delafontaine P. (2002) Neurohormonal factors in the development of catabolic/anabolic imbalance and cachexia. Int J Cardiol. 2002;85: 111-121.

Proteome

Endothelial function

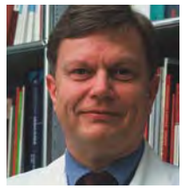
Apoptosis

Chronic heart failure

Ventricular assist devices

Valve surgery

Cardiothoracic Surgical Research



Prof. Dr. Hans-Reinhard Zerkowski
Universitätsklinik für Herz-und Thoraxchirurgie
Universitätsspital Basel

Group Members
Prof. Dr. Ivan Lefkovits
Dr. Martin Grapow
Dr. Peter Matt
Dr. Thomas Grussenmeyer
Dr. Else Müller-Schweinitzer
Dr. David Reineke
Benedikt Wiggli (MD student)
Emmanuel Traunecker (technician)

Basic Science in Cardiac-Surgery – Keeping the Distance Short to Clinical Treatment

Long-term outcome of coronary artery bypass surgery is in important part dependent on the excellence of grafts which are used for revascularisation. Therefore, we investigated functional differences in between grafts, i.e. arterial (radial vs. internal thoracic artery) and venous grafts, but also evaluated different preparation techniques and the impact of storage solutions on vascular function. Using organ bath experiments, we demonstrated that a worldwide accepted harvesting technique of the internal thoracic artery resulting in blocking the perfusion through the vessel for less than one hour has unfavourable influence on endothelial function. On the other hand, a slight modification of the preparation by keeping the artery under perfusion improves the early function. Furthermore we used biochemical and visualization methods (i.e. scanning electron microscopy) to support our findings. Functional, biochemical and structural investigations demonstrated that maintained perfusion of this vessel during grafting of the other coronary target vessels induces considerably less endothelial damage than the conventional method indicating the importance of changing historical surgical techniques for optimal arterial graft function.

Step by step hemodynamics, signal-transduction and gene expression in cardiac disease were performed as well as an analysis of changes in the proteome. Proteomic analysis investigates the entire protein composition of a cell or organism at a given state. The core technology of proteomic research is 2-dimensional gel electrophoresis. Proteins are separated on differences in their charge and mass of polypeptides 2-D gels are analysed using specialized software. The identification of protein spots is then performed by matching to a known master pattern or by mass spectrometry. First results of our group mark the rare publications of human protein analysis in cardiac disease. http://pubs.acs.org/subscribe/journals/jprobs/3/special_issue/

Dilative cardiomyopathy (DCM) is one important indication for heart transplantation (HTx). Although HTx is the gold-standard in treatment of DCM, many patients die awaiting HTx, due to shortage of donor-hearts. The implantation of ventricular assist devices (VAD) in DCM patients, leading to an immediate unloading of the dilated ventricle, was established as a bridge to transplantation. However, recent reports indicated that VADs might normalize the contractile function of the unloaded heart, leading to the idea of bridging to recovery. Our interest is to detect alterations on the humoral and cellular level, investigating the apoptosis related network, signal transduction pathways in human cardiac tissue, and various stress markers. Tissue samples of the left ventricular myocardium were obtained during implantation of the VAD and consecutively at cardiac transplantation.

First results demonstrated an increased transcription of anti-apoptotic sFas (FasEx06Del) and Bcl-xl indicating a myocardial phenotype shift towards less susceptibility for myocyte apoptosis as a consequence of reduced mechanical stress due to decreased ventricular wall tension during VAD support.

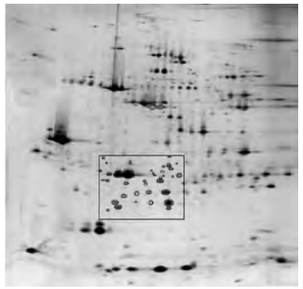
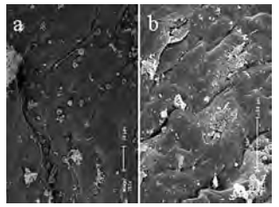
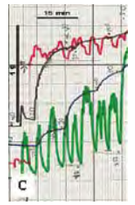


Fig. 1: Silver stained proteomic pattern of left ventricular tissue of the wild-type counterpart of the b1-ardenergic receptor transgenic strain. The proteomic pattern is based on wide range IEF separation (3-9 p*I* range) and size separation in 10–20% acrylamide gradient gels in SDS milieu.





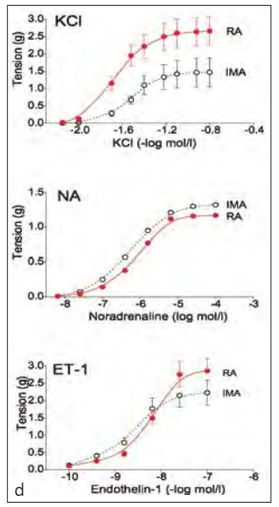


Fig. 2: Scanning electron micrographs of the endothelium of a perfused (a) and a clipped internal thoracic artery (b). Representative tracings showing spontaneous rhythmic activity of rings from radial arteries (RA) in comparison with rings from internal mammary (IMA) without any rhythmic activity (c). Cumulative concentration-response curves on rings from unstored human IMA and RA for KCl (top, n=8), NA (middle, n=10) and ET-1 (bottom, n=14). IMA and RA were taken from the same patients. Responses are expressed in g. Vertical bars represent mean SEM (d).

Division of Cardio-Thoracic Surgery, Deptartment of Surgery

Coronary Artery Bypass Surgery
Bypass surgery accounts for 59% of the operations performed in the Cardiothoracic Surgery Division, a significant figure. Almost 92% of these patients receive arterial revascularisation using internal thoracic and radial arteries. Around 20% of our bypass operations are performed on the beating heart without using the heart-lung-machine.

Timing of Valve Replacement and Repair
Surgery of the heart valves is routinely performed in our institution (using all techniques); the primary goal is preservation of the valve (reconstruction). If a valve replacement is required, prostheses of synthetic or biological materials are implemented. Special emphasis is laid on the optimal time for surgery. This can be defined as the latest date in the natural course of chronic heart valve disease at which all changes of myocardial adaptation are completely reversible. Clinical, echocardiographic and hemodynamic parameters do not offer a precise way to determine the stage of the disease so far. Changes of genome and proteome may provide us with data being helpful to find the optimal time frame for surgery.

Artificial Heart for Recovery
Public interest has focused for a long time on heart transplantation and the use of the "artificial hearts" (mechanical circulatory support systems), both procedures being performed in our institution as well. The growing shortage of donor organs resulted in a frequent use of those devices for bridge to transplantation. Few patients surprisingly recovered on the device and underwent explantation – the term bridge to recovery was introduced. Our Institution is involved with basic research to find predictors of outcome.

Kliniknahe Grundlagenforschung – fast track zum Fortschritt in der Chirurgie

Der Langzeiterfolg von *koronarchirurgischen Bypass-operationen* ist in grossem Masse von der Qualität der Venen und Arterien abhängig, die als Bypässe verwendet werden. Wir untersuchen Bypass-Gefässe auf ihre funktionellen Unterschiede innerhalb verschiedener Gefässgruppen, Einflüsse von Aufbewahrungslösungen und unterschiedliche Operationstechniken auf Gefässfunktion, Integrität der Gefässinnenschicht (Endothel) und Veränderungen der Serumproteine. Schritt für Schritt wurden Hämodynamik, extra- und intrazelluläre Signaltransduktion und Genexpression in unterschiedlichen Erkrankungen des Herzens untersucht. All dieses spiegelt sich wieder in Veränderungen der Proteinzusammensetzung in Gewebe und Blut. *Proteomics*, die Analyse des Proteoms, untersucht die gesamte Proteinzusammensetzung einer Zelle oder eines Organismus zu einem bestimmten Zeitpunkt. Erste Resultate unserer Gruppe in einem bislang wenig erforschten Gebiet sind abrufbar unter: http://pubs.acs.org/subscribe/journals/jprobs/3/specialissue/. Obwohl die Herztransplantation (HTx) der Goldstandard in der Behandlung der dilatativen Kardiomyopathie (DCM) ist, versterben viele Patienten auf ein Spendeherz wartend auf der Transplantationsliste mangels Spendeorgane. Die Implantation mechanischer Unterstützungspumpen, sog. *Ventricular Assist Devices* (VAD), welche zur sofortigen Entlastung der Herzkammer(n) führt, wurde als Überbrückungsmassnahme bis zur HTx eingeführt. In den letzten Jahren wurde zunehmend darüber berichtet, das VAD die kontraktile Funktion des entlasteten Herzens normalisieren kann und damit eine ev. Herzerholung möglich macht. Der Begriff Bridge to Recovery wurde geprägt. Unser Interesse gilt dem Aufspüren von Prädiktoren in Blut oder Gewebe, die in Zukunft Aussage darüber erlauben könnten, welcher Patient sich von Anfang an für eine solche Therapie eignet.

Selected Publications

- Ponicke K., Vogelsang M., Heinroth M., Becker K., Zolk O., Bohm M., Zerkowski HR., Brodde OE. (1998) Endothelin receptors in the failing and nonfailing human heart. Circulation 3; 97:744-51.
- Bartling B., Milting H., Schumann H., Darmer D., Arusoglu L., Koerner MM., El-Banayosy A., Koerfer R., Holtz J., Zerkowski HR. (1999) Myocardial gene expression of regulators of myocyte apoptosis and myocyte calcium homeostasis during hemodynamic unloading by ventricular assist devices in patients with end-stage heart failure.Circulation 100:II216-23.
- Morawietz H., Szibor M., Goettsch W., Bartling B., Barton M., Shaw S., Koerfer R., Zerkowski H.R., Holtz J. (2000) Deloading of the left ventricle by ventricular assist device normalizes increased expression of endothelin ET(A) receptors but not endothelin-converting enzyme-1 in patients with end-stage heart failure. Circulation 102:III188-93.
- Grapow M.T., Kern T., Reineke D.C., Brett W., Bernet F., Rueter F., Muller-Schweinitzer E., Zerkowski H.R. (2003) Improved endothelial function after a modified harvesting technique of the internal thoracic artery. Eur J Cardiothorac Surg. 23:956-60.
- Zerkowski H.R., Grussenmeyer T., Matt P., Grapow M., Engelhardt S., Lefkovits I. Proteomics Strategies in Cardiovascular Research. J Prot Res. 3(2):200-208

Carnitine

Mitochondrial energy metabolism

Hepatotoxicity

Rhabdomyolysis

Mitochondrial cytopathies

Clinical Pharmacology and Toxicology

Prof. Dr. Stephan Krähenbühl
Institut für Klinische Pharmazie
Universitätsspital Basel

Group members
Dr. Markus Wenk
Dr. Michael Török
Dr. Paul Roberts
Liliane Todesco (chemist)
Priska Kaufmann (Ph D student)
Andrea Knapp (PhD student)
Saskia Lüde (PhD student)
Bettina Link (PhD student)
Katri Waldhauser (PhD student)

Toxicology and Energy Metabolism

The carnitine system is important for tissues using fatty acids as energy source, since carnitine is needed for the import of fatty acids into mitochondria. In order to be able to study the pathological consequences of carnitine deficiency, we developed and characterized an animal model with biochemically-induced carnitine deficiency. Rats treated with trimethyl-hydrazonium-propionate (THP), a substance similar to carnitine and its biosynthetic precursor butyrobetaine, develop symptomatic carnitine deficiency within 2 to 3 weeks. THP interferes with renal carnitine reabsorption and inhibits carnitine biosynthesis. Such rats develop microvesicular fatty liver (Fig. 1). We could show that the principle mechanism leading to microvesicular steatosis is decreased β-oxidation of fatty acids due to carnitine deficiency, leading to an accumulation of cytosolic palmitoyl-CoA with an increase in the formation of VLDL. Furthermore, we could show that cardiac carnitine depletion is associated with functional but no morphological alterations of the heart. Our model is therefore suitable to study the development of cardiomyopathy associated with carnitine deficiency. Recent, so far unpublished, studies reveal also changes in the metabolism and structure of skeletal muscle.
Another focus in the carnitine field are clinical studies. We have shown that long-term ingestion of high amounts of carnitine is not able to elevate the carnitine content in skeletal muscle in healthy volunteers. Nevertheless, oral carnitine administration has been shown to be associated with a decrease in muscle sourness after eccentric exercise. We are therefore currently performing a controlled clinical study in healthy volunteers investigating whether carnitine administration is indeed able to prevent muscle sourness and which are the mechanisms involved. Furthermore, we are interested to study carnitine homeostasis and the effect of carnitine administration in vegetarians. Vegetarians develop carnitine deficiency over time and may therefore be able to profit from carnitine administration.
In order to perform clinical studies, suitable analytical methods are needed. We have recently developed an LC-MS/MS method for the determination of butyrobetaine, carnitine and acylcarnitines in urine and plasma (Fig. 2). The method has been used to characterize the carnitine profile in patients undergoing chronic hemodialysis with and without carnitine administration. Such patients have an increased amount of acylcarnitines in plasma (e.g. acetyl- and propionylcarnitine) and the elimination of acylcarnitines can be increased by treatment with carnitine.

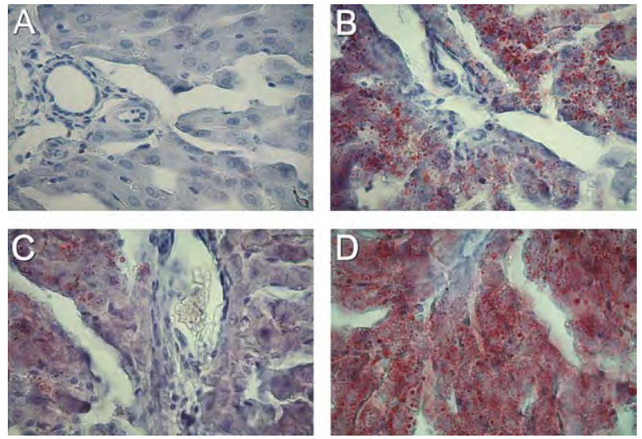


Fig. 1: Microvesicular steatosis in rats treated with THP. Treatment with THP over 3 weeks induces microvesicular steatosis in rat hepatocytes. Oil red stain (fat is stained red). (A) casein, (B) casein/THP, (C) vegetarian, (D) vegetarian/THP.

Considering our toxicological projects; we have recently provided a mechanism of the hepatic toxicity of amiodarone, a frequently used antiarrhythmic drug. Amiodarone uncouples oxidative phosphorylation and inhibits the mitochondrial respiratory chain and β-oxidation, possibly leading to apoptosis and/or necrosis of hepatocytes. Unpublished data show that this is also the case for benzbromarone and benzarone. Benzarone is structurally very close to amiodarone and capable of opening the mitochondrial membrane permeability transition pore (MPTP), leading to the disruption of the outer mitochondrial membrane and inducing apoptosis.
A last field of interest is rhabdomyolysis associated with statins. We have been able to show that statins are mitochondrial toxins, leading to inhibition of fatty acid oxidation and to opening of the MPTP. Current experiments investigate the question whether underlying mitochondrial diseases could be a risk factor for rhabdomyolysis associated with statins. Such experiments could also be usable to create test systems for early screening of chemical compounds for mitochondrial toxicity.

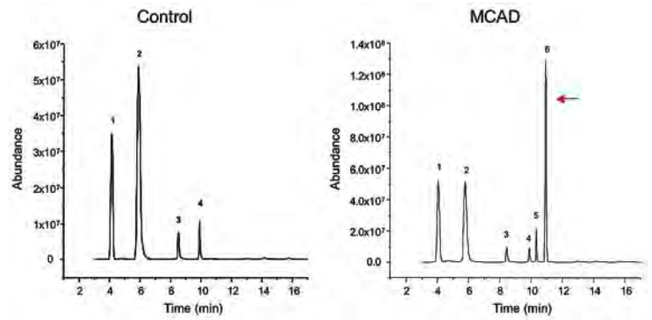


Fig. 2: Determination of urine acylcarnitines in a patient with medium chain acyl-CoA dehydrogenase deficiency (MCAD) using LC-MS/MS. In comparison to a control sample, the patient has significant peaks of hexanoyl- and octanoylcarnitine (arrow). 1=carnitine, 2=acetylcarnitine, 3=propionylcarnitine, 4=isovalerylcarnitine, 5=hexanoylcarnitine, 6=octanoylcarnitine.

Clinics

Our research is quite often closely related to clinical observations. In the case of carnitine metabolism and mitochondrial dysfunctions, there is a link to mostly pediatric diseases, i.e. organic acidurias and mitochondrial cytopathies. We can diagnose and classify organic acidurias in the urine or the plasma of suspected patients using own analytical methods. We are currently introducing these methods into the routine analytical spectrum of the Department of Clinical Chemistry at the University Hospital. In addition, we develop routine assays using our expertise in measuring the activities of enzymes involved in β-oxidation and in the activity of the respiratory chain, which should facilitate the diagnosis of mitochodrial disorders.
In collaboration with neurologists and neuropathologists, a special attention is given to investigate patients with rhabdomyolysis, as this disease is often associated with mitochondrial disorders and/or toxicities of chemicals or drugs.
Our research in toxicology is obviously connected to our own clinical activities, but also to many facets of internal medicine and pathology. Quite often, we notice poisonings by chemicals or drugs and we can then investigate possible mechanisms in the laboratory. Examples thereof are given by the toxicity of amiodarone, benzbromarone or benzarone and the elucidation of the mechanism underlying the hepato- and myotoxicity of the emetic toxin produced by Bacillus cereus (N Engl J Med 1997;336:1142-1148).
Basel offers optimal conditions for the whole spectrum of our activities as we have many highly qualified partners for scientific exchange in the clinic and in research in the University Hospital, at the University and in the local industry.

Toxikologie und Energiestoffwechsel

Die Forschung unserer Gruppe konzentriert sich auf 2 Gebiete, nämlich Energiemetabolismus (insbesondere Mitochondrien und Carnitinmetabolismus) sowie toxikologische Fragestellungen in Bezug auf Medikamente (insbesondere Toxizität auf die Leber und die Skelettmuskulatur).
Wir haben ein Tiermodell für die Carnitindefizienz entwickelt, indem wir Ratten mit dem Carnitinanalog Trimethylhydraziniumpropionat (THP) behandeln. Diese Ratten entwickeln innerhalb von 2 bis 3 Wochen einen schweren Carnitinmangel. In diesem Modell untersuchten wir die Entwicklung der charakteristischen Fettleber, Kardiomypathie und Myopathie der Skelettmuskulatur.
Zudem sind wir an der Analytik von Carnitin und Acylcarnitinen interessiert. Diese Methoden brauchen wir für in vivo Untersuchungen des Carnitinmetabolismus vor allem bei Sportlern.
Im Bereich Toxikologie haben wir den Mechanismus der Hepatotoxizität von Amiodarone beschrieben. Danach untersuchten wir das hepatotoxische Potential der Strukturanaloga Benzbromaron und Benzaron. Diese Substanzen entkoppeln die Mitochondrien, hemmen die β-Oxidation und die Atmungskette und öffnen eine Pore in den mitochondrialen Membranen. Durch diese Mechanismen können sie Nekrose und/oder Apoptose hervorrufen.
Ähnliche Eigenschaften haben die lipophilen Statine auf Mitochondrien aus der Skelettmuskulatur und können so zu Rhabdomyolyse führen. Gegenwärtig interessiert uns die Frage, ob mitochondriale Störungen ein Risikofaktor für die Rhabdomyolyse unter Statinen sind. Die Beantwortung dieser Frage könnte zur Herstellung von in vitro Systemen führen, welche ein frühzeitiges Screening von Substanzen auf mitochondriale Toxizität erlauben.

Selected Publications

- Spaniol M, Brooks H, Auer L, Zimmermann A, Solioz M, Stieger B, Krähenbühl S. (2001) Development and characterization of an animal model of carnitine deficiency. Eur J Biochem, 268:1876-1887.
- Spaniol M, Bracher R, Ha HR, Follath F, Krähenbühl S. (2001) Toxicity of amiodarone and amiodarone analogues on isolated rat liver mitochondria. J Hepatol, 35:628-36.
- Spaniol M, Kaufmann P, Beier K, Wüthrich J, Török M, Scharnagl H, März W, Krähenbühl S. (2003) Mechanisms of liver steatosis in rats with systemic carnitine deficiency due to treatment with trimethylhydraziniumpropionate. J Lipid Res, 44:144-153.
- Zaugg CE, Spaniol M, Kaufmann P, Bellahcene M, Barbosa V, Tolnay M, Buser PT, Krähenbühl S. (2003) Myocardial function and energy metabolism in carnitine-deficient rats. Cell Mol Life Sci, 60:335-40.
- Vernez L, Wenk M, Krähenbühl S. (2004) Determination of carnitine and acylcarnitines in plasma by high-performance liquid chromatography-electrospray ionization ion trap tandem mass spectrometry. Rapid Commun Mass Spectrom, 18:1233-1238.

Drug-drug interaction
Transport porteins
Drug safety
Resistance

Clinical Pharmacology and Toxicology

Prof. Dr. Jürgen Drewe
Institut für Klinische Pharmazie
Universitätsspital Basel

Group Members
Dr. Heike Gutmann
Dr. Petr Hruz (MD PhD student)
Ursula Behrens (technician)
Marco Netsch (PhD student)
Manisha Poddar (PhD student)
Philipp Schlatter (PhD student)
Christian Zimmermann (PhD student)

Drug Transporters and Drug-Drug Interactions

Drugs are often given orally. However, their site of action is usually not in the gastrointestinal tract (gut). They have to travel through the body to their site of action and have to pass different physiological barriers (such as gut wall, blood-brain barrier). Our main research interests are to study the mechanisms of the involved transport processes and their disturbances. The latter could lead to loss of drug effect or toxicity (increased blood levels, drug-drug interactions). These transport processes are mainly mediated by specific transport proteins. The most important group of these proteins are the superfamily of ABC-transporters (such as multidrug resistance proteins) and organic anion transporters.
For some of these transporters it was shown that they are involved in the development of clinically relevant diseases: for example, a defect of the ABC-transporter CFTR causes cystic fibrosis, and P-glycoprotein and some multidrug resistance associated protein transporters (MRPs) are involved in the development of resistance to various drugs (such as anticancer medication).
Effects on transport protein function or their gene expression may lead to clinically significant drug-drug interaction. One major research focus is the development of in vitro screening models to investigate the molecular mechanisms of clinically observed drug-drug interactions. These models may by helpful to anticipate potentially dangerous drug combinations, which may lead to drug-drug interaction and adverse effects by affecting transport protein function. This would reduce the risk of pharmacotherapy for future patients

Gut
The epithelium of the gut is the most important barrier for enteral absorption of drugs. In the gut mucosa there are various transport proteins expressed, which may secrete absorbed drug immediately back into the gut lumen. This may lead to substantially decreased oral bioavailability of these drugs. We have developed several in vitro screening models to assess the mechanisms of enteral drug absorption their interaction with different drugs. Currently, we are investigating the functional regulation of these transporters and how it can be modulated by different drugs or endogenous factors.
The main project in this area is the investigation of the importance of ABC-transporters in the development of inflammatory bowel diseases (ulcerative colitis, Crohn's disease). Disturbancies in transporter function may be an important mechanisms or cofactor for the frequently observed treatment resistance (20-30% of the patients). We know that several drugs used in the treatment of IBD are transported by some of these transport proteins. Impaired function may lead to decreased cellular availability of those drugs and a loss of their function. In cooperation with the Division of Gastroenterology (Prof. C. Beglinger) we investigate in a large clinical study mucosal biopsies from IBD patients and we try to develop in vitro models to mimic drug-induced treatment resistance in IBD.

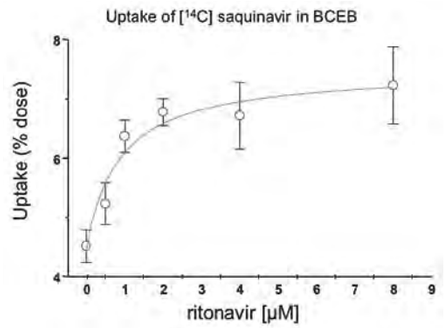


Fig. 1: Dose-dependent inhibition of P-glycoprotein mediated export of absorbed radiolabelled saquinavir from BCECs by increasing concentrations of the P-glycoprotein inhibitor ritonavir. Inhibition results in an increased cellular uptake and accumulation of saquinavir.

Blood-brain barrier (BBB)
BBB is another physiological barrier, which controls brain uptake in order to protect the brain from potentially toxic xenobiotics, such as drugs. The BBB is built by the endothelial layer of brain capillary endothelial cells (BCEC). To study these transport processes across the BBB, we have established an in vitro model of the BBB based on primary cell cultures of porcine BCEC. Using the porcine BCEC model, we have investigated a series of different drugs to predict cerebral uptake and could validate the predicted uptake with literature animal data on brain penetration (Fig. 1). Currently, we are developing an in vitro model based on human cells.

Kidney
Transport processes are importance physiological functions of the kidneys. Tubular function is studied by us in a killifish in situ model of proximal tubules (in collaboration with Dr. David S. Miller, NIEHS (North Carolina) and Prof. G. Fricker, University of Heidelberg, Germany). A cell culture model based on primary cell cultures of proximal tubular cells is currently in validation (Fig. 2).

Genetic Polymorphisms
A large part of the pharmacokinetic variability of drugs may be caused by genetic differences between different individuals. There are several single nucleotide polymorphisms (SNPs) described for many of these transport proteins. We are investigating the functional importance of these SNPs and their relevance for the development or modulation of certain diseases (risk factor, treatment resistance, and prognosis).

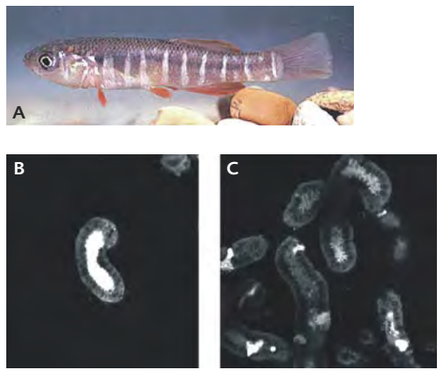


Fig. 2: Study of kidney transport of fluorescence labelled HIV protease inhibitor saquinavir in isolated proximal tubules of the killifish (Fundulus heteroclitis) (A): without inhibitor (B), with inhibitor of transport (C)

Medikamenten-Transporter und Arzneimittelinteraktionen

Medikamente werden häufig oral verabreicht, der Wirkungsort der Medikamentenwirkstoffe ist aber in der Regel nicht im Magen-Darm Trakt. Sie müssen vielmehr erst an den Wirkungsort gelangen und dazu verschiedene biologische Membranen (Darm, Bluthirn-Schranke usw.) passieren. Hauptgegenstand unserer Arbeit sind die Mechanismen dieser Membrantransporte und deren Störungen, die dann in Wirkungsverlust oder Toxizität (erhöhte Blutspiegel, Interaktionen) münden können. Häufig sind spezielle Transportproteine für die Permeation durch Membranen verantwortlich. Von der Vielzahl der bisher bekannten Transporter interessieren uns vor allem die für die Multidrug-Resistenz verantwortlichen ABC-Transporter, sowie spezielle organische Anionentransporter.
Einigen Vertreter der ABC-Transportern kommt eine besondere klinische Bedeutung zu, so verursacht z.B. ein Defekt des ABC-Transporters CFTR die Erbkrankheit Mukoviszidose, während z.B. P-Glykoprotein (P-gp) und Multidrug-Resistenz assozierte Proteine (MRPs) eine wichtige Rolle beim Auftreten von sog. Multidrug-Resistenzen z.B. gegen Zytostatika in der Tumortherapie spielt.
Schwerpunkt unserer Arbeitsgruppe ist es, Interaktionen, die auf Transportern beruhen, auf molekularer Ebene zu erklären, bzw. vorauszusagen. Dazu haben wir in unserer Forschungsgruppe verschiedene in-vitro Modelle etabliert, an denen Transportprozesse untersucht werden können. Mit solchen Modellen lassen sich potentielle Risiken neuer Wirkstoffe, die Mechanismen aufgetretener unerwünschter Arzneimittelnebenwirkungen untersuchen, potentiell gefährliche Arzneimittelkombination vorherzusagen und somit das Risiko für künftige Patienten verringern.

Selected Publications

- Bogman K., Peyer A.K., Török M., Küsters E. and Drewe J. (2001) HMG-CoA reductase inhibitors and P-glycoprotein modulation. Br J Pharmacol, 132:1183-1192.
- Gutmann H., Fricker G., Drewe J., Toeroek M. and Miller D.S. (1999) Interactions of HIV protease inhibitors with ATP-dependent drug export proteins. Mol Pharmacol, 56:383-389.
- Pfrunder A., Gutmann H., Beglinger C. and Drewe J. (2003) Gene expression of CYP3A4, ABC-transporters (MDR1 and MRP1-MRP5) and hPXR in three different human colon carcinoma cell lines. J Pharm Pharmacol, 55:59-66.
- Pfrunder A., Schiesser M., Gerber S., Haschke M., Bitzer J. and Drewe J. (2003) Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. Br J Clin Pharmacol, 56: 683-690.
- Sieber C.C., Beglinger C., Bart S., Tschoepl M., Currie G., Larsen F. and Drewe J. (2004) Lanreotide effect on splanchnic blood flow in healthy subjects: effect of the rate of infusion. Clin Pharmacol Ther, 75:70-79.

Structural Cell Biology

Prof. Dr. Lukas Landmann
Institut für Anatomie

Group Members
Dr. Piotr Maly
Dr. Permsin Marbet
Mireille Toranelli (technician)
Jean Paul Boeglin (technician)
Eva Bryson (technician)

Mechanisms of Cholestasis

Bile secretion is a major function of the liver and depends on vectorial transport of cholephilic compounds from blood to bile. The high concentration in bile of some constituents (> 1000-fold for bile acids) is mediated by polar expression of specific transport systems (Fig. 1) the export proteins of which belong to the ABC gene family of active transporters. Regurgitation of secreted bile from the canaliculus to the blood space is prevented by hepatocellular tight junctions which are the only barrier between the two compartments. Cholestasis interferes with bile formation or bile flow resulting in decreased hepatic secretion of water and/or organic anions, e.g. bilirubin and bile acids. Clinically, cholestasis is defined by increased serum levels of cholephilic compounds and specific enzymes. Therefore, possible alterations resulting in cholestasis include impaired expression and/or subcellular distribution of transport systems as well as damage of the sealing tight junctional belt.

Most of the transport systems are known to be downregulated by all types of cholestasis within days. However, as soon as 6 h after experimentally induced cholestasis, accumulation of canalicular export systems in subcanalicular (subapical) vesicles becomes apparent (Fig. 2). This short term alteration may be caused by two mechanisms: (i) Defective insertion of newly synthesized apical membrane proteins, which are sorted indirectly by the transcytotic route to their final destination. This defect is induced by carrier vesicles having lost their competence for fusion with the apical membrane. As a matter of fact, cholestasis severely affects functional transcytosis in hepatocytes as demonstrated by biliary secretion of various markers for transcytosis including polymeric IgA. (ii) Internalization of transport systems by apical endocytosis and reinsertion into the apical plasma membrane may be a regulatory mechanism controlling the number of functional transport proteins. Using high resolution confocal microscopy in combination with various markers we demonstrated an apical endocytic pathway in hepatocytes. It is conceivable that the apical recycling pathway is also affected by cholestasis. Current work characterizes endocytic routes in greater detail in order to localize and define the mechanisms by which cholestasis affects membrane traffic in liver cells.

Tight junctions are known to be affected functionally and structurally. Cholestasis induced alterations include increased permeability for peroxidase and other marker molecules as well as disorganization of the junctional network resulting in a decreased number of strands. Strand quality, however, as reflected by size and spacing of the constituent particles is not affected. Preliminary results indicate that subcellular distribution of integral and peripheral junctional proteins is not altered by cholestasis. In addition, mRNA and protein expression levels are not changed. Therefore, the inhomogenously expressed membrane proteins (claudin1 and 3) will be characterized to greater detail and the role of macromolecular interactions involved in the maintenance of junctional integrity will be explored.

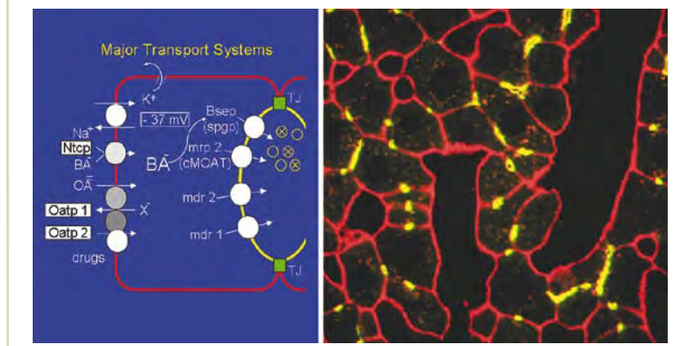


Fig. 1: Fig. 1: Polar expression of basolateral uptake (red) and canalicular export (green) systems in rat hepatocytes. BA = bile acids, OA = organic anions, TJ = tight junctions.

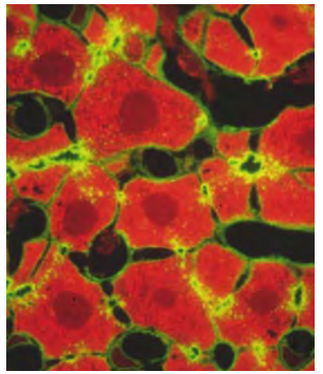


Fig. 2: Accumulation of pericanalicular (subapical) vesicles that display immunoreactivity for canalicular membrane proteins including export pumps after bile duct ligation in the rat. Human hepatocytes show a similar response in various forms of cholestasis.

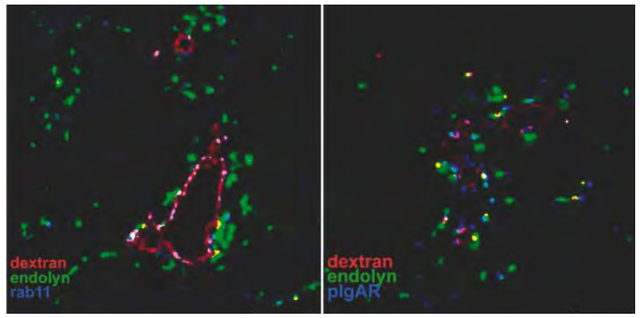


Fig. 3: TxR-labeled dextran (red) infused retrogradely through the common bile duct shows colocalization (white) with endolyn76 (green) and rab11 (blue, left panel) or pIgA (blue, right panel). All three marker proteins travel through a subapical compartment. Bar = 0.5 mm.

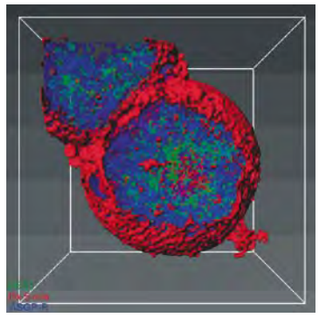


Fig. 4: 3D characterization of the early endosomal compartment in rat hepatocyte couplets. After uptake of TxR-conjugated dextran (red) for 5 min cells were fixed and immunostained for the recycling basolateral receptor for asialoglycoprotein (blue) and the early endosomal antigen 1 (green). Overlap of all three markers defines unambiguously functional early endosomes

Mechanismen der Cholestase

Die Sekretion von Galle ist eine Hauptfunktion der Leber. Sie beruht auf dem gerichteten Transport gallepflichtiger Substanzen vom Blut- ins Gallenkompartiment und wird von polar exprimierten Transportproteinen in der Zellmembran der Leberzellen vermittelt. Tight Junctions zwischen den Leberzellen stellen die einzige Barriere zwischen Galle und Blut dar; sie verhindern die Regurgitation von sezernierter Galle aus dem Canaliculus. Cholestase manifestiert sich in reduziertem Gallenfluss und erhöhten Serumwerten gallepflichtiger Substanzen. Sie kann auf dem Niveau der Leberzelle mit beeinträchtigter Expression von Transportsystemen und/oder ihrer veränderten subzellulären Verteilung als auch mit Defekten der Tight Junctions assoziiert sein. Alle Arten von Cholestase resultieren innert Tagen zu einer verminderten Expression der Transportsysteme. Bei einem Verschluss des Gallengangs akkumulieren aber schon nach 6 h canaliculäre Exportsysteme in subapikalen Vesikeln. Diese Veränderung kann durch 2 Mechanismen erklärt werden: 1) Neu synthetisierte apikale Membranproteine, die in Leberzellen indirekt über die transcytotische Route zu ihrer Destination transportiert werden, verlieren ihre Fähigkeit, in die apikale Zellmembran inkorporiert zu werden. 2) Transportsysteme in der apikalen Membran werden endocytotisch internalisiert und in subapikalen Vesikeln akkumuliert. Dass der erste Mechanismus involviert ist, konnte gezeigt werden; eine Beteiligung des Zweiten ist plausibel. Die durch Cholestase verursachte Zunahme der Tight Junction Permeabilität verändert weder die Verteilung von junctionalen Proteinen noch die Menge von mRNA und Proteinen. Deshalb sollen die inhomogen exprimierten Membranproteine Claudin 1 und 3 detaillierter charakterisiert werden.

Selected Publications

- Stieger, B.; Meier, P., and Landmann, L. (1994) Effect of obstructive cholestasis on membrane traffic and domain-specific expression of plasma membrane proteins in rat liver parenchymal cells. Hepatology 20, 201-212.
- Rahner, C.; Stieger, B., and Landmann, L. (1996) Structure-function correlation of tight junctional impairment after intrahepatic and extrahepatic cholestasis in rat liver. Gastroenterology 110, 1564-1578.
- Rahner C.; Stieger, B., and Landmann, L. (2000) Apical endocytosis in rat liver cells in situ involves clathrin, passes the subapical compartment and leads into lysosomes. Gastroenterology 119, 1692-1707.
- Landmann, L. and Stieger, B. (2001) Tight junctions in liver disease. In: Tight Junctions, 2nd Ed. (Cereijido, M. and Anderson, J.M., Eds).:CRC Press, Baton Rota, FA, 575-597.
- Landmann, L. (2002) Deconvolution improves colocalization analysis of multiple fluorochromes in 3D confocal data sets more than filtering techniques. J Micr (Oxford) 208, 134-147.

Opiate

Peripheral nerve

Cell differentiation and growth

Itch

Wound healing

Aging

Neuroimmuno-dermatology

Dr. Mei Bigliardi-Qi
Departement Forschung
Universitätsspital Basel

Group members
PD Dr Paul Bigliardi
Goran Vucelic (technician)
Katrin Pfaltz (MD student)
Hao Cai (trainee)

Pathophysiology of Opioid Receptor in Skin

Neuro-immuno-dermatology is a novel research field studying the influence and effects of various neuropeptides, cytokines and growth factors from nervous and immune systems on skin physiology and pathology. All of these factors are involved in wound healing, itching and various skin diseases. Our research group is interested in neuroimmunology of opiate system in skin. Opiate receptor system is involved in cell differentiation and growth in skin and regulates pain and itch. This has great therapeutic potential in itching, topical pain relief, wound healing, aging and cancer.

Clinically applied methylnaltrexone (quaternary derivative of naltrexone that does not cross the blood-brain barrier) has been used to treat opioid induced itching and bowel motility. This suggests that the effects of opioids on itching are not only on the CNS system but also on the peripheral nerve system. Our group was the first to publish on μ-opiate receptor expression and its function in skin physiology and pathology. Our studies have shown that human epidermal keratinocytes express μ-opiate receptor on both mRNA and protein level. We have not only shown a functional active μ-opiate receptor in human keratinocytes but also μ-opiate receptor on peripheral epidermal, non-myelinated C-fibers. This suggests a direct interaction of μ-opiate receptors on keratinocytes and nerve endings and is a possible explanation for the flare-up of different skin diseases such as atopic dermatitis and psoriasis by stress. We are especially interested in the involvement of the μ-opiate receptor system on keratinocytes and peripheral epidermal nerve endings in itch (e.g. hepatogenic) and pruritic skin diseases like atopic dermatitis, prurigo nodularis, and psoriasis.
We also investigated the opiate receptor system in wound healing and study if epidermal μ-opiate receptor expression is changed at the wound margins in acute and chronic wounds. Using classical and confocal microscopy, we were able to compare the expression level of μ-opiate receptors and the influence of β-endorphin on TGF-β type II receptor in organ culture. Our results show indeed a significantly decreased expression of μ-opiate receptors on keratinocytes close to the wound margin of chronic wounds compared to acute wounds. Additionally β-endorphin upregulates the expression of TGF-β type II receptor in human skin organ cultures. These results suggest a crucial role of opioid peptides not only in pain control but also in wound healing. Opioid peptides have already been used in animal models in treatment of wounds, they induce fibroblast proliferation, growth of capillaries, accelerate the maturation of granulation tissue and the epithelialization of the defect. Furthermore, opioid peptides may fine-tune pain and the inflammatory response while healing takes place. This new knowledge could be potentially used to design new locally applied drugs to improve the healing of painful chronic wounds.
The common, troublesome skin problems of old age such as cancer and xerosis with pruritus senilis remain a major cause of morbidity and yet are poorly explained. Opiatergic neurons undergo significant functional changes by producing opiate peptides. Altered peptides may trigger the loss of reproductive capacity. The midlife shift in opiate peptide production is a component of natural developmental processes that begin in the neonate and continue through old age. Our observations of opiates involvement in cell migration, differentiation and growth in skin proved their important role in cancer and aging as well. Currently, we are investigating opioid receptor knockout mice model. The results obtained so far confirmed our hypothesis and revealed new fascinating opioid receptor functions involved in itching and wound healing.
Recently, we have received Roche Prize 2003 Dermatology and granted US patent on wound healing.

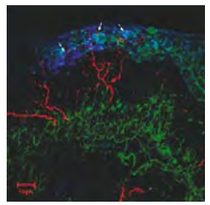
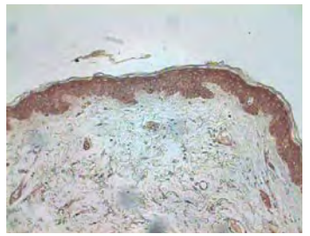


Fig. 1: Interaction of β-Endorphin, μ-opioid receptor positive keratinocytes and nerve ending in human epidermis. Red: PGP 9.5 positive nerve endings; Green: μ-opioid receptor positive keratinocytes; blue: β-endorphine positive keratinocytes.



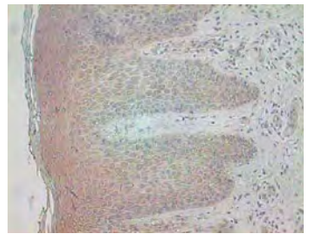


Fig. 2: (a) μ-opioid receptor expression in human normal skin epidermis (b) μ-opioid receptor expression in atopic dermatitis epidermis.

New Therapeutic Approach to Pruritus and Wound Healing

Our research discovery that opiate system is actively involved in cell differentiation and growth in skin and regulate pain and itch has great therapeutic potentials in topical pain and itch relief, wound healing, aging and cancer.
There is increasing evidence that the reinnervation of the skin is important for the wound healing and that keratinocytes directly influence innervation. Patients with diabetes mellitus (Fig. 3) or leprosy have peripheral neuropathy and also a severely impaired wound healing. Not much is known about the impact of damaged peripheral nerve endings on wound healing. Therefore our research is focused on the basic mechanisms and influences of nerve endings and neuropeptides such as opioids in acute, chronic wound and neuropathic diabetic wounds.
Itching is one of the major symptoms in pruritic skin diseases such as atopic dermatitis, prurigo nodularis, and psoriasis. Antihistamines can treat acute itching but are not effective against chronic itching. Opioid receptor antagonists are used to treat different forms of chronic pruritus and involved in the activation of chronic itching as seen in atopic dermatitis (Fig. 4) or cholestatic pruritus. Therefore, it is crucial to distinguish between chronic and acute forms of itching to understand the complexity of the different itching mechanisms. Novel effective topical drugs with minimum side effect for treatment of pruritus with different origins

Prof. Dr. Theo Rufli
Dermatologische Universitätsklinik
Universitätsspital Basel

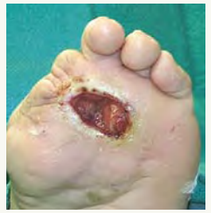


Fig. 3: Wound from diabetes mellitus patients

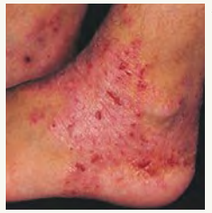


Fig. 4: Lesion from atopic dermatitis patients

Die Opiat-Rezeptoren der Haut

Das Gebiet der Neuro-Immuno-Dermatologie umfasst das Studium der Funktionen verschiedener neuronaler Botenstoffe und deren Interaktion mit verschiedenen Wachstumsfaktoren, Hormonen, und Signalmolekülen in der Haut. Unser Labor untersucht die Rolle von Opiat-Rezeptoren in der Haut und deren Wechselwirkung mit dem Nerven- und Immunsystem. Das Opiat Rezeptorsystem der Haut ist wichtig für die Differenzierung der Hautzellen und für das Wachstum der Haut, hat aber auch eine Rolle im Schmerzempfinden und beim Juckreiz. Dieses Opiat-Rezeptor System stellt somit ein enormes Potential an Therapieansätzen für Krankheiten mit starkem Juckreiz, wie Neurodermitis oder Psoriasis dar, aber auch bei der Wundheilung, bei Alterungsprozessen der Haut und bei Hautkrebs.
Wir konnten erstmals die Gegenwart von funktionellen Opiatrezeptoren in Hautzellen (Keratinozyten) und in Nervenendigungen der Haut nachweisen. Dass auch Nervenendigungen der Haut Opiatrezeptoren und deren Liganden exprimieren, kann zur Erklärung beitragen, weshalb Stress häufig Hauterkrankungen wie Neurodermitis oder Psoriasis verstärkt.
Verschiedene Experimente zeigten uns, dass die Opiatrezeptoren nicht nur beim Juckreiz, sondern auch bei der Wundheilung und im Schmerzempfinden eine Rolle spielen. Das Opiat-Rezeptor System der Haut ist vor allem bei chronischem Juckreiz von Bedeutung, bei akutem Juckreiz spielen Botenstoffe wie zum Beispiel Histamin eine Rolle. Auch ist bei chronischen, nichtheilenden Wunden die Opiat-Rezeptoren Dichte in der Haut verändert. Diese völlig neuen Erkenntnisse, welche an Hautbiopsien von Menschen gewonnen wurden, werden nun mit Experimenten an transgenen Mäusen bestätigt. Diese Mäuse können keine Opiat-Rezeptoren in der Haut ausbilden. Die bisher erzielten Resultate bestätigen die Erkenntnisse, dass die Opiat-Rezeptoren in der Haut eine wichtige Rolle beim chronischen Juckreiz und auch in der Wundheilung spielen.

Selected Publications

- Bigliardi-Qi M, Lazar Sumanovski, Büchner S, Rufli T and Bigliardi PL,: Expression of μ-opiate receptor and β-endorphin in peripheral nerve endings in skin. Dermatology in press
- Bigliardi PL, Sumanovski LT, Büchner S, Rufli T and Bigliardi-Qi M (2003) Different expression of μ-opiate receptor in chronic and acute wounds and the effect of β-endorphin on TGF-β type II receptor and cytokeratin 16 expression. J Invest Dermatol. 120 (1): 145-152.
- Bigliardi PL, Büchner S, Rufli T and Bigliardi-Qi M (2002) Specific stimulation of migration of human cultured foreskin keratinocytes in vitro by μ-opiate receptor agonists. Journal of Receptor and Signal transduction 22(1-4): 191-199.
- Bigliardi-Qi M, Bigliardi PL, Büchner S and Rufli T (2000) b-Endorphin stimulates expression of differentiating factor cytokeratin 16 and downregulate μ-opiate receptor expression. J Invest Dermatol ,114: 527-532.
- Bigliardi PL, Bigliardi-Qi M, Büchner S and Rufli T (1998): Expression of μ-opiate receptor in human epidermis and keratinocytes. J Invest Dermatol, 111: 297-301.

Development
Mouse
Molecular genetics
Organogenesis
Signalling
Stem cells

Developmental Genetics

Prof. Dr. Rolf Zeller
Institut für Anatomie

Group Members
Dr. Aimée Zuniga
Dr. Antonella Galli
Nadege Lagarde (technician)
Cristina Torres de los Reyes (technician)
Cornelia Lehmann (technician)
Jean-Denis Bénazet (PhD student)
Odyssé Michos (PhD student)
Lia Panman (PhD student)

Signals Coordinating Growth and Patterning in Vertebrate Embryos

During embryonic development, cells with so-called organiser properties control the balance of growth, patterning and differentiation. Organisers emit both positive and negative (antagonistic) signals to instruct undetermined cells with respect to their fate and eventual differentiation. In the advent of the complete sequencing of several genomes, many of the candidate genes involved in these determinative processes are now known and research is rapidly shifting towards functional analysis of whole cascades, cross-talk and interactions in their entirety (systems biology). Therefore, a major challenge is now to unravel the regulatory networks and feedback loops, which control these determinative embryonic processes over time. The importance of tight regulation of embryonic cell-cell signalling is best illustrated by the fact that any deregulation of organiser signalling results in severe congenital malformations. Furthermore, inappropriate (re-) activation of embryonic signalling cascades during post-natal life causes disease, as many embryonic regulator genes are e.g. proto-oncogenes or tumour suppressor genes.

Our group uses mouse molecular genetics and embryology to study vertebrate organogenesis and in particular the epithelial-mesenchymal signalling interactions coordinating embryonic growth with patterning. *Sonic Hedgehog* (SHH) is a long-range signal that controls proliferation and patterning of many organs. In particular in the developing limb, SHH signalling is maintained by a signalling feedback loop between ectoderm (expressing FGFs, fibroblast growth factors) and the mesenchyme (expressing SHH; called SHH/FGF feedback loop). One of our main goals is to understand the molecular mechanisms controlling establishment of such feedback loops and how they regulate embryonic development. We have recently shown that signal antagonists such as *Gremlin*, which inhibits BMP (bone morphogenic protein) signalling, are crucial to both establish and propagate epithelial-mesenchymal signalling feedback loops during organogenesis. We are currently exploring the use of such antagonists and small molecules either mimicking their function or constitutively activating signal transduction cascades to analyse the cell-cell signal interactions during mammalian limb and kidney organogenesis.

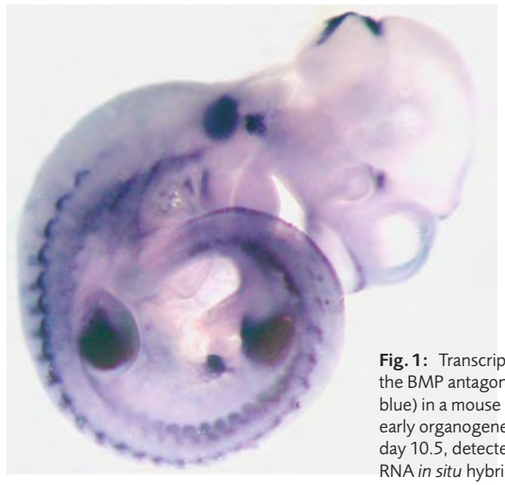


Fig. 1: Transcript distribution of the BMP antagonist *Gremlin* (dark blue) in a mouse embryo during early organogenesis (embryonic day 10.5, detected by whole mount RNA *in situ* hybridization). Note the high levels of *Gremlin* expression in specific regions of the limb buds, somites, brain, otic vesicle etc.

The expression of such potent morphoregulatory signals is tightly controlled as changes in their temporal and spatial expression patterns disrupt organogenesis and cause malformations. Therefore, we have begun to analyse the molecular mechanisms underlying regulation of their tissue-specific expression. In the course of these studies, we have identified the large regulatory landscape that controls expression of the BMP antagonist *Gremlin* in the limb bud mesenchyme. This novel type of regulatory landscape encodes a so-called global control region (GCR) that regulates tissue-specific expression of functionally and structurally unrelated genes located next to one another on mouse chromosome 2. *In silico* and transgenic analysis indicates that the GCR consists of several highly conserved cis-regulatory elements scattered over a large distance. These elements function cooperatively to regulate activation of genes whose promoters are located at least 150–200kb up- and down-stream. Evidence indicates that such regulatory landscapes are possibly more common than so far assumed and serve to co-regulate tissue-specific expression of apparently unrelated neighbouring genes. The analysis of tissue-specific activation, modulation and fine-tuning of genes functioning in signalling cascades is one aspect crucial to understanding how morphogenesis of different organs is controlled by repeated use of the same type of signals and antagonists. By combining mouse molecular genetics with *in vitro* manipulation of embryonic organ rudiments and genome-wide expression profiling, we hope to gain insights into the temporal and spatial regulation of the cell-cell signalling interactions that control establishment and activity of organising centres during vertebrate organogenesis.

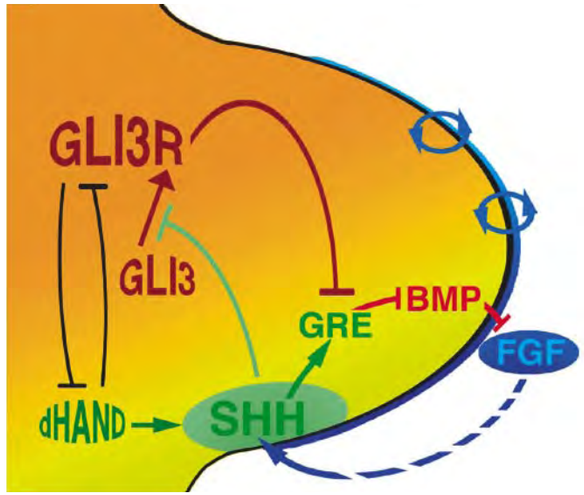


Fig. 2: Schematic representation of the genetic cascades and key regulator genes we analyse to gain insight into the molecular mechanisms controlling establishment and epithelial-mesenchymal signaling by the SHH expressing limb bud organizer.

Die embryonale Entwicklung braucht Signale für die Koordination von Wachstum und Musterbildung

Während der embryonalen Entwicklung übernehmen gewisse Zellen wichtige Rollen in der balancierten Organisation von Wachstum, Differenzierung und Musterbildung. Stimulierende und hemmende Signale werden durch diese Zellen ausgesandt. Damit erhalten andere Zellen Instruktionen für ihre Bestimmungen (Determination). Determination für eine Zelle bedeutet die Übernahme einer «Verpflichtung» eine gewisse Rolle zu übernehmen und sich entsprechend zu differenzieren.

Wie wichtig der Signalaustausch zwischen den Zellen während der embryonalen Entwicklung ist, zeigen die schwerwiegenden Missbildungen zu denen es bei fehlerhafter Regulation im Embryo kommt. Werden andererseits nach der Geburt embryonale Signalketten eingeschaltet, so führt dies zu schweren Erkrankungen u.a. zu Krebs.

Unsere Gruppe untersucht den Signalaustausch zwischen verschiedenen embryonalen Geweben. Eines unserer Hauptziele ist es, die molekularen Hintergründe zu verstehen, welche bei der Entstehung und Aufrechterhaltung von Signal-Rückkoppelungs-Mechanismen im Spiel sind. Bei einem dieser Rückkoppelungs-Mechanismen sind das genaue zeitliche und örtliche Expressionsmuster von BMP (bone morphogenic protein) und von seinen Antagonisten «Gremlin» unerlässlich für die korrekte Ausbildung von Organen und Gliedmassen. Bei der Untersuchung, wie diese komplexe Koordination zustande kommt, entdeckten wir eine ganze Regulationsbatterie, eine sogenannte GCR (global control region). Verschiedene Gene, welche alle auf Maus-Chromosom 2 nebeneinander lokalisiert sind, bilden diese GCR. Sie teilen sich ihre Steuerungselemente, was die koordinierte Expression sichert. Mit der Analyse dieses und von weiteren GCRs versprechen wir uns Aufschluss über die Feinheiten des Zell-Zell Signalaustausches in solchen Organisationszentren zu erhalten.

Selected Publications

- Panman L. and Zeller R. (2003) Patterning the Limb Before and After SHH Signalling. J. Anatomy (Review) 202, 3-12.
- Zuniga A, Michos O., Spitz F., Haramis A.P.G., Panman L., Vintersten K., Klasen C., Mansfield W., Kuc S., Duboule D., Dono R. and Zeller R. (2004) Mouse *limb deformity* mutations disrupt a global control region within the large regulatory landscape required for *Gremlin* expression. Genes Dev. 18, 1553-1564.
- teWelscher P., Zuniga, A, Kuijper S., Drenth T., Goedemans H, Meijlink F. and Zeller R. (2002) Progression of Vertebrate Limb Development through SHH-Mediated Counteraction of GLI3. Science 298, 827-830.
- teWelscher P, Fernandez-Teran M, Ros M. and Zeller R. (2002) Mutual genetic antagonism involving GLI3 and dHAND prepatterns the vertebrate limb bud mesenchyme prior to SHH signalling. Genes Dev. 16, 421-426.
- Zuniga A., Haramis A.G., McMahon A.P. and Zeller R. (1999) Signal relay by BMP antagonism controls the SHH/FGF-4 feedback loop in vertebrate limb buds. Nature 401, 598-602.

Peptides
Tumor targeting
Melanoma metastases
Human adipocytes
Obesity

Endocrinology

Prof. Dr. Alex N. Eberle
Departement Forschung
Universitätsspital Basel

Group Members
Dr. Sylvie Froidevaux
Dr. Kerstin Wunderlich
Dr. Martine Calame-Christe
Dr. Gabriele Mild
Dr. Kurt Müller
Verena Jäggin (technician)
Heidi Tanner (technician)
Olivier Wenger (PhD student)
Matthias Hoch (PhD student)
Jean-Philippe Bapst (PhD student)
Steven Knecht (PhD student)

Peptide Targeting of Melanoma Tumor Metastases

Melanoma is one of the most rapidly increasing malignancies in the white population and has a poor prognosis after formation of metastases because it is relatively resistant to conventional chemotherapy or external beam irradiation. New immunological methods long awaited for, e.g. melanoma vaccination, have not yet reached a state of general applicability. Our approach is therefore to develop novel tools for internal radiotherapy of tumor metastases using radiolabelled peptides or peptide-coated nanoparticle carriers for delivery of high doses of chemotherapeutics specifically (in-)to metastases. Most melanoma cells (over-)express the melanocortin-1 receptor (MC1R) which binds and internalizes α-melanocyte-stimulating hormone (α-MSH); hence MC1R is considered as potential target for internal radiotherapy or targeted chemotherapy. Over several years of research, we have analyzed the in vitro and in vivo expression, regulation and internalization of MC1R in mouse and human melanoma cells and recently, we have developed and tested a first series of promising new MSH radiopeptides, including DOTA-MSH_{OCT}, which localize almost exclusively to experimental melanoma metastases after in vivo application (except for the kidneys). Figure 1 shows the structure of a very recent MSH radiopeptide, DOTA-NAPamide, and the experimental steps for its in vivo application. We could demonstrate that DOTA-NAPamide exhibits an almost 7-fold higher MC1R binding potency as compared to DOTA-MSH_{OCT}, and in B16F1 melanoma-bearing mice, both [^{111}In]DOTA-NAPamide and [^{67}Ga]DOTA-NAPamide radiopeptides exhibited higher tumor and lower kidney uptake, leading to tumor-to-kidney ratios that were 4.6 times (^{111}In) and 7.5 times (^{67}Ga) greater than that obtained with [^{111}In]DOTA-MSH_{OCT}. In addition, the 4-h kidney uptake of [^{67}Ga]DOTA-NAPamide could be reduced by 64% by co-injection of 15 mg L-lysine, without affecting tumor uptake. Skin primary melanoma as well as lung and liver melanoma metastases could be easily visualized on tissue section autoradiographs after systemic injection of [^{67}Ga]DOTA-NAPamide or [^{111}In]DOTA-MSH_{OCT} (Fig. 2). The melanoma selectivity of DOTA-NAPamide was further confirmed with positron emission tomography (PET) imaging studies using the positron emitter [^{68}Ga]DOTA-NAPamide (Fig. 3).
Currently we are developing and clinically assessing smaller MSH radiopeptides with even better tumor-to-kidney ratios, with the purpose of offering a tool for a more specific localization of disseminated melanoma microdeposits (by PET, SPECT) and, more importantly, for targeting cytotoxic radiometals (β-emitters, α-emitters) into these microdeposits (for internal radiotherapy). If successful, melanoma patients may soon benefit from a new way of palliative if not curative treatment.

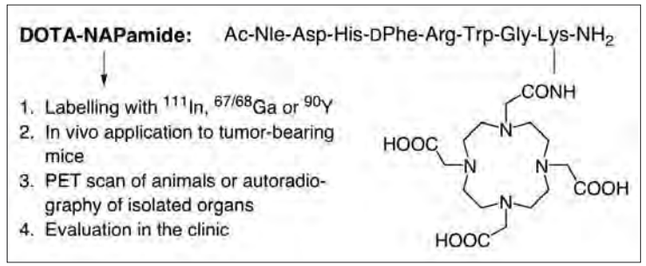
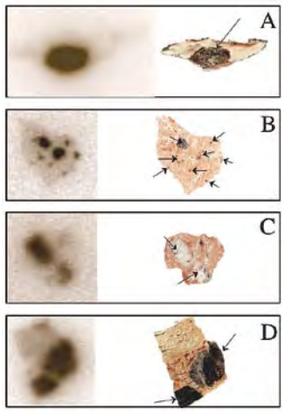


Fig. 1: Chemical structure and steps of labelling and application of the highly selective MC1R agonist DOTA-NAPamide for targeting melanoma metastases.

Another part of the project is directed to the development of a nanoparticle delivery system for targeting metastatic melanoma cells. The aim is to eventually offer nanoparticles as "magic bullets" for a potentially more effective curative treatment for larger melanoma lesions, owing to higher intensities of ionizing radiation or of toxins delivered to the metastases by these particles. In the frame of this project, the nanoparticles will primarily be evaluated with the experimental B16 melanoma tumor model, in order to determine the selectivity of targeting and the distribution, penetration and accumulation of nanoparticles in melanoma metastases.

Fig. 2: Autoradiographs of tissue sections from melanoma-bearing mice. [^{111}In]DOTA-MSH_{OCT} was injected to mice inoculated with B16-F1 cells and tissues were collected 4 h postinjection. A–D, Autoradiographs (left panel) and scanner images (right panel) of a primary melanoma with surrounding skin tissue (A), lung with melanotic melanoma metastases (B), lung with amelanotic melanoma metastases (C), liver with melanotic melanoma metastases (D). Arrows indicate the melanoma lesions.



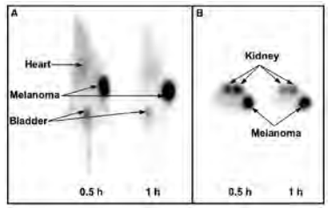


Fig. 3: PET imaging of melanoma-bearing mice with [^{68}Ga]DOTA-NAPamide. Coronal (A) and transaxial (B) images of mice 0.5 h and 1 h after injection. Only melanoma, kidneys, bladder and to a lesser extent heart are detectable (in collaboration with Dr. J. Schuhmacher, Dr. R. Saffrich and Dr. M. Henze from the Department of Diagnostic and Therapeutic Radiology, German Cancer Research Center, Heidelberg, Germany).

The Bariatric Patient as Model for the Study of Factors Influencing Obesity

In a collaborative project between Dr. Ralph Peterli (surgeon) and PD Dr. Thomas Peters (endocrinologist/internist) of the St.Claraspital Basel and our laboratory, we are studying genetic causes and endocrine factors that contribute to the condition of obesity in a large group of bariatric patients undergoing gastric banding or gastric by-pass operations (compared to healthy controls). In a first subproject, we analyzed melanocortin-4 receptors (MC4R) for mutations known to be associated with up to 6% of monogenetic causes of obesity. Correlations between defects of MC4R and complications of laparoscopic gastric banding operation have recently been reported. However, we could not confirm these observations in a group of 37 patients analyzed for MC4R mutations. At present, omental and subcutaneous adipose tissue of these patients is used for a comparative study of the functional role of melanocortins and their receptors, as well as related regulators, with respect to activation of mitochondria and lipolysis. It appears that in obese patients MC1R expression is elevated as compared to controls.

Peptide und Rezeptoren für Tumor-Targeting und Regulation von metabolischen Prozessen

Das Labor Endokrinologie befasst sich schwerpunktmässig mit Peptiden und deren Rezeptoren, insbesondere MSH, MCH, Agouti, Leptin, Ghrelin, GLP-1 und PYY. Eines der Hauptthemen ist das so genannten rezeptorvermittelte Targeting von Melanommetastasen mit Hilfe von radioaktiv markierten Peptidderivaten des -MSH, deren Funktion es ist, durch Bindung an den MC1-Rezeptor die Radionuklide spezifisch in die Melanomzellen einzuschleusen. Auf diese Weise kann entweder mit Szintigraphie der Tumor sichtbar gemacht werden (diagnostisches Targeting) oder mit therapeutisch wirksamen Radioisotopen behandelt werden (therapeutisches Targeting). Anhand eines Maus-Melanommodells konnten neue Derivate hergestellt werden (z.B. NAPamid; Figur 1), die ein spezifisches Targeting von kleinsten Metastasen in Lunge und Leber ermöglichen (Figur 2) und den Tumor mit PET sichtbar machen (Figur 3). Gegenwärtig arbeiten wir insbesondere daran, die unerwünschte unspezifische Akkumulation von Radiopeptiden in den Nieren zu vermindern, um eine bessere Tumor-Selektivität zu erhalten.
Weitere Projekte des Labors betreffen (1) vergleichende Untersuchungen von Regulationsmechanismen am Fettgewebe von Patienten mit schwerer Adipositas (siehe englischer Text); (2) zusammen mit Prof. J. Flammer das Studium von Veränderungen von Signalmechanismen und metabolischen Zuständen (u.a. von Mitochondrien) bei Glaukompatienten; (3) den Transport von Peptiden durch Monolayer-Zellschichten als Modell für das Dünndarmepithel und deren Modulation durch Begleitsubstanzen, und (4) den Einfluss von schwachen Wechselwirkungen auf biologische Regulationsprozesse, z.B. das Wachstum von Tumorzellen.

Selected Publications

- Froidevaux S, Calame-Christe M, Schuhmacher J, Tanner H, Saffrich R, Henze M, Eberle AN. (2004) A gallium-labeled DOTA-α-melanocyte-stimulating hormone analog for PET imaging of melanoma metastases. J. Nucl. Med. 45, 116-23.
- Froidevaux S, Eberle AN, Christe M, Sumanovski L, Heppeler A, Schmitt JS, Eisenwiener K, Beglinger C, Mäcke HR. (2002) Neuroendocrine tumor targeting: study of novel gallium-labeled somatostatin radiopeptides in a rat pancreatic tumor model. Int. J. Cancer 98, 930-7.
- Schlumberger SE, Jäggin V, Tanner H, Eberle AN. (2002) Endogenous receptor for melanin-concentrating hormone in human neuroblastoma Kelly cells. Biochem. Biophys. Res. Commun. 298, 54-9.
- Eberle AN, Bodi J, Orosz G, Süli-Vargha H, Jäggin V, Zumsteg U. (2001) Antagonist and agonist activities of the mouse agouti protein fragment (91-131) at the melanocortin-1 receptor. J. Recept. Signal Transduct. 21, 25-45.
- Eberle AN, Froidevaux S. (2003) Radiolabeled α-melanocyte-stimulating hormone analogs for receptor-mediated targeting of melanoma: from tritium to indium. J. Mol. Recognit. 16, 248-54.

Hematopoietic stem cells
Leukemia
Myeloproliferative disorders
Severe aplastic anemia
Stem cell transplantation
Immunotherapy

Experimental Hematology

Prof. Dr.
Radek Skoda

Prof. Dr.
Aleksandra
Wodnar-Filipowicz

Departement Forschung
Universitätsspital Basel

Group members
Dr. Christian Kalberer
Dr. Robert Kralovics
Dr. Jörn Coers
Dr. Ralph Tiedt
Dr. Andreas Buser
Dr. Alexandre Theocharides
Emilie Bouliong (technician)
Verena Dalle Carbonare (technician)
Silvia Sendelov (technician)
Hui Hao-Shen (technician)
Soon-Siong Teo (technician)
Kun Liu (PhD student)
Karolina Nowak (PhD student)
Pegah Nowbakht (PhD student)
Tibor Schomber (PhD student)
Uwe Siegler (PhD student)
Stephanie Bridenbaugh (MD student)
Andreas Rohner (MD student)

Control of Blood Cell Development and Pathogenesis of Hematopoietic Stem Cell Disorders

Blood cells have a limited life span and must be continuously replaced throughout life. This regenerative process is called hematopoiesis and is characterized by rapid cell division, commitment and differentiation of progenitor cells. Hematopoietic stem cells (HSC) are essential for maintaining hematopoiesis, as all functional subtypes of blood cells are derived from these multipotent cells. A large number of blood diseases, including leukemia, myeloproliferative disorders and severe aplastic anemia, are now recognized as stem cell disorders and for many of these life-threatening conditions transplantation of normal HSC has become a first line therapy that often can cure a patient. Our research aims at advancing our understanding in three areas of normal and aberrant hematopoiesis:

The pathogenesis of myeloproliferative disorders
Myeloproliferative disorders (MPD) are a group of diseases characterized by aberrant proliferation of one or more myeloid lineages. They represent clonal stem cell disorders of unknown etiology with an inherent tendency towards leukemic transformation. MPD can be subdivided into three disease entities: polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (IMF). We combine genetic and genomic approaches for the search of the molecular alterations that cause MPD. We identified the first mutations in the thrombopoietin (TPO) gene as the cause for an inherited form of thrombocythemia. More recently, we identified 3 additional genomic intervals that harbor the genes mutated in other familial forms of MPD. We are pursuing a candidate gene approach to search for the mutations. In addition, we examine sporadic forms of MPD. Using genome-wide microsatellite screening, loss of heterozygosity (LOH) on chromosomes 9p was identified as the most frequent chromosomal aberration in PV, present in approximately 30% of patients. We defined a minimal common LOH region and we are now searching for the alterations that provide a selective clonal advantage to cells bearing 9pLOH. These studies are complemented by expression profiling using microarrays, which defined a set of genes up- or downregulated in MPD (Fig. 1). The observed changes are part of the transcriptional fingerprint of MPD that will allow us to examine correlations with the clinical course of the disease and derive new hypotheses about the pathogenetic mechanisms involved.

The control of hematopoiesis and stem cell behavior
Using a knock-in mouse model, our earlier work showed that the decision of hematopoietic progenitors to commit to megakaryopoiesis or granulopoiesis is not influenced by lineage dominant cytokines such as thrombopoietin (TPO) or granulocyte colony-stimulating factor. To assess the importance of individual signaling pathways on hematopoiesis we are studying the effects of TPO-receptor mutants in transgenic mice. Mutated TPO-receptors did not affect differentiation of megakaryocytic progenitors, but rather change platelet numbers, further supporting the conclusions from our knock-in studies. To create lineage specific knockouts in the megakaryocytic lineage, we generated transgenic mice that express the cre-recombinase under the control of the regulatory elements from the platelet factor 4 (PF4) gene. These mice allow the excision of genomic regions that are flanked by loxP sites (Fig. 2). To allow studies on human HSC and progenitors, we devised a lentiviral siRNA vector and showed that stable and efficient silencing can be obtained in transduced human CD34+ cells. We are using these tools to extend our studies on how hematopoietic progenitors make cell fate decisions by analyzing components of the TGF-beta and Wnt signaling pathways.

Further studies aim at understanding the mechanisms, which regulate the bone marrow function during hematopoietic and immune recovery after hematopoietic stem cell transplantation (HSCT). We demonstrated that engraftment of stem cells after HSCT is preceded by a profound overexpression of flt3 ligand (FL), suggesting that this hematopoietic cytokine is important for restoring the normal bone marrow function. This is further supported by findings that patients with bone marrow failure due to severe aplastic anemia (SAA) have constitutively elevated FL serum levels. T cells were identified as a reservoire of FL stored in the Golgi apparatus during steady-state hematopoiesis and rapidly released in response to activation associated with stem cell deficiency (Fig. 3). We are studying the influence of FL on the stem cell engraftment and the development of dendritic cells and natural killer (NK) cells after HSCT. Further, we are investigating the molecular mechanisms, which regulate the expression of FL during hematopoiesis in humans. These include studies on the role of FL receptor signaling and the effect of drugs targetting the mutated flt-3 receptor in human acute myeloid leukemias.

The potential of NK cells for immunotherapy against leukemia
Our studies address the molecular interactions between NK cells and malignant cells in human leukemia. We analyse the role of activating NK receptors and ligands in recognition and killing of leukemic targets (Scheme 1). These studies include NK cells from patients with leukemia and the genetically modified NK cells generated *in vitro* following lentiviral vector-mediated transfer of genes encoding natural cytotoxicity receptors. To assess the cytotoxic properties of NK cells *in vivo*, we have established a human leukemia transplantation model of nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice. The goal of this project is to develop NK cells as an immunotherapy tool to enhance the anti-tumor response and prevent disease relapse after HSCT.

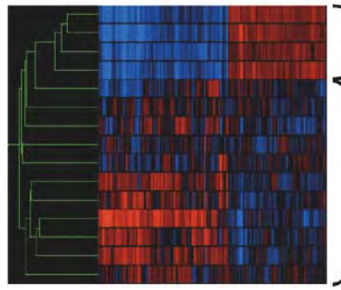


Fig. 1: Gene expression profiling of myeloproliferative disorders. Microarray analysis of granulocyte RNA of healthy controls and patients with myeloproliferative disorders (MPD) revealed 280 differentially expressed genes. Red color in MPD represents up-regulated genes, blue color down-regulated genes. To assess gene expression similarity among the samples, cluster analysis was performed which clearly separated the healthy individuals from patients. Green line represents the assigned relation between the samples.

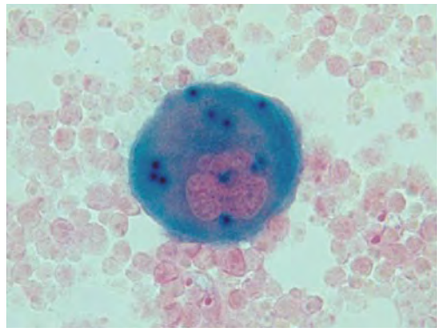


Fig. 2: Megakaryocyte-specific expression of Cre-recombinase in a transgenic PF4-Cre mouse. The presence of functional Cre recombinase protein in bone marrow megakaryocytes was visualized by blue staining. Note that non-megakaryocytic cells do not express Cre and therefore do not stain blue.

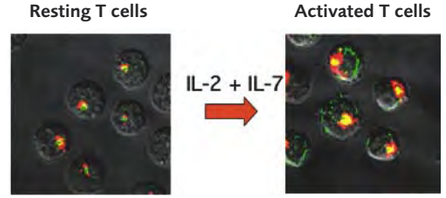
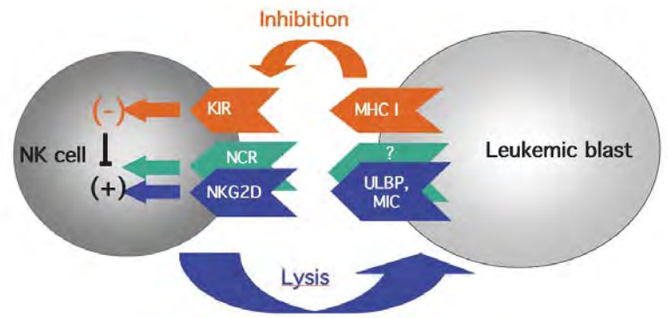


Fig. 3: Expression of flt3 ligand by human T cells. Confocal microscopy of purified human peripheral blood T cells, resting and activated with interleukins IL-2 and IL-7. Cells were stained with antibodies against flt3 ligand (green signals) and the Golgi marker, giantin (red signals).



Scheme 1: NK cell – target recognition. KIR, killer inhibitory receptor; NCR, natural cytotoxicity receptor; MHC I, major histocompatiblity complex class I; ULBP and MIC, ligands for NKG2D receptor. NK cells recognize their targets using 2 types of receptors: Inhibitory receptors, such as KIRs, interact with class I molecules. This recognition protects healthy cells from attack by the NK cell. Activatory receptors, such as NKG2D, interact with several ligands, called ULBP and MIC molecules. These ligands have been shown to be upregulated in virus-infected cells and in tumors of epitherlial origin.

Clinics

Prof. Dr. Alois Gratwohl
Abteilung Hämatologie
Universitätsspital Basel

Prof. Dr. André Tichelli
Abteilung Hämatologie
Universitätsspital Basel

Leukemias and severe aplastic anemia (SAA) are rare disorders and at first sight appear to have little in common. Massive proliferation of malignant cells, leukemic blasts and tumor formation in all hematopoietic organs are the hallmark of the typical acute leukemias; absence of all normal elements of circulating blood, so-called severe pancytopenia, and an empty bone marrow, characterize SAA. Both disorders are due to an aberrant production of blood cells by a sick hematopoietic stem cell. In leukemia it is too much, in SAA it is too little. The defect can be intrinsic to the leukemic stem cells as it occurs in patients with chronic myeloid leukemia (CML) after chromosome 9/22 translocation, which leads to a constitutive activation of the tyrosine kinase BCR/ABL, and it can be extrinsic via an autoimmune blockade of stem cells in SAA. Hence, two different therapeutic approaches for the two disease categories: complete replacement of an abnormal hematopoietic system by a hematopoietic stem cell transplantation (HSCT) or an approach, which is targeted directly to the primary defect. Diagnostic and Therapeutic Hematology at the University Hospital in Basel has pioneered HSCT and targeted therapies for leukemias and SAA for thirty years. Over 80 HSCT are now performed annually by the Basel Stem Cell Transplant team for malignant and non-malignant disorders of the hematopoietic system. Bone marrow, peripheral blood and cord blood are used as stem cell sources from the patients themselves (autologous HSCT) or from HLA-identical siblings, haploidentical family members or unrelated volunteer donors (allogeneic HSCT). They are used directly or after intensive in vivo manipulation and selection ex vivo in the laboratory. As an alternative to replacement therapy, targeted therapy is used in patients with leukemias. An increasing number of targeted drugs bring about the arrest of leukemic proliferation, such as retinoic acid receptor blockade by all trans retinoic acid in acute promyelocytic leukemia, BCR/ABL blockade by imatinib mesylate in CML or flt-3 receptor blockade by PKC412 in patients with acute myeloid leukemias carrying flt-3 mutations in the leukemic cells. In SAA, the targeted therapy is in the form of selective inhibition of the presumed T-cell mediated stem cell blockade by anti-thymocyte globulin (ATG) and cyclosporine. Applying current knowledge and all available tools, risk adapted tailored therapy for individual patients is becoming a reality in leukemias and SAA.

CML was the first disease in which a recurrent chromosomal abnormality was found. Today, the diagnosis of CML is made when in a patient with typical blood changes the Philadelphia chromosome or its molecular fusion gene BCR/ABL can be demonstrated. CML was originally considered part of a syndrome called "myeloproliferative disorders" (MPD). Based on BCR/ABL, today CML is regarded as a separate entity. For the remaining three MPD subtypes, polycythemia vera (PV) essential thrombocytemia (ET) or chronic idiopathic myelofibrosis (IMF), no specific genetic defect known. The diagnosis of these entities is based upon morphologic findings from blood and bone marrow with laboratory and clinical observations. However, overlaps between PV, ET and IMF exist. Importantly, there is currently no curative treatment available and these disorders pose therapeutic dilemmas for practicing hematologists. As a regional reference center, Diagnostic and Therapeutic Hematology at the University Hospital in Basel treats more than 100 patients with MPD. Correlation between diagnosis, prognostic criteria, clinical history and the molecular genetic markers is analyzed in close collaboration with the research laboratory. The goal of these studies is to improve the management of patients with MPD and to provide a basis for the search of the primary cause of MPD. These efforts also aim at identifying new drug targets, which ultimately could lead to the development of specific new drugs for the treatment of MPD.

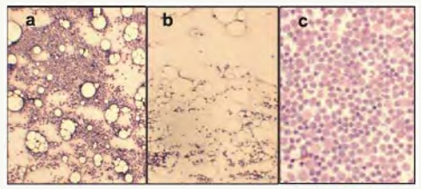


Fig. 4: Bone marrow cellularity: (a) normal (b) aplastic (c) leukemic

Fig. 5: Patient and donor 10 years after successful hematopoietic stem cell transplantation.

Krankheiten der Hämopoiese

Blutzellen haben eine beschränkte Lebensdauer und müssen kontinuierlich ersetzt werden. Dieser Ersatz, genannte Hämopoiese, wird durch Proliferation, und Differenzierung von Stammzellen gewährleistet. Eine Vielzahl von Blutkrankheiten wird durch eine Pathologie der Stammzelle verursacht. Unter diesen Stammzellkrankheiten sind die akuten Leukämien, die Myeloproliferativen Krankheiten und die schwere aplastische Anämie. Unsere Forschung untersucht die abnorme Hämopoiese in 3 Gebieten:

Die Pathognenese der myeloproliferativen Krankheiten
Wir haben die erste Mutation im Thrombopoietingen als Ursache einer vererbten Thrombozytämieform identifiziert. Durch Kombination von genetischen und genomischen Methoden ist es uns gelungen weitere genetische Aberrationen aufzudecken, welche bei familiären myeloproliferativen Krankheiten vorkommen. Der Verlust der Heterozygosie auf dem langen Arm des Chromosoms 9 (9pLOH) ist die häufigste chromosomale Anomalie in Polycythemia vera Patienten und betrifft 30% dieser Patienten. Die Microarray (GenChip)-Analysen dienen dazu diese genetischen Regionen besser zu charakterisieren. Anhand der molekularen Studien und der Korrelation zum klinischen Verlauf kommen wir zu neuen Hypothesen über die Mechanismen dieser Krankheiten.

Die Kontrolle der Hämopoiese
Wir studieren die Wege der Signalübermittlung in Transgenen Mäusen, denen ein bestimmtes Gen ausgeschaltet wurde. Damit wollen wir aufklären, in welchem Moment, welche Signale benötigt werden damit sich die spezifischen Zelllinien ausdifferenzieren. Die hierbei erworbenen Kenntnisse überprüfen wir mit menschlichen Zelllinien und der Technik der RNA-Interferenz. Zudem Untersuchen wir die Mechanismen welche die Immunrekonstitution nach Stammzelltransplantation beeinflussen. Wir konnten zeigen, dass eine Zunahme der hämopoietischen Wachstumsfaktors, flt3 Ligand, dem Angehen des Transplantates vorausgeht. Die T-Zellen dienen hierbei als Reservoir für den flt3 Liganden. Zurzeit untersuchen wir dessen Wirkung auf das Angehen der Stammzellen im Knochenmark, sowie beim Ausreifen von dendritischen Zellen und Natural Killer (NK)–Zellen nach einer Stammzelltransplantation.

Das Potential der NK-Zellen in der Immuntherapie gegen Leukämien
Unser Studien dienen dem besseren Verständnis der molekularen Interaktionen zwischen NK-Zellen und malignen Zellen. Unser Ziel ist eine Entwicklung der Immunotherapie mit NK-Zellen, als Zusatz zum antitumoralen Effekt der Stammzelltranplantation. Wir arbeiten mit einem Mausmodel einer humanen Leukämie, sowie mit genetisch-veränderten NK-Zellen.

Klinik
Die Diagnostische und Therapeutische Hämatologie des Kantonsspitals Basel war ein Pionier in der Stammzelltransplantationen für schwere Aplastische Anämien und Leukämien. Mit diese Erfahrung werden aktuell über 80 Stammzelltransplantationen pro Jahr in Basel durchgeführt. Es handelt sich dabei sowohl um autologe (vom Patienten selbst stammende Stammzellen) wie um allogene (von HLA-identischen Geschwistern oder von Fremdspendern stammende Stammzellen) Transplantationen. Diese werden direkt oder nach in vitro Manipulation im hämatologischen Labor verabreicht. Zunehmend werden auch gezielte Therapien wie all-trans-Retinsäure in der akuten Promyelozytenleukämie, Glivec und PKC412 in der chronisch myeloischen Leukämie und ATG in der schweren aplastischen Anämie verwendet. Es entstehen somit für jeden Patienten massgeschneiderte Therapien. Die Diagnostische und Therapeutische Hämatologie behandelt als regionales Referenzzentrum mehr als 100 Patienten mit einem myeloproliferativen Syndrom pro Jahr. Die Korrelation von Diagnose, prognostischen Kriterien, klinischem Verlauf und genetischen Markern werden in Zusammenarbeit mit dem Forschungslabor untersucht. Diese Arbeiten erlauben eine optimierte Behandlung der Patienten und die Weiterentwicklung neuer Therapiemodalitäten.

Selected Publications

- Chklovskaia, E., Nowbakht, P., Nissen, C., Gratwohl, A., Bargetzi, M., Wodnar-Filipowicz A. (2004) Reconstitution of dendritic and natural killer-cell subsets after allogeneic stem cell transplantation: effects of endogenous flt3 ligand. Blood, 103:3860-3868.
- Schomber, T., Kalberer, C., Wodnar-Filipowicz, A., Skoda, R.C. (2004) Gene silencing by lentivirus-mediated delivery of siRNA in human CD34 cells. Blood, 103:4511-4513.
- Kalberer, C.P., Siegler, U., and Wodnar-Filipowicz, A. (2003) Human NK cell development in NOD/SCID mice engrafted with cord blood CD34 cells. Blood 102: 127-135.
- Kralovics, R., Buser, A.S., Teo, S.S., Coers, J., Tichelli, A. van der Maas, A.P.C., Skoda, R.C. (2003) Comparison of molecular markers in a cohort of patients with myeloproliferative disease. Blood 102: 1869-1871.
- Ziegler, S., Bürki, K., Skoda, R.C. (2002) A 2 kb c-mpl promoter fragment is sufficient to direct expression to the megakaryocytic lineage and sites of embryonic hematopoiesis in transgenic mice, Blood 100: 1072-1074.
- Chklovskaia, A., Nissen, C., Landmann, L., Rahner, C., Pfister, O. and Wodnar-Filipowicz, A. (2001) Cell surface trafficking and release of flt3 ligand from T lymphocytes is induced by common cytokine receptor gamma chain signaling and inhibited by cyclosporin A. Blood 97: 1027-1034.
- Luther-Wyrsch, A., Costello, E., Thali, M., Buetti, E., Nissen, C., Surbek, D., Holzgreve, W., Gratwohl, A., Tichelli, A. and Wodnar-Filipowicz, A. (2001) Stable transduction with lentiviral vectors and amplification of immature hematopoietic progenitors from cord blood of preterm human fetuses. Human Gene Therapy 12: 377-389.
- Stoffel, R., Ziegler, S., Ghilardi, N., Ledermann, B., de Sauvage, F.J., and Skoda, R.C. (1999) Permissive role of mpl and G-CSF-receptors in hematopoietic cell fate decisions in vivo. Proc. Natl. Acad. Sci. USA 96: 698-702.
- Chklovskaia, E., Jansen, W., Nissen, C., Lyman, S.D., Rahner, C., Landmann, L. and Wodnar-Filipowicz, A. (1999) Mechanism of flt3 ligand expression in bone marrow failure: translocation from intracellular stores to the surface of T lymphocytes following chemotherapy-induced suppression of hematopoiesis. Blood 93: 2595-2604.
- Wiestner, A., Schlemper, R.J. van der Maas, A.P.C., and Skoda, R.C. (1998) An activating splice donor mutation in the thrombopoietin gene causes hereditary thrombocythemia. Nature Genetics 18: 49-52.

Appetite regulation
Perception
Gastrointestinal signals
Obesity
Functional disorders

Gastro-enterology

Prof. Dr. Christoph Beglinger
Departement Forschung
Universitätsspital Basel

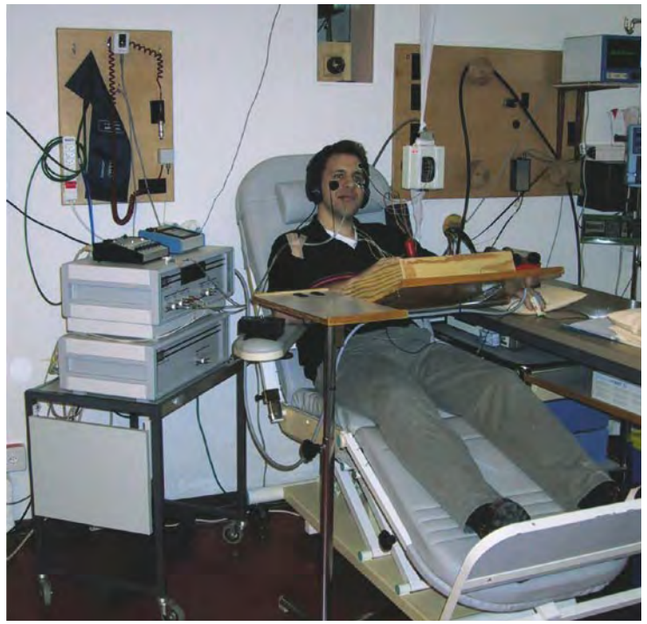
Group Members
PD Dr. Lukas Degen
Dr. Franziska Piccoli
Silvia Ketterer (technician)
Gerdien Gamboni (technician)
Luisa Baselgia (technician)
Claudia Bläsi (research nurse)
Sibylle Oesch (PhD student)
Sandro Schroller (MD student)
Michel Casanova (MD student)

Regulation of Appetite

The gastroenterology laboratory in the Department of Research of the University Hospital Basel focuses on two specific projects in the field of appetite regulation in health and disease:

I. Gastrointestinal signals in the regulation of food intake
The investigation of human eating behavior, especially the regulation of appetite and satiety, has become a very active field of research with potential for the development of a specific therapy for obesity. Limited information is available about the biochemical processes that control hunger and satiety. However, there is evidence that pre-absorptive factors are important cofactors in this regulation. Nutrient intake 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 have been shown to affect the short-term control of food intake in healthy subjects, but also in specific patient groups. The three peptides have been proposed to act as hormonal satiety signals. Our group is interested to characterize the specific gastrointestinal pathways, which are initiated after food intake with a focus on the peptides GLP-1 and PYY. We are especially interested to investigate potential interactions between individual satiety signals.

II. Pathways of gastrointestinal perception
The last two decades experienced an increase of emotion research, much of which was focusing on the physiology of affective processing. This became possible by advanced models generalizing affective mechanisms into a broader biological context, shared by animal species and humans. One of such mechanisms refers to the polysynaptic startle reflex, which is modulated by amygdala-brainstem associations. The startle reflex is facilitated in unpleasant context, such as threat, and diminished during pleasure. This phenomenon, called 'affective startle modification', has been shown to reflect the affective dimensions of classical sensory inputs (visual, auditory, olfactory, somato-sensory) – but effects of visceral afferents are not established. This is surprising, as visceral afferent sensations have already been linked to subjective emotional experience one century ago.
We recently assessed the consequences of gastrointestinal stimulation on startle responsiveness by the means of Barostat procedures. The Barostat system has been developed and applied in numerous studies to describe changes of visceral perception induced by mechanical distension. The Barostat maintains a constant pressure within an air-filled flaccid bag positioned in the lumen of the organ to be studied. When this organ contracts, the Barostat aspirates air to maintain a constant intrabag pressure.
In a doctoral thesis we could demonstrate that antral Barostat distension may enhance auditory startle responsiveness. This was true regardless whether distensions were consciously perceived (supraliminal) or whether distensions were too weak to be consciously perceived (subliminal). We also found evidence that the effect of antral distensions are not mediated by somato-sensory afferents. As duodenal stimulation did not have effects on auditory startle responsiveness, it may be concluded that antral/gastric afferents, specifically activate fight–flight operating amygdala–brainstem networks, could increase auditory startle responsiveness.
These results fit well to clinical observations that gastrointestinal processes may have profound emotional consequences. They furthermore suggest a concept that subliminal gastrointestinal stimuli potentially induce aversive-like emotional processing. A concept of *"visceral subliminal afferent signals shaping emotions"* may prove helpful to explain affective disturbances and the preference of reassuring, help-seeking behaviour in certain clinical populations, such as patients with functional gastrointestinal disorders.



The figure depicts a happy subject intubated with a barostat bag. The barostat consists of a double-lumen polyvinyl tube connected to an ultrathin polyethylene bag (1100 ml capacity, 20 cm maximum diameter) which is placed in the gastrointestinal tract (stomach, small intestine). The barostat measures either the volume or the pressure at a constant pre-selected level by an electronic feedback mechanism. A dial in the electronic system allows selection of the desired volume level or pressure level to be maintained within the bag. The barostat can be used to induce gastric or small intestinal distension.
The bag of the barostat is introduced through the mouth into the stomach or small intestine. After placement of the barostat assembly, the participant is placed in a 30° recumbent position and asked to relax comfortably.
The computer unit besides the bed controls the barostat and records the parameters of interest.

Clinics

Obesity is a growing epidemic that results in an increasing morbidity and mortality. It is causally associated with a number of medical conditions, including diabetes mellitus, coronary heart disease, and a number of cancers. Recent discoveries have expanded our knowledge on the regulation of food intake and appetite, and significant advances have been made in our understanding of the peripheral signals that regulate appetite and energy homeostasis. Several peptides synthesized and secreted within the gastrointestinal tract are known to regulate eating behavior. Our research interest focuses on a better understanding of these mechanisms in order to understand the development of obesity.

Die Regulierung des Appetits

Im Labor befassen wir uns mit zwei Aspekten der Appetit-Regulierung.
1. Die Signale aus dem Gastrointestinaltrakt, welche die Nahrungsaufnahme beeinflussen: Das Interesse dieses Forschungsgebiet wird vor allem durch die Suche nach Therapieformen gegen die Fettleibigkeit motiviert. Wenig ist bekannt wie biochemisch Hunger und Sättigung kontrolliert werden. Sicher ist aber, dass Signale vor der Absorption der Nahrung eine entscheidende Rolle spielen. Verschiedene Peptidhormone werden im Moment der Nahrungsaufnahme ausgeschüttet und kontrollieren die Kurzzeit-Nahrungsaufnahme. Wir untersuchen wie es zur Ausschüttung dieser Peptidhormone kommt und sind insbesondere an potentiellen Interaktionen zwischen diesen Sättigungssignalen und an möglichen Therapieansätzen bei Fettleibigkeit interessiert.
2. Die Wahrnehmung aus dem Verdauungstrakt: Die Physiologie der Gefühlsempfindungen wird seit einiger Zeit intensiv studiert. Eine dieser Affekte, der bei Tier und Mensch vorkommt, ist der Angstreflex. In unangenehmen Situationen ist dieser Reflex intensiviert, während er bei Freude abnimmt. Die Modulation dieses Reflexes wird durch alle klassischen Sinneswahrnehmungen beeinflusst. Bislang fehlt jedoch die Aufklärung, welchen Einfluss hierbei Signale aus dem Verdauungstrakt haben. Mit Hilfe eines Barostaten untersuchen wir nun diesen Einfluss. Wir können mit diesem Gerät Spannungsveränderungen in den Verdauungsorganen messen ,ob diese vom Probanden wahrgenommen werden oder nicht. In einer Doktorarbeit wurde aufgezeigt, dass Verspannungen in der Magenkuppel den durch Schall ausgelösten Angstreflex steigert. Solche Befunde passen gut zu unseren klinischen Beobachtungen. Abläufe im Gastrointestinaltrakt können schwerwiegende emotionale Konsequenzen haben. Unbewusst erlebte Signale aus dem Verdauungstrakt scheinen zur negativen Verarbeitung von Gefühlen beizutragen. Diese Erkenntnisse müssen bei der Behandlung von Patienten mit Verdauungsstörungen berücksichtigt werden.

Selected Publications

- Beglinger C, Degen L, Matzinger D, D'Amato M, Drewe J. (2001) Loxiglumide, a CCK-A receptor antagonist, stimulates calorie intake and hunger feelings in humans. Am J Physiol Regul Integr Comp Physiol;280(4):R1149-1154.
- Degen L, Matzinger D, Drewe J, Beglinger C. (2001) The effect of cholecystokinin in controlling appetite and food intake in humans. Peptides;22(8):1265-1269.
- Feinle-Bisset C, Meier B, Fried M, Beglinger C. (2003) Role of cognitive factors in symptom induction following high and low fat meals in patients with functional dyspepsia. Gut;52(10):1414-1418.
- Gutzwiller JP, Tschopp S, Bock A, Zehnder CE, Huber AR, Kreyenbuehl M, et al. (2004) Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin resistant obese men. J Clin Endocrinol Metab;89:3055-3061.
- Gutzwiller JP, Degen L, Matzinger D, Prestin S, Beglinger C. (2004) Interaction between GLP-1 and CCK33 in inhibiting food intake and appetite in men. Am J Physiol Regul Integr Comp Physiol;287(3): R562-567.

Ovary
Follicle
Apoptosis
Granulosa
Oocyte
Infertility

Gynaecological Endocrinology

Prof. Dr. Christian De Geyter
Abteilung für Gynäkologische Endokrinologie
und Reproduktionsmedizin
Universitäts-Frauenklinik Basel

Group members
Dr. Hong Zhang
Hsuping Gao (PhD student)

Interplay Between the Hormonal Regulation of Follicular Development and Oocyte-centered Signaling in Ovarian Physiology

The principal components of the ovarian follicle are the egg (e.g. oocyte), the granulosa and the surrounding theca. Whereas the oocyte depends on the nutritive action of the granulosa, the latter relies on the theca for the provision of androgenic substrate in order to ensure the production of estrogens. Most women are endowed with several millions of follicles at birth, but only a few hundred of them will develop up to ovulation. The fate of most follicles depends on the equilibrium between the proliferation and apoptosis of granulosa, culminating either in the development of the dominant follicle or in its degeneration (e.g. atresia). The factors involved in the selection process of the dominant follicles are largely unknown. The development of the ovarian follicle during the menstrual cycle is predominantly regulated by hormones, most particularly those secreted by the pituitary. However, the role of these hormones can only partially explain the changes observed during the menstrual cycle and those during the woman's life cycle. If the number of follicles drops below a critical level, the ovaries will stop the production of follicles and the transition into the postmenopausal status will ensue despite the strengthened stimulatory action of various hormones secreted by the pituitary. The factors involved in these processes are still largely unknown. It is increasingly thought that signaling originating in the oocytes plays a crucial role. Several factors originating from the oocyte and influencing the surrounding granulosa during various phases of follicular development have already been identified, but many aspects of the interplay between the oocyte-centered signaling and the hormonal factors involved must still be determined.
The goal of our research is to identify new factors and pathways acting in ovarian physiology and in reproductive organs. We are particularly interested in the hormonal regulation of tissue modeling in ovarian follicular development and in closely related organ systems, such as the breast. In order to study the interaction between granulosa and oocytes, a large set of human granulosa cell lines was established and characterized, either using cells from granulosa cell tumors or by transfection of hTERT into granulosa cells recovered from infertile women treated with assisted reproduction. In addition, a human ovary-gene expression profile was established by identifying the expression, the abundance and the corresponding annotation from ESTs of NCBI GenBank derived from non-normalized human ovarian cDNA libraries, such as the Stanford microarray database, the HUGE database of the Kazusa DNA Research Institute and PubMed. These profiles provided data of transcripts for genes of both known and unknown function that were ovary-specific or ovary-enriched and lead to the identification of several novel genes involved in follicular maturation, such as Kiaa1573, inhbp, o/t ring, ADAMTS-16 and others. Further elaboration of another gene, human **B**cl-2-related **o**varian **k**iller gene (hBok), demonstrated that it blocked apoptosis induced by IL-3 withdrawal and Bax expression and that it was expressed in ovarian granulosa, in testicular tissue as well as in various estrogen-dependent breast cancer cell lines. The hormonal regulation of hBok expression was studied in detail using several immortalized cell lines, such as those of granulosa, breast cancer and heart muscle.
In order to further construct an in vitro model for studying the interaction between the oocytes and its surrounding granulosa, immature human oocytes were matured in vitro both with and without immortalized granulosa cells. The effect of the granulosa on the maturation of the oocyte was studied with high frequency videography. The signals originating in the co-cultured oocyte and acting on the surrounding granulosa was studied with cDNA array technology. The results of these experiments will provide further clues for the co-regulation of follicular development by the oocyte.
Unraveling oocyte-centered signaling may not only be crucial for our understanding of the mechanisms in the selection of the dominant follicle, but also for the study of ovarian ageing and menopause altogether. The hormonal changes observed during menopause seem to be caused by a progressive loss of function of all reproductive tissues, which may very well originate in the aged oocytes. As the transition from reproductive life into menopause is associated with an upsurge of several diseases, such as breast cancer, cardiovascular events and osteoporosis, the results of this research may have clinical implications far beyond reproductive medicine.

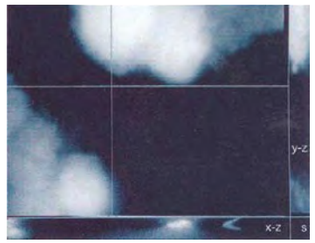


Fig. 1: Immortalized granulosa cells (COV434) in the absence of an oocyte, as demonstrated by confocal light microscopy.

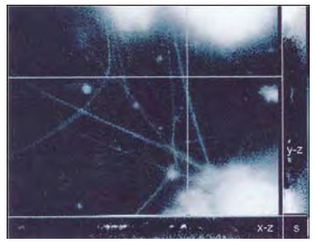


Fig. 2: Immortalized granulosa cells (COV434) in the presence of a human oocyte, as demonstrated by confocal light microscopy. Within hours intercellular connections are formed between the granulosa cells.
The molecular nature of the signalling originating in these immature oocytes is currently under investigation.

Reproductive Medicine

Infertility is a widespread problem in modern society affecting 10 to 15 % of all couples. It frequently causes an emotional crisis in the patients involved often lasting many years and compelling the individuals involved to seek medical care over prolonged periods of time. Nowadays, various methods of assisted reproductive technology are available, such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). However, all these techniques heavily rely on the concomitant stimulation of ovarian function with gonadotropins. The response of the ovaries to these treatments decreases with age and those patients, who do not react properly to the activity of the hormonal preparations administered, are not likely to achieve pregnancy. In addition, those individuals, who react well to these treatments, bear some risk to suffer from complications, such as the ovarian hyperstimulation syndrome (OHSS) or multiple pregnancies. Therefore, these treatments must be monitored using some of the biological signals originating in the developing follicles. The quality of the maturing follicle is assessed with serial measurements of the estradiol concentration in the serum and with ultrasound. However, final maturity of the follicle is substantiated by visualizing the perifollicular vascularization with Power Doppler Ultrasound and with the incremental rise of the progesterone concentration in the serum. The timely coordination of follicular maturity and the oocyte´s meiosis can only be achieved, if it is assumed that some of these signals are coordinated by the oocyte. The effect of these events is not only limited to the ovary, but results in changes throughout the woman´s body, as demonstrated by the modification of the adrenal steroidogenesis during the periovulatory phase. Therefore, knowledge of the interaction between the oocyte and the surrounding tissues may help to develop new treatment modalities aiming at improving the sensitivity of the body to the signalling from the oocyte. Furthermore, better understanding of these phenomena will also contribute to cure some of the changes occurring during the menopausal transition and thereafter.

Das Zusammenwirken der Eizelle und dem Hormonmilieu im Eierstock für die Fertilität

Der Eierstock besteht im Wesentlichen aus drei Komponenten: den Eizellen, der Granulosa und der Theka. Während die Theka für die Bereitstellung des Grundsubstrates für die Produktion der weiblichen Geschlechtshormone verantwortlich ist, ist das enge Zusammenwirken der Granulosa und der Eizelle für die Follikelreifung entscheidend. Die Granulosa produziert die weiblichen Geschlechtshormone, und umgibt die Eizelle, die von der adäquaten Funktion dieser Zellen abhängig ist. Die Granulosazellen stehen in enger Verbindung mit der Eizelle und versorgen diese mit Sauerstoff und "Bausteinen". Umgekehrt beeinflusst die Eizelle auch die sie umgebende Granulosazellschicht. Die Signale der Eizelle werden dort verstärkt und an die umgebende Theka weitergereicht. Klinisch-experimentelle Untersuchungen haben gezeigt, dass eine Unterdrückung der Eierstockfunktion, z.B. mit einem oralen Ovulationshemmer, auch die Hormonproduktion in der Nebennierenrinde unterdrückt. Möglicherweise verursacht der Verlust der Signalwirkung von der Eizelle zur Granulosa die Veränderungen der Menopause, welche auftritt, wenn der Vorrat an Eizellen aufgebraucht ist. Somit kann eine Aufschlüsselung der Signalwirkung der Eizelle auch Erklärungen für die Veränderungen im Alter der Frau bieten.
Unser Ziel ist die Erforschung der Signalwirkung im Ovar, insbesondere zwischen Eizelle und ihrer engeren Umgebung. Hierfür verwenden wir die modernsten Methoden der Molekularbiologie und der Bioinformatik. Es ist uns gelungen, verschiedene neuartige Gene, die für die Wechselwirkung zwischen der Hormonwirkung und dem programmierten Zelltod (sogenannte "Apoptose") verantwortlich sind, zu identifizieren. Darüber hinaus führten wir im Labor experimentelle Untersuchungen durch, in denen wir die Signalwirkung zwischen menschlichen Eizellen, die im Rahmen der in-vitro Fertilisation (IVF) gewonnen wurden, und den Granulosazellen untersuchten. Zu diesem Zweck identifizierten und charakterisierten wir einen immortalisierten Granulosazellstamm, welcher im Labor auch interzelluläre Verbindungen zur Eizelle aufnehmen kann. Mit der Genchipanalyse versuchen wir derzeit neue Signale, ausgehend von der Eizelle, zu identifizieren und deren Funktion zu evaluieren.

Selected Publications

- De Geyter, Ch., De Geyter, M., Huber, P.R., Nieschlag, E., Holzgreve, W. (2002) Progesterone levels during the follicular phase of the menstrual cycle originate from the crosstalk between the ovaries and the adrenal cortex. Human Reproduction 17: 933-939.
- Vollmer, M., Wenzel., F., De Geyter, Ch., Zhang, H., Holzgreve, W., Miny P. (2000) Assessing the chromosome copy number in metaphase II oocytes by sequential fluorescence in situ hybridization (FISH). Journal of Assisted Fertilization and Genetics 17: 596-602.
- Zhang, H., Holzgreve, W., De Geyter, Ch. (2000) Evolutionarily conserved Bok proteins in the Bcl-2 family. FEBS Letter 480: 311-313.
- Zhang, H., Holzgreve, W., De Geyter, Ch. (2001) Bcl2-L-10, a novel anti-apoptotic member of the Bcl-2 family, blocks apoptosis in the mitochondria death pathway but not in the death receptor pathway. Human Molecular Genetics 10: 2329-2339.

Jak-STAT signaling
Hepatitis C virus
Interferon
Liver regeneration

Hepatology

Prof. Dr. Markus Heim
Departement für Innere Medizin
Universitätsspital Basel

Group Members
Dr. F. Duong
Elke Bieck (technician)
Simone Stutvoet (PhD student)
Verena Christen (PhD student)
Sabina Hernandez (PhD student)
Michael Dill (MD student)
Xueya Wang (diploma student)

Intracellular Signaling in Liver Disease and Repair

The hepatology laboratory in the Department of Research of the University Hospital Basel focuses on two specific projects in the field of intracellular signaling in liver diseases and during hepatic repair processes after liver damage.

I. Intracellular signaling through the Jak-STAT pathway in liver cell proliferation, apoptosis and differentiation
The liver has an enormous capacity to regenerate after damage. A better understanding of the molecular mechanisms that control the repair processes can lead to better prevention and better therapies of liver diseases in the future. Over the last years, our group has investigated the role of interleukin-6 and Stat3 signaling in the liver during regeneration after partial hepatectomy. Using IL-6 deficient mice, we found that IL-6 signaling is important for survival after partial hepatectomy, but not essential for the proliferation of liver cells during liver regeneration (Blindenbacher et al. 2003b). We now focus our efforts on the generation of 3 transgenic mouse lines that express fusion proteins between a mutated estrogen receptor ligand binding domain and signal transducer and activator of transcription (Stat) 1, Stat3 and Stat5, respectively, in hepatocytes. These fusion proteins can be activated by 4-hydroxy tamoxifen, a synthetic steroid, independently from endogenous ligands (gain-of-function models). We plan to study the effects of Stat activation in various physiological and pathophysiological models of liver development, liver damage, and liver repair.

II. Hepatitis C virus interference with interferon induced intracellular signaling through the Jak-STAT pathway
Hepatitis C virus (HCV) has a striking capacity to establish a chronic infection. In order to do so, HCV must escape the host immune response. Type I interferons (IFN) are crucial and potent components of the early host response against virus infection. The most important signal transduction pathway for IFNs is the Jak-STAT pathway (Figure 1). IFNa and IFNb activate STAT1, STAT2 and often STAT3. Signal transducers and activators of transcription (STAT) proteins are activated by members of the Jak kinase family through the phosphorylation of a single tyrosine residue. Activated STATs form dimers, translocate into the nucleus and bind specific DNA elements in the promoters of target genes. This activation cycle ends by tyrosine dephosphorylation in the nucleus, followed by the decay of dimers and the nuclear export of STATs. IFN induced gene transcription can be inhibited by protein inhibitor of activated STAT1 (PIAS1). The binding of PIAS1 to STAT1 is regulated by methylation of STAT1 on arginine 31 by protein arginine methyl-transferase PRMT. Arginine methylation inhibits binding of PIAS1 to STAT1, whereas demethylation of STAT1 enhances its association with PIAS1.
Several years ago we found that the expression of HCV proteins in human osteosarcoma cell lines inhibits IFN induced signaling through the Jak-STAT pathway (Heim et al. 1999). These findings could be confirmed in transgenic mice that express the entire open reading frame of the hepatitis C virus genome in the liver under the control of the hepatocyte specific alpha1-antitrypsin promoter (Blindenbacher et al. 2003a). Recently, we observed that IFN signaling is also inhibited in liver biopsy samples of patients with chronic hepatitis C (Duong et al. 2004). Furthermore we identified Stat1 as the cellular target of HCV interference with IFN signaling. In the presence of HCV proteins, Stat1 molecules are hypomethylated on arginine 31. This hypomethylation leads to an increased association with the inhibitor PIAS1. As a consequence, STAT1 can not induce interferon target genes. By inhibiting IFN signaling, HCV can protect itself from endogenous and exogenous IFN.

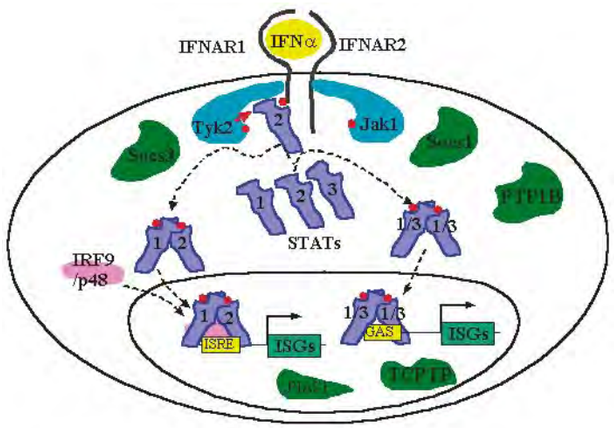


Fig. 1: Interferon signal transduction through the Jak-STAT pathway.

Clinics

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide. An important and striking feature of hepatitis C is its tendency towards chronicity. In over 70% of infected individuals, HCV establishes a persistent infection over decades that may lead to cirrhosis and hepatocellular carcinoma. Chronic hepatitis C is treated with a combination therapy with pegylated (long-acting) interferon alpha injected subcutaneously and ribavirin taken as capsules. The treatment duration is 6 to 12 months, and the overall success rate is 45-60%. The reasons for treatment failures in up to half of the patients are currently not understood.

Signalaustausch in der Leber während Regeneration und Krankheit

Die Leber hat eine enorme Kapazität zur Regeneration. Infektionen mit dem Hepatitis C Virus Infektionen gehören zu den weltweit wichtigsten chronischen Lebererkrankungen, welche zu Zirrhose und Leberkrebs entarten können. Mit der aktuellen Behandlung (u.a. mit Interferonen) können rund 45-60% der chronisch erkrankten Patienten geheilt werden.
Unsere Gruppe befasst sich daher mit zwei spezifischen Projekten: Einerseits geht es darum die molekularen Grundlagen der Regenerationskapazität der Leber besser zu verstehen, um neue Therapieansätze für Lebererkrankungen oder nach partieller Leberentfernung (Hepatektomie) zu finden. Andererseits möchten wir verstehen warum das Hepatitis C Virus in so vielen Fällen der Interferonbehandlung ausweichen kann, um Wege zu finden wie man dies verhindern kann.
Mit Hilfe von transgenen Mäusen konnten wir zeigen, dass der Wachstumsfaktor Interleukin 6 (Il-6) für das Überleben, jedoch nicht das Wachstum der Leberzellen nach einer Hepatektomie wichtig ist. Für Regenerationsprozesse, d.h. Zellteilung scheinen Elemente der sogenannte STAT Signalkette (Stat: signal transducer and activator of transcription) die entscheidende Rolle zu spielen. Welche Element dies sind überprüfen wir zurzeit mit einer Reihe von transgenen Mäusen.
Die Resistenz des Hepatitis C Virus gegenüber Interferonen scheint ähnliche Signalmechansimen zu betreffen. Körpereigene, sowie medikamentöse Interferone schalten selber Zielgene über die sogenannte Jak-STAT Signalkette an. Dieser Signalmechanismus ist eine entscheidende und effiziente frühe Reaktion von Virus-infizierten Zellen. Wir stellten fest, dass diese Signalkette sowohl in der Leber von transgenen Mäusen, welche das Hepatitis C Virus tragen, als auch in Leberbiopsien von chronisch Hepatitis C erkrankten Patienten unterbrochen ist. Wir sind dabei den Mechanismus dieser Unterbrechung auf molekularer Ebene aufzuklären.

Selected Publications

- Blindenbacher, A., Duong F.H., L. Hunziker, Stutvoet S.T., Wang X., Terracciano L., Moradpour D., Blum H.E., Alonzi T., Tripodi M., La Monica N., and Heim M.H. (2003a) Expression of hepatitis c virus proteins inhibits interferon alpha signaling in the liver of transgenic mice. Gastroenterology 124: 1465-75.
- Blindenbacher, A., Wang X., Langer I., Savino R., Terracciano L., and Heim M.H. (2003b) Interleukin 6 is important for survival after partial hepatectomy in mice. Hepatology 38: 674-82.
- Duong, F.H., Filipowicz M., Tripodi M., La Monica N., and Heim M.H. (2004) Hepatitis C virus inhibits interferon signaling through up-regulation of protein phosphatase 2A. Gastroenterology 126: 263-277.
- Heim, M.H., Moradpour D., and Blum H.E. (1999) Expression of hepatitis C virus proteins inhibits signal transduction through the Jak-STAT pathway. J Virol 73: 8469-75.

Obesity
Diabetes mellitus
Adipocytes
Isle-derived stem cells
Hormokines

Metabolism

Prof. Dr.
Ulrich O. Keller
Departement Forschung
Universitätsspital Basel

PD Dr.
Beat Müller

Dr. Henryk Zulewski
(principle investigator stem cell project)

Group Members
Dr. Philippe Linscheid
Dalma Seboek (PhD student)
Michael Eberhard (PhD student)

New Ways toApproach the Problem of Diabetes and Inflammation-studies Involving Hormokines, Adipocytes and Islet-derived Stem Cells.

Obesity is one of the most expanding health problems world-wide. It is characterized by the excess accumulation of body fat. Consecutively, obesity-related insulin resistance leads to an array of inflammatory complications, diabetes mellitus type 2 with a relative insulin deficit and impaired insulin action on glucose and lipid metabolism, metabolic syndrome, more severe infections including a higher mortality in sepsis. Conversely, aggressive insulin infusion therapy to counter the insulin resistance and improve glycemic control reduced mortality by 50% in septic patients. Procalcitonin, a precursor of the hormone calcitonin, is circulating in large amounts in many infection-related diseases, e.g. bacterial sepsis. Though procalcitonin measurements are now routinely used in clinical practice, the induction mechanisms and the source this enigmatic family of peptides are still obscure.
Our research aims to unravel the common underlying molecular mechanisms using three innovative approaches using human cell culture models and combining clinical and experimental research:

a) Human adipose tissue as source of hormokines and inflammatory peptides
Based on our published data on ubiquitous procalcitonin production in sepsis, we postulated the presence of microbial infection-specific response-elements (MISRE) in the CALC I gene promoter, which, upon an inflammatory stimulus, override the tissue-selective neuroendocrine expression pattern. The term "hormokines" depicts this inflammation-related, widespread expression of hormones. Accordingly, we reported a sepsis- and inflammation-mediated CT-mRNA transcription and procalcitonin secretion in human adipose tissue and in mesenchymal stem cell- (MSC) derived adipocytes. In analogy to the non-neuroendocrine expression of CT peptides, we hypothesized that other hormones (e.g. SRIF) might be "ectopically" expressed upon inflammatory stimulation, characteristic for so-called "hormokines". Accordingly, we also identified that SRIF is secreted by human adipose tissue, both, ex vivo upon LPS and IL-1β stimulation.

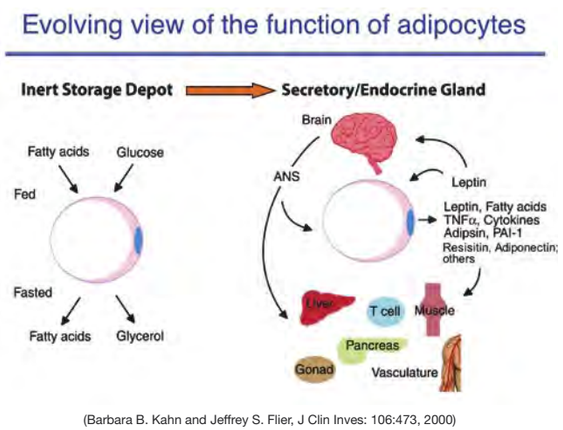


Fig. 1: Adipocytes are not only an inert storage depot of fat but also a secretory-endocrine gland

b) Human adipose tissue as site action of inflammatory peptides
The role of adipose tissue is by far not limited to inert triglyceride storage (Fig 1). We want to elucidate whether adipose-tissue-derived cytokines, CT-peptides, and SRIF plays a role in the metabolic regulation during inflammatory diseases, e.g. by modulating insulin secretion in conditions of insulin resistance and relative insulin deficiency (e.g. obesity or sepsis). To assess insulin resistance we measure glucose uptake and lipolysis in our human adipocyte model. Nitric oxide (NO), the main synthesis product of iNOS is a suspected mediator of insulin resistance. We found the respective mRNAs of CT receptor, CT receptor like receptor (CRLR)-, RAMP 1- and 2-mRNA to be expressed in preadipocyte- and MSC-derived adipocytes (Fig 2). Hence, we expect CT-peptides to exert defined effects on adipocytes (e.g. induction of insulin resistance, modulation of iNOS activity)

c) Ex vivo generation of human insulin producing cells
Both, diabetes mellitus Typ 1 and 2 are characterized by an absolute and relative Insulin deficit, respectively. After discovery of potential stem cells in the islets of Lanherhans by members of our group we were able to isolate and reversibly immortalise these stem cells that express not only several stem cell marker but also the transcriptionfactor islet-1 that is critical for development of endocrine pancreatic cells (Fig 3). In addition, in a proof of principle study we show in a SCID mouse transplantation model that human islet derived stem cell are able to adopt a hepatic phenotype in vivo.

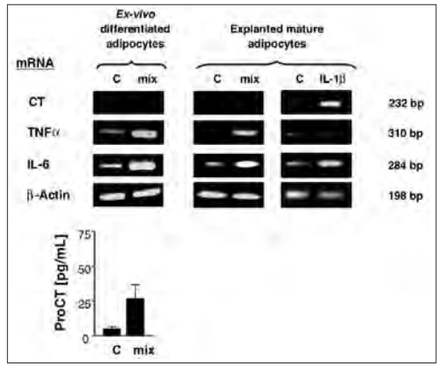


Fig. 2: Adipocytes were subjected to inflammatory treatments ("mix" of cytokines, i.e. IFNg, TNFα, IL-1β, and LPS) for 6 hours. Thereafter, CT mRNA was analysed by RT-PCR. TNF mRNA and IL-6 mRNA were analyzed as controls. After stimulation procalcitonin mRNA was expressed and the peptide was secreted in supernatants as measured by a sensitive chemilumometric assay with a detection limit of 5 pg/mL.

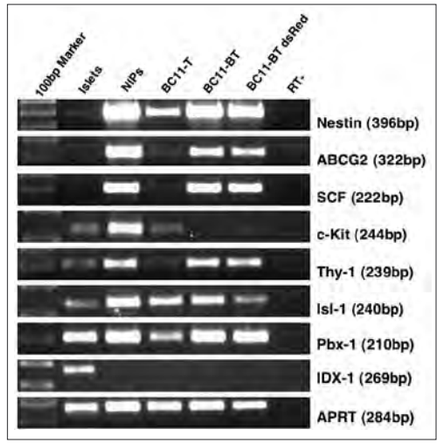


Fig. 3: Expression of stem cell markers and isl-1 in human islets of Langerhans and different islet derived stem cells. NIP=nestin positive islet derived progenitor cells, islet derived stem cell lines BC11-T, BC11-BT, BC11-BT dsRed.

Hormokine und das Fettgewebe bei Entzündungen: Fettleibigkeit ist eines der wichtigsten Gesundheitsprobleme weltweit; die Vermehrung des Fettgewebes bewirkt eine Insulin-Resistenz und zieht damit eine Reihe von Komplikationen nach sich, darunter Typ 2 Diabetes. Übergewichtige weisen zudem einen Zustand einer leichtgradigen, chronischen Entzündung auf, die für die Insulinresistenz mitverantwortlich ist. Schwerkranke mit Insulinresistenz und Sepsis profitieren von einer Überwindung der Insulinresistenz durch eine Insulintherapie mit einer ca. 50% Abnahme der Mortalität Hormokine sind die im Zusammenhang mit Entzündungen ausgeschütteten Hormone, wobei uns besonders die Kalzitonin-Peptide interessieren. Wir zeigten, dass das neben anderen Geweben, auch menschliches Fettgewebe Hormokine herstellt, und dass die Gene, die z.B. für Prokalzitonin kodieren im Falle von Sepsis und bei Entzündungen eingeschaltet werden. Es muss also in der Regulation dieser Gene Elemente haben, welche auf die Signale von mikrobiellen Eindringlingen reagieren. Zum Studium dieser Mechanismen verwenden wir innovative Techniken mit menschlichen Zellkulturen und eine Kombination aus experimenteller und klinischer Forschung. Insbesondere erforschen wir, ob diese den Stoffwechsel während Entzündungsreaktionen beeinflussen. Unsere Resultate weisen darauf hin, dass CT Peptide in den Zellen des Fettgewebes eine Rolle bei der Entstehung der Insulin-Resistenz spielen.

Stammzellen als Quelle von Insulin produzierenden Zellen: Unter der Leitung von H. Zulewski wird nach einer neuen auf Stammzellen basierten Therapie für Diabetes mellitus gesucht. Die ersten Resultate zeigen, dass in der Bauchspeicheldrüse des Menschen, in der normalerweise Insulin produziert wird auch Stammzellen existieren und unter besonderen Bedingung ebenfalls in Insulin produzierende Zellen verwandelt werden können. Diese Stammzellen haben aber auch die Fähigkeit sich in Leber- und Fettzellen zu verwandeln, was ein Hinweis auf deren besonderes Entwicklungspotenzial ist. Ähnliche Stammzellen werden auch im Knochenmark vermutet und gegenwärtig in unserem Labor untersucht.

Selected Publications

- Linscheid P., Seboek D., Nylen E.S., Langer I., Schlatter M., Becker K.L., Keller U., Müller B. (2003) In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. Endocrinology 144 (12): 5578-5584.
- Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Muller B. (2004) Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 363: 600-607.
- Linscheid P., Keller U., Blau N., Schaer D.J., Müller B. (2003) Diminished production of nitric oxide synthase cofactor tetrahydrobiopterin by rosiglitazone in adipocytes.Biochem Pharmacol 65 (4): 593-598
- Linscheid P., Seboek D., Schaer D.J., Zulewski H., Keller U., Müller B. (2004) Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. Crit Care Med. 32(8):1801-1802.

Asthma

COPD

Fibrosis

Transcription factor interaction

CCAAT/enhancer binding protein

Glucocorticoid receptor

Pneumology

PD Dr.
Michael Roth
Departement Forschung
und Klinik für Pneumologie
Universitätsspital Basel

Prof. Dr.
Michael Tamm,

Group Members
Dr. Michel Bihl
Dr. Jochen Rüdiger
Dr. Mesut Cornelson Gencay
Dr. Martin Brutsche
Dr. Lukas Hunziker
Dr. Pieter Borger
Stéphanie Goulet (PhD student)
Jingqing Yang (PhD student)

Cell Differentiation and Transcription Factors in Asthma, COPD and Lung Fibrosis

Inflammatory lung diseases including asthma, chronic obstructive pulmonary disease (COPD), lung fibrosis, and emphysema have been considered to result from either a defect in the immune response to allergens, or infections, or are based on a disturbed balance between protein synthesis and protein degradation. Most of these hypotheses were established in animal models but it was recently concluded that none of the models could be proven in humans. In our laboratory we exclusively work with human cells that are established routinely from patient lung tissue specimen and that are not transformed.

Our research on inflammatory lung diseases is focused on the role of transcription factors as the major regulators for cell proliferation and differentiation and how these transcription factors are modulated by the cells' direct environment.

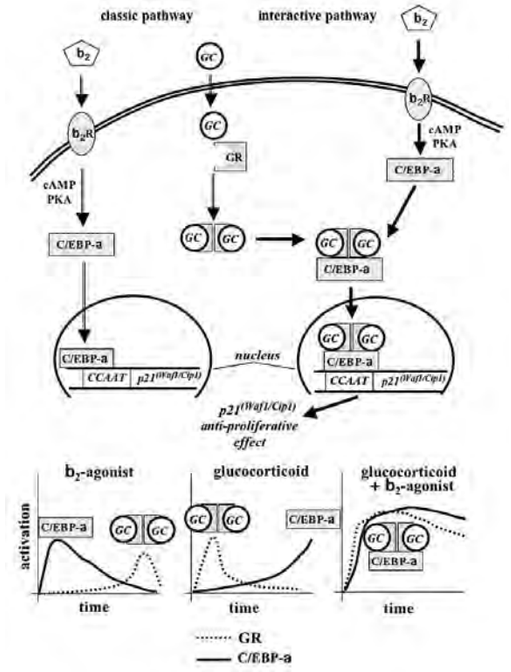
Since 5 years we have a close co-operations with The Woolcock Institute of Medical Research, University of Sydney, Australia, that is specialised in lung diseases. Based on this co-operation we could demonstrate that asthmatic bronchial smooth muscle cells from asthmatic patients proliferate much faster than those from controls. This could explain the increased mass of muscle bundles in asthmatic airways and its hyperresponsiveness to environmental triggers such as inhaled grass pollen, cat hair, or house dust mite. We could further demonstrate that the clinically observed beneficial effect of combined glucocorticoids together with long acting β_2-agonists is based on the synchronised activation of transcription factors: the glucocorticoid receptor and the CCAAT/enhancer binding protein-α (C/EBP-α). Only when both transcription factors are activated at the same time they form a complex that than induces the transcription/activation of the negative cell cycle regulator $p21^{(Waf1/Cip1)}$ which in consequence inhibits cell proliferation (figure 1) (1-2).

This system does not work in asthmatic bronchial smooth muscle cells. The reason why the proliferation of asthmatic bronchial smooth muscle cells cannot be inhibited by glucocorticoids is due to a lack of C/EBP-α. (3). The lack of C/EBP-α does not affect the anti-inflammatory action of glucocorticoids, a finding that fits well with the drugs' clinically documented action. Our findings imply that the pathology of asthma is based on an alteration of cell differentiation. We also could show that an asthma associated micro-organism, *Chlamydia pneumoniae*, uses the same signalling pathway to modify the cells response (4).

In a recently submitted manuscript we demonstrate that the lack of C/EBP-α in asthmatic cells is due to an impaired translation of the mRNA of C/EBP-α and not to a gene defect. Furthermore, this study shows for the first time a molecular difference between asthma and COPD/emphysema. Both diseases were considered to represent two extreme phenotypes of the same pathology. Our study clearly demonstrated that both diseases are linked to a de-regulation of the C/EBP protein family, however, while asthma is linked with a lack of C/EBP-α protein, COPD/emphysema is associated with an up-regulation of C/EBP-δ.

In ongoing studies we investigate the feedback mechanism of: (a) the consequences of the lack/overexpression of C/EBP-proteins on cell differentiation, (b) the modification of the transcription factors by the extracellular matrix and vice versa, (c) the effect of micro-organisms linked to asthma (Respiratory Syncytial Virus, Rhino virus, *Chlamydia pneumoniae*) on the transcription factors, and (d) new drugs on the above described transcription factors.

Our cell culture models using primary human fibroblasts, vascular smooth muscle cells, bronchial smooth muscle cells and epithelial cells of the lung offer the unique opportunity to study pathogenic mechanisms of asthma, COPD and fibrosis. Our findings allow to investigate risk factors for the development these diseases. Furthermore, new therapeutic approaches and drugs can be tested at an early stage on human tissue. These methods might allow to define individual optimal treatment in the near future. The success of our research group is decisively based on the good collaboration of clinicians with the molecular biologists. A close international network allows addressing specific questions in an efficient way.



Die Regulation der Zelldifferenzierung durch Transkriptionsfaktoren und ihre Bedeutung für Asthma, COPD und Lungefibrose

Asthma und chronisch obstruktive Lungenerkrankung (COPD) sind die häufigsten entzündlichen Lungenerkrankungen mit weltweit stetig ansteigender Inzidenz. Bisher wurde die Entzündungsreaktion als Hauptursache dieser Erkrankungen angesehen. Man nahm an, dass infolge die Balance zwischen Gewebeaufbau und –abbau in der Lunge gestört sei und es je nach Verschiebung dieser Balance zu einer Gewebezunahme bzw. –abnahme käme. Die Grundlage dieser Hypothesen bezog sich meistens auf Tiermodele. Neue Ergebnisse an menschlichem Gewebe und Zellkulturen weisen in eine andere Richtung. In unserem Labor arbeiten wir ausschliesslich mit Zellkulturen die aus Gewebeproben der menschlichen Lunge angezüchtet werden. An diesen Zellen untersuchen wir, ob es Unterschiede in der Zelldifferenzierung gibt, die zu einem bestimmten Krankheitsbild passen. Wir untersuchen hierbei die Zellreaktion so breit wie möglich und bestimmen die Rolle von sogenannten Transkriptionsfaktoren und ihrer Interaktion inbezug auf: (i) die Zellteilung und ihre Regulatoren, (ii) den Auf- und Abbau des Bindegewebes (extrazelluläre Matrix), (iii) Zellzuckermoleküle (Glykosamionoglykane), und (iv) die Ausschüttung von Wachstumsfaktoren und deren Inhibitoren.In enger Zusammenarbeit mit der Universität Sydney (Australien) haben wir ein erhöhtes Wachstum bronchialer Muskelzellen von Asthmatikern zeigen können (1). Diese Pathologie konnte auf die fehlerhafte Produktion eines Transkriptionsfaktors (C/EBP-α) zurückgeführt werden und erklärt warum Asthma gut behandelt, aber nicht geheilt werden kann (2-5). Auch bei Patienten mit COPD liegen grundlegende Störungen des Zellverhaltens vor. Mit Hilfe dieser menschlichen Zellkulturen wird die Krankheitsentstehung von Asthma COPD und Lungenfibrosen besser verstanden und können neue Medikamente und Behandlungsarten im Frühstadium getestest werden. Von grosser Wichtigkeit ist uns die enge Zusammenarbeit von Klinikern und Grundlagenwissenschaftlern die wir in unserem Team täglich praktizieren.

Selected Publications

- Ruediger J.J., Roth M., Bihl M.P., Cornelius B.C. Johnson M., Ziesche, R., and Block L.H.(2002) Glucocorticoids act through a C/EBP-α-glucocorticoid receptor complex. FASEB-J, 16: 177-184.
- Roth, M., Johnson, P.R.A., Rüdiger, J.J., King G., Ge Q., Burgess J.K., Anderson G., Tamm, M., and Black, J.L (2002) Interaction between glucocorticoids and β_2-agonists on bronchial airway smooth muscle cells through synchronised cellular signalling. The Lancet, 360: 1293-1299.
- Roth M, Johnson PR, Borger P, Bihl MP, Rudiger JJ, King GG, Ge Q, Hostettler K, Burgess JK, Black JL, Tamm M. (2004) Dysfunctional interaction of C/EBPalpha and the glucocorticoid receptor in asthmatic bronchial smooth-muscle cells. N Engl J Med, 351:560-574.
- Gencay-Cornelsen M. M., Tamm, M., Glanville, A., Perruchoud, A.P., and Roth, M. (2003) Chlamydia pneumoniae activates epithelial cell proliferation via NF_KB and the glucocorticoid receptor. Infection and Immunity, 71:5814-22.

Non-invasive prenatal diagnosis
Erythroblast-differentiation
Cell free fetal DNA
Size separation
Placentally-derived microparticles

Prenatal Medicine

PD Dr. Sinuhe Hahn
Departement Forschung
Universitätsspital Basel

Group members
Prof. Dr. Wolfgang Holzgreve
Dr. Satheesh KR Chinnapapagari
Dr. Susanne Mergenthaler
Dr. Corinne Rusterholz
Dr. Andreina Schoeberlein
Dr. Xiao Yan Zhong
Nicole Chiodetti (technician)
Lisbeth Dudler (technician)
Vivian Kiefer (technician)
Tatiana Babochina (PhD student)
Anurag K Gupta (PhD student)
Ying Li MSc (PhD student)
Sashka Hristoskova (PhD student)
Bernhard Zimmerman (PhD student)
Sonja Seelman (MD student)

Development of Risk Free Methods for Fetal Assessment

Prenatal diagnosis addresses mainly the detection of fetal chromosomal aberrations and single gene disorders, which affect almost 3% of all fetuses. Current methods to retrieve fetal material rely on invasive practices (amniocentesis, CVS), associated with a risk of fetal loss. In the developed world, many professional women consider pregnancy only at a relatively advanced maternal age, which is associated with a naturally elevated risk for an aneuploid fetus. Often, these couples chose to have only one child and are therefore reluctant to expose the fetus to the invasive prenatal diagnostic procedure. Therefore concerted efforts world-wide are undertaken to develop safe efficacious non-invasive alternatives.

The most promising strategies are the enrichment of rare fetal nucleated red blood cells from the blood of pregnant women, and the isolation of cell free fetal DNA from maternal plasma or serum.

After enrichment fetal erythroblasts can be examined by FISH to detect aneuploidies or by single cell PCR following micro-manipulation for single gene disorders. A large scale multi-centre clinical study conducted by the National Institutes of Health (NIH), with our laboratory as the only non-US participant, examined the efficacy of this approach but found it currently not sufficiently robust to reliably permit large scale analyses. Further studies will now be performed in a newly established EU Network of Excellence, SAFE.

Spin-off examinations from these studies concerning erythroblast differentiation and their enucleation showed that this event uses apoptotic processes without invoking actual cell death, in that the nuclear DNA is cleaved, cell organelles like mitochondria are lost, but there is no loss of membrane integrity.

The caveat in analysing fetal DNA from maternal plasma or serum is the maternal origin of the majority of total cell free DNA in the maternal circulation. Thus it was initially suggested that this technique may only be suitable to reliably examine paternally inherited fetal loci absent in the maternal genome, such as fetal sex and rhesus D status in Rhd pregnancies.

Investigating biochemical properties of the circulatory DNA, we recently found that fetal DNA species were generally smaller than comparable maternal ones, and that this observation can be used to selectively enrich fetal DNA, permitting the ready detection of fetal genetic loci not otherwise discernible. First applications of this size-separation approach to detect fetal Mendelian disorders, particularly the hemoglobinopathies are very promising.

Furthermore we found that circulatory fetal nucleic acids are associated with placentally-derived microparticles. These particles, released in increased amounts by the syncytiotrophoblast monolayer in pathological conditions such as preeclampsia, have been implicated in the inflammatory cascade and endothelial damage associated with this disorder.

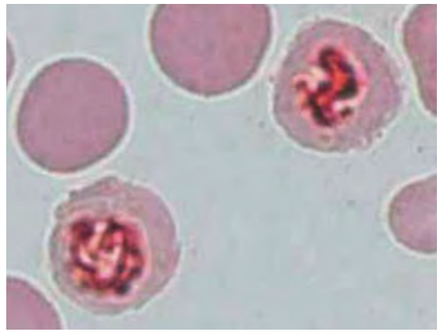


Fig. 1: Fragmented DNA in erythroblast nuclei detected by TUNEL assay

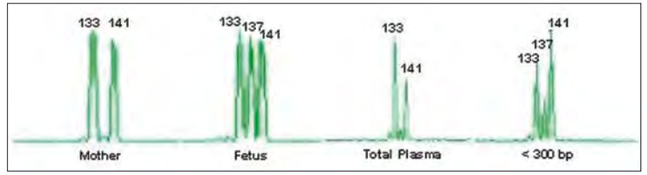


Fig. 2: Size fractionation permits detection of fetal genetic loci which are otherwise masked by maternal DNA sequences. Mother: maternal STR pattern (133 & 141 bp), Fetus: fetal STR pattern (133, 137, 141 bp), indicative of trisomy 21, Total plasma: Only maternal STR loci are detected. <300bp: Analysis of size-fractionated plasma DNA permits detection of fetal STR loci.

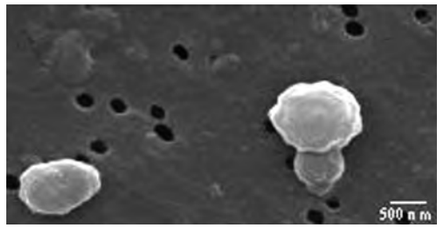


Fig. 3: Syncytiotrophoblast micro-particles generated in-vitro.

Clinical Applications

The analysis of cell free fetal DNA in maternal plasma has been found to be very robust and reliable, and a number of large studies have indicated that sensitivities of close to 99% with 100% specificity can be attained. Consequently this method is already being used clinically, including our centre in Basel, for the examination of the fetal RhD status in pregnancies with a rhesus constellation and sex in those at risk for an X-linked genetic disorder.

These aspects are being addressed in a newly established EU Network of Excellence "SAFE", where our centre is acting as overall Scientific Coordinator and Work-package Leader.

Risikofreie Pränataldiagnose

Die aktuell vielversprechendsten Ansätze zu Etablierung einer sicheren und effizienten, riskiofreien, nicht-invasiven Pränataldiagnostik basieren auf der Untersuchung seltener fetaler kernhaltiger Zellen aus mütterlichem Blut einerseits, sowie der Analyse zellfreier fetaler DNA aus mütterlichem Plasma oder Serum andererseits.

Die Analyse der zellfreien fetalen DNA während der Schwangerschaft gilt mittlerweile als sehr robuste und verläßliche Analysemethode, und eine Vielzahl großer Studien belegen Sensitivitäts-Werte von nahezu 99% mit 100% Spezifität.

Auf dieser Basis wird diese Methode bereits in Kliniken, wie auch in unserem Zentrum in Basel, zur Untersuchung des fetalen Rhesus D-Status in Schwangerschaften mit einem Risiko für Rhesus-Inkompatibilität, sowie zur Bestimmung des fetalen Geschlechts in Schwangerschaften mit einem Risiko für X-chromosomal-gekoppelte Erkrankungen durchgeführt.

Diese Aspekte stehen zudem im Mittelpunkt des neu etablierten EU-Netzwerkes "SAFE", innerhalb dessen unser Zentrum als übergreifender wissenschaftlicher Koordinator und Projektleiter tätig ist.

Selected Publications

- Troeger C, Zhong X.Y, Burgemeister R, Minderer S, Tercanli S, Holzgreve W and Hahn S (1999) Approximately half the erythroblast in maternal blood are of fetal origin. Human Mol Reprod 5:1162-1165.
- Zhong XY, Holzgreve W, and Hahn S (2002) The levels of circulatory fetal DNA in maternal plasma are elevated prior to the onset of preeclampsia. Hyp Pregnancy 2002: 21: 77-83.
- Hristoskova S, Holzgreve W, Hahn S (2003) Fetal nucleated erythrocytes in maternal circulation do not display a classic membrane-associated apoptotic characteristic (phosphatidylserine exposure) despite being positive by terminal dUTP nuclear end labeling. Clin Chem. 49:1934-1937.
- Li Y, Zimmerman B, Rusterholz C, Kang A, Holzgreve W, Hahn S (2004) Size Separation of Circulatory DNA in Maternal Plasma Permits Ready Detection of Fetal DNA Polymorphisms. Clin Chem 50:1002-1011.
- Gupta A, Holzgreve W, Huppertz B, Malek A, Schneider H, Hahn S (2004) Detection of fetal DNA and RNA in placentally derived syncytiotrophoblast microparticles generated in-vitro. Clin Chem (in press).

Hematopoiesis

In utero thearpy

Stem celll treatment

Fetal immunocompetence

Prenatal Medicine

Prof. Dr. Dr. h.c. mult. Wolfgang Holzgreve
Universitäts-Frauenklinik Basel

Stem Cell Transplantation for in Utero Therapy

Most genetic diseases with prenatal origin can not be treated any more postnatally and the advantages of the proposed in-utero stem cell application approach include the lack of immune competence in the fetus, avoiding rejection of donor stem cells, and the potential to prevent severe prenatal morbidity.
Prenatal stem cell transplantation is now at the edge of moving from preclinical research into clinical application. The first clinical experiences have already shown that inborn diseases, which lead to a severe immunodeficiency, can be treated successfully in-utero by transplantation of haploidentical adult or fetal liver stem cells. No therapeutic success has been achieved so far in genetic disorders which do not severely affect the immune system. Therefore, we are trying to develop new strategies to improve the success.
By making use of two distinct animal models (immunodeficient fetal mice and sheep) we test strategies such as graft modification, prenatal conditioning of the fetus, postnatal transplantation after prenatal induction of immune tolerance, and fetal gene therapy using autologous fetal stem cells (ex-vivo fetal gene therapy).
Initially we used the immunodeficient NOD/SCID mouse model for in-utero transplantations. Human-to-mouse transplants yielded engraftment rates of only 2.2% (1 of 45 pups) with a very low level of chimerism, detectable only by nested PCR at 4 weeks of age in the spleen. In contrary, allogeneic in-utero transplants yielded 80% chimeric recipients with high-level engraftment.
Overall, engraftment levels increased in the given timeframe, reaching 50%, 5% and 88% in peripheral blood, bone marrow and spleen, respectively. In all cases, recipients with donor cells in the peripheral blood also showed engraftment in the bone marrow and the spleen. Donor cells in the peripheral blood and the spleen 4 and 16 weeks after transplantation consisted mostly of B- and T-cells, as represented by the specific markers B220 and CD3 respectively. In the bone marrow, however, the cell markers Mac 1 and Gr 1, specific for myeloid lineages and granulocytes were more prominent, both increasing with time after transplantation. The relative number of c-kit positive donor cells in the bone marrow slightly increased between 4 and 16 weeks after transplantation.
In fetal sheep we transplanted human cord blood stem cells across xenogeneic barriers and achieved low-level engraftment. In recent experiments, we aimed to compare engraftment of autologous and non-matched allogeneic stem cells in an immunocompetent recipient to assess the role of immunologic rejection among MHC (major histocompatibility) barriers. Time-mated white alpine ewes were used. As donor SC, either allogeneic male fetal liver cells at 49 days' gestation, or autologous fetal liver cells were collected using an ultrasound-guided technique which we previously described. Stem cells were labeled and cryopreserved until transplantation. Fetuses were sacrificed and donor cell engraftment was analyzed by FACS and real-time PCR targeting the SRY gene (in allogeneic grafted animals). We found that donor cells engrafted preferentially in the spleen (1.14 ±1.62%), followed by bone marrow (0.56 ±0.54%), thymus (0.40 ±0.69%), liver (0.23 ±0.25%) and peripheral blood (0.11 ±0.12%) by FACS. Real-time PCR data showed similar distribution. Future strategies will now focus on providing growth advantage to donor cells rather than immunosuppressive manipulation of the recipient. A further interest of our group is the use multipotent mesenchymal stem cells stem cells obtained from bone marrow or fetal liver as donor cells for in-utero transplantation. First experimental series show multitissue-engraftment in fetal sheep recipients including neural tissue in the fetal brain. These engrafted cells are now being analysed regarding functional transdifferentiation.
Within the framework of an EU-funded European collaboration (ENFET project) which includes centers in the U.K., France, Italy, and Israel, our group is developing standards for clinical protocols and ethical frameworks. Ethical implications, in particular regarding fetal gene therapy and the use of pluripotent stem cells, are being addressed.

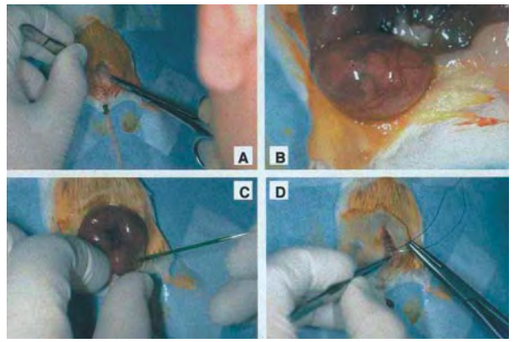


Fig. 1: Peritoneal injection of stem cells into the mouse fetus at gestation day 13.5 under narcosis.

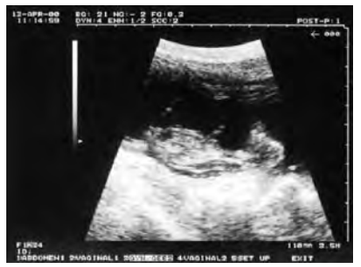


Fig. 2: Longitudinal view of an ultrasound scan at the end of the first trimester of gestation (day 50) in a sheep model.

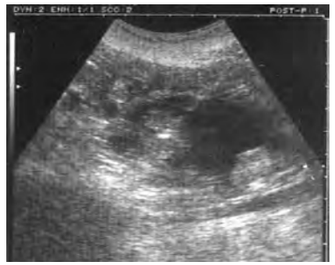


Fig. 3: Ultrasound scan during intra-uterine puncture and injection of stem cells into the peritoneal cavity of the sheep fetus at the end of the first trimester.

PD Dr. Daniel Surbek
Universitäts-Frauenklinik Basel

Stammzelltransplantation für in-utero Therapie

Viele genetisch bedingten Erkrankungen beeinträchtigen die fetale Entwicklung erheblich, und können postnatal nicht mehr behandelt werden. Um schwere pränatale Schäden zu vermeiden, verfolgen wir daher die Entwicklung eines Stammzell-basierten Ansatzes zur in-utero Therapie. Der Vorteil dieser Methode ist die unvollständige fetale Immunkompetenz, wodurch die Abstossung von Donor-Zellen verhindert wird. Erste klinische Anwendungen dieser in-utero Therapie für fetale Erkrankungen mit schwerer Immundefizienz berichteten positive Ergebnisse, wohingegen Erbkrankheiten ohne Immundefizienz nicht erfolgreich behandelt werden konnten.
Zur Entwicklung neuer Strategien testeten wir xenogene und allogene Transplantation in NOD/SCID Maus-Föten und Schafen, wobei xenogene Transplantation nur in 2.2%, jedoch allogene Transplantation in 80% der Empfänger erfolgreich war. Anteile von Donor-Zellen betrugen bis 50% im Blut, 5% im Knochenmark und 88% in der Milz. In Blut und Milz dominierten die Donor-Zellen als B- und T-Zellpopulationen, während sie im Knochenmark v.a. myeloide Linien und Granulozyten bildeten.
Weiterhin verglichen wir das Engraftment-Ausmass zwischen autologer und allogener Stammzell-Transplantation in einem immunkompetenten Empfänger, um die Rolle immunologischer Abstossung unter Berücksichtigung von MHC-Barrieren zu untersuchen.
Zukünftige Studien werden sich auf Möglichkeiten zur Proloferationsförderung der Donor-Zellen konzentrieren, sowie die Verwendung mesenchymaler Stammzellen für die in-utero Transplantation prüfen.
Darüberhinaus erarbeitet unsere Gruppe innerhalb eines EU-Projekts (ENFET) klinische Protokolle und ethische Grundlagen für die in-utero Transplantation.

Selected Publications

- Surbek D.V., Holzgreve W., Nicolaides K.H. (2001) Hematopoietic stem cell transplantation and gene therapy in the fetus: Ready for clinical use? Hum Reprod Update; 7: 85-91
- Surbek D.V., Schatt S., Holzgreve W. (2001) Stem Cell Transplantation and gene therapy in-utero. Infusion Therapy and Transfusion Medicine; 28: 150-158
- Surbek D.V., Young A., Danzer E., Schoeberlein A., Holzgreve W. (2002) Ultrasound-guided stem cell sampling from the early ovine fetus for prenatal ex-vivo gene therapy. Am J Obstet Gynecol; 187: 960-963
- Young A., Holzgreve W., Dudler L., Surbek D. (2003) Engraftment of human cord blood-derived stem cells in ovine fetuses after ultrasound-guided in-utero transplantation. Am J Obstet Gynecol; 189: 698-701
- Schoeberlein A., Holzgreve W., Dudler L., Hahn S., Surbek D.V. (2004) In utero transplantation of autologous and allogeneic fetal liver stem cells in ovine fetuses. Am J Obstet Gynecol; (in press)

Occlusive Vascular Disease
Tissue Remodelling
Angiogenesis
Cell Phenotype
Cell Adhesion Molecules
T-cadherin

Signal Transduction

Prof. Dr. Thérèse Resink
Departement Forschung
Universitätsspital Basel

Group Members
Dr. Maria Philippova
Dr. Danila Ivanov
Roy Allenspach (technician)
Vanya Morf (PhD student)
Manjunath Joshi (PhD student)

Cell Adhesion Molecules in Vascular Remodelling and Neovascularization

Our basic research interests lie in the field of vascular remodelling and encompass the control of both smooth muscle cell (SMC) function in the context of restenosis/atherosclerosis and endothelial cell (EC) function in the context of angiogenesis. Our objectives are two-fold: (A) basic understanding of the function and molecular mechanisms of action of molecules participating in regulation of smooth muscle cell and endothelial adhesion, migration and proliferation, with focus on cell adhesion molecules; (B) Extrapolation of knowledge gained from basic research toward therapeutic targeting (pharmaco- or gene- based) of SMC and EC functions relevant to restenosis, atherosclerosis and angiogenesis.
Vascular occlusion is morphologically characterized by extensive intimal expansion that develops through activation of SMC's, whereas angiogenesis, the formation of new blood vessels, is initiated through activation of EC's. Although occlusion and angiogenesis are distinct processes, analogies exist with respect to cell migration, growth, (de)differentiation and survival responses. These responses require positional reorganization and movement of the participating cells (SMC and EC) and are dependent upon modulations in the cell-cell and cell-matrix adhesive interactions that supply cues for attachment, detachment, attraction, repulsion and navigation. Various cell adhesion molecules including integrins, members of the immunoglobulin superfamily, selectins and cadherins mediate these interactions, and impaired expression or function of such molecules have been implicated in a number of occlusive cardiovascular disorders such as atherosclerosis, (re)stenosis, as well as their common clinical complications (thrombosis, myocardial ischaemia and infarction), and deregulated angiogenesis.
T-cadherin (T-cad) is an atypical GPI-anchored (GPI glycosylphosphatidylinositol) member of the cadherin family of homophilic cell adhesion molecules. Although widely expressed in the cardiovascular system, and with elevated expression in vascular cells in atherosclerosis, restenosis and tumour angiogenesis, the physiological functions of T-cad in vascular tissue are unknown. Given its GPI-anchorage, T-cad has been proposed to act as a signalling/recognition receptor rather than as a true adhesion molecule. We have shown that unlike the classical cadherins, T-cad is globally distributed and not located at intercellular junctions of resting vascular cells and it undergoes redistribution to the leading edge of migrating cells (Fig. 1A). Mimicry of homophilic ligation by seeding cells onto immobilized substrata of recombinant T-cad results in poor spreading, inhibited adhesion and changes in the morphology and cytoskeletal distribution of adherent cells characteristic of a more motile phenotype (Fig. 1B). Moreover, T-cad overexpression in vascular cells increases the rate of proliferation.
We hypothesize that T-cad modulates vascular cell phenotype and behaviour by facilitating de-adhesion. The notion that a member of the cadherin family of cell adhesion molecules should function in an anti-adhesive capacity is perhaps paradoxical, but not to be ignored. Cellular de-adhesion is as important as adhesion in modulating the attachment, detachment, attraction, repulsion and navigation processes that enable cells to appropriately migrate, grow, (de)-differentiate and survive in the process of tissue development and remodelling and as well as for cell transmigration.
Our specific current goals are to: (a) demonstrate that T-cad can regulate migration, survival and angiogenic/invasive properties of human vascular cells by modulating adhesiveness to the matrix and/or influencing cell navigation negative guidance, (b) elucidate mediatory cellular and signalling mechanisms, and (c) determine the functional domain(s) of T-cad, and generate modifications which abrogate or sustain de-adhesion /negative guidance/ repulsive responses.

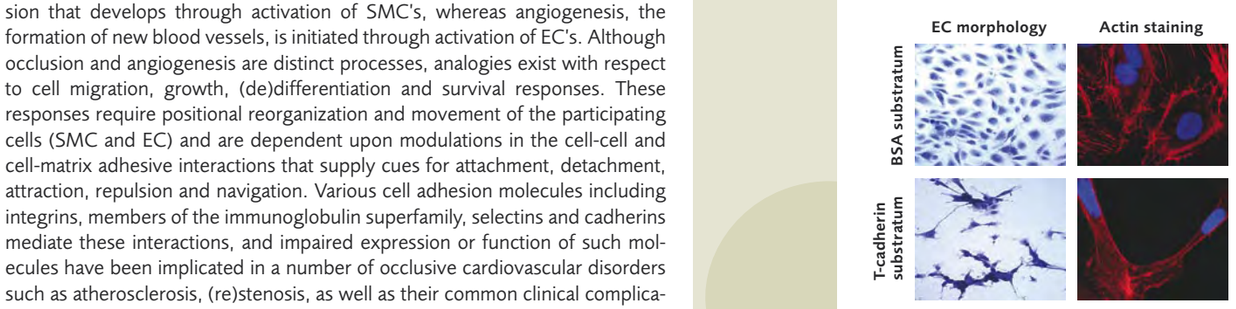


Fig. 1 A: T-cadherin in vascular EC and SMC is globally distributed in resting cultures but undergoes redistribution to the leading edge of migrating cells (arrows indicate direction of migration).

Fig. 1 B: In EC, homophilic ligation (i.e. by seeding on T-cad coated substratum) induces alterations in morphology and cytoskeletal distribution that are characteristic of the more motile, angiogenic phenotype.

Clinical Partner

We focus on four clinical research programs. Silent Ischemia: Our department coordinates two long-lasting prospective, multicenter studies to evaluate the course and prognosis of patients with silent ischemia. In the first study, a preventive treatment is compared to no treatment in patients that had no overt coronary heart disease before. In the second study, maximal anti-ischemic treatment is compared to PTCA (percutaneous transluminal coronary angioplasty) in patients with silent ischemia after a myocardial infarction. Malign Ventricular Arrhythmias: We evaluate the accuracy of 3 non-invasive analyses in the case of arrhythmias retrospectively with data collected since 1991, and, prospectively determine the criteria to predict the risk of cardiac arrest or the need of therapy based on the collected data. Angina Pectoris without coronary heart disease: Coronary heart disease can be excluded in ca. 10% of the patients investigated invasively for angina pectoris. In these cases, the symptoms have their origins in a vasospastic heart disease, in pulmonary hypertension or in small vessel diseases. Data for 600 patients with right heart catheterization and after intracoronary infusion of acetylcholine has been collected. We are documenting the course of these patients for 1-6 years. Vasospastic Heart Disease: We repeatedly noticed a marked reduction of the symptoms of vasospastic heart disease after a local radiotherapy. In addition, the extensive vasoconstriction was diminished after intracoronary infusion of acetylcholine. This led us to conduct a prospective investigation with patients who have severe vasospastic disease and who are resistant to available therapies. We irradiate a vasospastic segment of the coronary artery and monitor the course of the symptoms.

Prof. Dr. Paul Erne
Departement
Kardiologie
Kantonsspital Luzern

Zelladhäsionsmoleküle und Blutgefässe

Die Angiogenese – die Bildung von neuen Blutgefässen – und der Gefässverschluss sind zwei grundlegend verschiedene Vorgänge. Die Angiogenese wird durch Aktivierung der Endothelialzellen eingeleitet, während beim Gefässverschluss eine interne Expansion von glatten Muskelzellen beteiligt ist. Bei beiden Vorgängen spielen sich jedoch gemeinsame Mechanismen ab. Diese erlauben den beteiligten Zellen (Endothelialzellen oder glatte Muskelzellen) eine örtliche Reorganisation, Bewegungen, Wachstum und ihr Überleben. Wir untersuchen die Rolle von Zelladhäsionsmolekülen bei Veränderungen in Blutgefässen. Zellahäsionsmoleküle sind für die den Kontakt zwischen den Zellen und zwischen Zellen und deren Umgebung (Matrix) verantwortlich. Insbesondere interessieren wir uns für T-Cadherin. T-Cadherin ist in Zellen von allen Blutgefässen zu finden, scheint aber eine besondere Rolle im Falle von Arteriosklerose, Restenose (Gefässverschluss nach chirurgischer Gefässerweiterung) und Tumor-Angiogenese zu spielen. Wir konnten zeigen, dass T-Cadherin sich homogen um ruhende Zellen verteilt aber bevorzugt an der Front von wandernden Zellen zu finden ist . Bringt man Endothelialzellen auf eine Kulturplatte, welche T-Cadherin enthält, so kommt es zu morphologischen Veränderungen, welche für die Angiogenese typisch sind. Wir vermuten, dass T-Cadherin für phenotypische Veränderungen der Zellen verantwortlich ist und eine De-adhäsion (ein Loslösen) fördert.
In der Abteilung Kardiologie des Kantonsspital Luzern befassen wir uns mit vier klinischen Forschungsprogrammen: 1. Stumme Ischämie 2. Eine nicht-invasive Charakterisierung des Risikos maligner ventrikulärer Arrhthmien. 3. Angina pectoris bei Patienten ohne koronare Herzkrankheit und 4. Die Evaluation einer lokalen Strahlentherapie bei Patienten mit vasospastischer Herzkrankheit.

Selected Publications

- Ivanov, D., Philippova, M., Tkachuk, V., Erne, P., and Resink, T. (2004). Cell adhesion molecule T-cadherin regulates vascular cell adhesion, phenotype and motility. Exp Cell Res 293, 207-218.
- Philippova, M., Ivanov, D., Tkachuk, V., Erne, P., and Resink, T.J. (2003). Polarisation of T-cadherin to the leading edge of migrating vascular cells in vitro: a function in vascular cell motility? Histochem Cell Biol 120, 353-360.
- Ivanov, D., Philippova, M., Antropova, J., Gubaeva, F., Iljinskaya, O., Tararak, E., Bochkov, V., Erne, P., Resink, T., and Tkachuk, V. (2001). Expression of cell adhesion molecule T-cadherin in the human vasculature. Histochem Cell Biol 115, 231-242.
- Kudrjashova, E., Bashtrikov, P., Bochkov, V., Parfyonova, Y., Tkachuk, V., Antropova, J., Iljinskaya, O., Tararak, E., Erne, P., Ivanov, D., Philippova, M., and Resink, T.J. (2002). Expression of adhesion molecule T-cadherin is increased during neointima formation in experimental restenosis. Histochem Cell Biol 118, 281-290.
- Philippova, M.P., Bochkov, V.N., Stambolsky, D.V., Tkachuk, V.A., and Resink, T.J. (1998). T-cadherin and signal-transducing molecules co-localize in caveolin-rich membrane domains of vascular smooth muscle cells. FEBS Lett 429, 207-210.

Cell differentiation
Growth factors
Biomaterials
3D cultures
Bioreactors

Tissue Engineering

Dr. Ivan Martin
Institut für Chirurgische Forschung und Spitalmanagement, ICFS
Universitätsspital Basel
Leiter Forschungsgruppe Tissue Engineering

Prof. Dr. Michael Heberer
Leiter Institut für Chirurgische Forschung und Spitalmanagement, ICFS
Universitätsspital Basel

Group members
Dr. Andrea Barbero
Dr. Sylvie Miot
Dr. Arnaud Scherberich
Dr. David Wendt
Francine Wolf (technician)
Alessandra Braccini (PhD student)
Silvia Francioli (PhD student)
Sourabh Ghosh (PhD student)
Anna Marsano (PhD student)
Simon Ströbel (PhD student)
Daniel Vonwil (diploma master student)
Ulas Gogus (diploma student)

Tissue Engineering of Cartilage and Bone using Human Cells

The goal of the research group is to generate grafts for the treatment of damaged or lost articular and meniscus cartilage, bone, as well as for more complex, large osteochondral lesions. Our approach involves fundamental investigations on (i) the biology of differentiated and progenitor human mesenchymal cells, (ii) the effect of growth factors on cell proliferation, commitment and differentiation, (iii) the interaction between cells and 3D scaffolds of defined compositions and architectures, and (iv) the controlled application of physical stimuli using tissue culture bioreactors. The engineered constructs are not only being considered as potential grafts, but also as controlled 3D model systems of cell differentiation and tissue development. Research is strongly financially supported in the context of european consortia (a total of 4 projects within EU Frameworks V and VI) and has led to filing of a number of patent applications.

Recent achievements of the group:

1. We have demonstrated that a limited fraction of clones of human articular chondrocytes, expanded in the presence of specific growth factors, exhibit multilineage differentiation capacity. Studies are ongoing to identify markers to selectively isolate chondrocyte subpopulations with an increased capacity of differentiation.
2. We have developed and validated a bioreactor for the efficient, reproducible and uniform seeding of mesenchymal cells into three-dimensional scaffolds, based on direct perfusion of cell suspensions through the scaffold pores. The system has been further developed to integrate perfusion seeding and perfusion culture of cells into porous scaffolds within a single bioreactor module while monitoring oxygen consumption. Seeding and culturing cells in a 3D carrier under controlled perfusion is expected to improve the quality of the resulting cartilaginous and bone-like tissues by enhancing cell survival and extracellular matrix synthesis.
3. Using a bioreactor allowing highly controlled mechanical loading of cell-scaffold constructs, we have demonstrated that dynamic compression of engineered cartilaginous tissues enhances the deposition of cartilage-specific molecules, if cells are embedded within sufficient amounts of extracellular matrix prior to loading. The bioreactor system is currently being evaluated as a 'functional quality control system' to determine at which stage engineered cartilage is sufficiently developed to tolerate physiological loading regimes.
4. We have evaluated the suitability of several human cell sources (periosteal cells, bone marrow stromal cells, synovial membrane cells, fat pad cells, meniscus cells, as well as ear, nasal, rib and articular chondrocytes) to engineer bone and cartilage tissues. Under our experimental conditions, bone marrow stromal cells and articular chondrocytes have been identified as the cell types allowing the most reliable generation of respectively bone and cartilage tissues.
5. We have validated that composites consisting of a layer of engineered cartilage combined with an osteoconductive material can structurally and functionally restore large experimental osteochondral defects in rabbit joints. The approach is now being extended to a larger size animal model, i.e., goats.

Fig. 1: Bioreactor system for seeding and 3D culture of cells into porous scaffolds under controlled perfusion. Controlled regimes of fluid flow are necessary to uniformly distribute cells in the scaffold and to maintain their viability and function even in the innermost pores (Wendt et al., 2003).

Fig. 2: Bioreactor system for the application of controlled regimes of compressive deformation to native or engineered tissues. Assessing the response of engineered cartilage to dynamic loading may help to determine if it is sufficiently functional for grafting in a loaded joint (Démarteau et al., 2003)

Clinics

In the three clinical scenarios, engineered tissues are envisioned to be produced within the Hospital, using specialized bioreactor systems. By automating and standardizing tissue manufacture, these bioreactors could assure the production of functional grafts with reproducible quality at acceptable cost.

1. Trauma and disease of joints frequently involve structural damage to the articular cartilage surface and the underlying subchondral bone. These pathologies result in severe pain and disability for millions of people world-wide and represent a major challenge for the orthopaedic community. Albeit a series of therapeutic approaches has been developed to treat osteochondral defects, none of them has proved yet to ensure long-lasting regeneration. The vision of our group consists in the implantation of cell-based, functional osteochondral composite tissues. These would replace autologous osteochondral units harvested from a minorly loaded area of the same joint (mosaicplasty technique).
2. Congenital malformations of the ear and of the nasal septum are currently surgically corrected by grafting autologous cartilage (e.g., from the ribs), with extensive 'handcraft' work to match the required size and shape. Engineered cartilage would provide an attractive alternative to autologous tissue, with the additional advantage of precise shaping.
3. The current standard in a variety of bone repair procedures (e.g., fusion in spinal surgery or bone reconstruction following tumor excision) is based on autologous bone (e.g., from the iliac crest), which requires operation at an additional site and frequently leads to donor site morbidity. The goal of our group is to replace autologous bone with engineered cell-based osteoinductive grafts.

Group Members
Jian Farhadi, MD (Plastic and Reconstructive Surgery)
Marcel Jakob, MD (Orthopaedic and Trauma Surgery)
Claude Jaquiery, MD (Plastic and Reconstructive Surgery)
Dirk Schäfer, MD (Orthopaedic Surgery)
Stefan Schären, MD (Orthopaedic Surgery)

Gewebeengineering von Knorpel und Knochen mit menschlichen Zellen

Wir entwickeln Gewebe für die Wiederherstellung von Knochen- und Knorpel- defekten. Ziel ist die Behandlung von verletzten Gelenken, Menisken, Knochen sowie von komplexen, grösseren osteochondralen Läsionen. Gewebeproben werden dem Patienten entnommen, und die isolierten Zellen im Labor vermehrt. Auf speziell entwickelten Trägermaterialien lassen sich die vermehrten Zellen in Bioreaktoren kultivieren. Hierbei lässt sich die Reifung in Richtung des gewünschten Gewebetyps beeinflussen. Derart kultivierte Gewebe können den Patienten wieder eingesetzt werden.
Unsere Forschung befasst sich daher (1) mit der Untersuchung der Biologie der mesenchymalen Zellen, (2) mit dem Einfluss von Wachstumsfaktoren auf die Vermehrung, Ausreifung und Differenzierung dieser Zellen, (3) mit der Interaktion der Zellen mit 3-dimensionalen Gerüsten definierter Architektur und (4) mit dem Einfluss physikalischer Stimuli in den Bioreaktoren.
Wir konnten die Entstehung von 3-dimensionalen Geweben im von uns entwickelten, geprüften Bioreaktor nachweisen und fanden Ausgangsgewebe, die gute Kapazitäten besitzen, sich in verschiedene gewünschte Zelltypen und Gewebe zu differenzieren. Im Kaninchenmodell konnten wir mit unserem System die Struktur und Funktion von experimentell erzeugten osteochondralen Läsionen in Gelenken ersetzen.
Für eine Vielzahl von Knochen- und Knorpeldefekten verspricht diese Methode eine qualitative Verbesserung der Reparatur. Oft sind nach Verletzungen, Abnützungen oder im Falle von erblich bedingten Defekten die chirurgischen Eingriffe mit autologen Knochen- oder Knorpeltransplantationen aufwendig, nicht immmer zufriedenstellend und beinhalten das Risiko von sekundären Beschwerden. Unser Ziel ist es, mit unserer Methode eine bahnbrechende Alternative zu bestehenden Behandlungsmethoden zu offerieren.

Selected Publications

- Démarteau O, Wendt D, Braccini A, Jakob M, Schäfer D, Heberer M, Martin I. (2003) Dynamic compression of cartilage constructs engineered from expanded human articular chondrocytes. Biochem Biophys Res Comm 310:580-588
- Wendt D, Marsano A, Jakob M, Heberer M, Martin I. (2003) Oscillating perfusion of cell suspensions through three-dimensional scaffolds enhances cell seeding efficiency and uniformity. Biotech Bioeng 84:205-214
- Barbero A, Ploegert S, Heberer M, Martin I. (2003) Plasticity of clonal populations of de-differentiated adult human articular chondrocytes. Arthritis Rheum 48:1315-1325
- Schäfer D, Martin I, Jundt G, Seidel J, Heberer M, Grodzinsky AJ, Bergin I, Vunjak-Novakovic G, Freed LE. (2002) Tissue engineered composites for the repair of large osteochondral defects. Arthritis Rheum 46:2524-2534
- Frank O, Heim M, Jakob M, Barbero A, Schäfer D, Bendik I, Dick W, Heberer M, Martin I. (2002) Real-time quantitative RT-PCR analysis of human bone marrow stromal cells during osteogenic differentiation in vitro. J Cell Biochem 85:737-746

Angiogenesis
RAAS System
Hypoxia/Ischemia
mTOR-Signaling
Left Ventricular Hypertrophy (LVH)
Hypertension

Vascular Biology

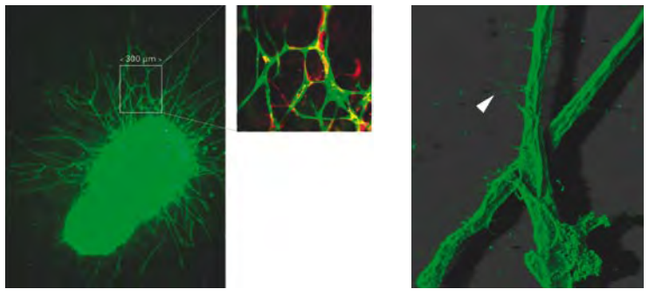
Prof. Dr. Edouard J. Battegay
Medizinische Universitätspoliklinik
Departement Forschung
Universitätsspital Basel

Group members:
Dr. Rok Humar
Dr. Nicole Butz
Kaija Paris (technician)
Fabrice Kiefer (PhD student)
Shiva Neysari (PhD student)
Weimin Li (PhD student)
Veronica Munk (PhD student)
Marco Petrimpol (PhD student)

Mechanisms of Angiogenesis during Hypertension and Left Ventricular Hypertrophy

Angiogenesis, the formation of microvascular networks from existing ones, is a highly regulated process that arises in response to hypoxia and other stimuli and relieves tissue ischemia in patients with ischemic heart and peripheral vascular disease. The renin-angiotensin-aldosteron-system (RAAS) plays an essential role in the maintenance of vascular homeostasis. Inhibition of Angiotensin Converting Enzyme (ACE) with its resulting increase in bradykinin (BK) and decrease in angiotensin II levels is a powerful treatment against hypertension. Several lines of evidence suggest a role of angiotensin II and BK in angiogenesis. Indeed, we demonstrate that under hypoxia specific ACE inhibitors (e.g. Quinapril), that are used in the treatment of hypertension, induce an angiogenic response in an in vitro assay of angiogenesis of the heart muscle (Fig. 1). This angiogenic effect is due to increased BK levels, dependent on a hypoxic environment and nitric oxide (NO) biosynthesis. We have shown previously, that reduced NO biosynthesis, a main attribute of arterial hypertension, contributes to impaired formation of new vessels, i.e., angiogenesis, and thus to microvascular rarefaction. Specifically, NO plays a crucial role both in mediating angiogenesis in portal – and arterial hypertension. We currently investigate how BK induces angiogenesis at the molecular and cellular level. Specifically we will determine presence and role of BK receptor subtypes (BK type1, type2 receptors), key signaling relay enzymes (PI3K, Akt, mTOR, MAPK) and effector molecules of BK-induced angiogenesis (iNOS, eNOS/HSP90, VEGF, bFGF, PDGF-BB).
In connection with these projects we examine specific hypoxia- and growth factor-induced signaling pathways that regulate vascular cell proliferation and the induction of hypoxia-inducible factor 1α (HIF-1α). This transcription factor induces hypoxia-adaptive genes such as Vascular Endothelial Growth Factor (VEGF), a potent angiogenic molecule. We have characterised a specific, evolutionally highly preserved signaling pathway via the molecule PI3K and mTOR (mammalian target of rapamycin) to be driven by hypoxia. This rapamycin dependent pathway enhances the mitogenic response of vascular wall cells and angiogenesis to PDGF- and other growth factors. In line with this we could show, that hypoxia- and growth factor-triggered mTOR signaling enhances HIF-1α nuclear accumulation. Further analysis of signaling pathways showed, that MAPK (ERK)-signaling is required for GF-induced proliferation and HIF-1α nuclear accumulation specifically under conditions of normoxia. These results suggest that active HIF-1α is regulated at different levels that depend on oxygen saturation, growth factor-triggered mTOR and MAPK-signaling (Fig. 2).
Thus, altered signaling plays a role in mediating the angiogenic response during ischemia in heart disease and peripheral vascular disease. Novel therapeutic targets in intracellular signaling downstream of ACE inhibition and/or BK may be discovered that will improve microvascularization of ischemic left ventricle in hypertension.

Fig. 1: (A) Angiogenesis assay in vitro. A piece (ca. 1 mm³) of the left ventricular myocardium of a mouse heart is embedded in a fibrin-gel, overlayed with growth medium and angiogenic stimulant (basic Fibroblast Growth Factor, 10ng/ml). After 10 days, double in-gel-staining with FITC-coupled seed lectin from G. simplicifolia (green) and Cy3-coupled antibody against -smooth muscle actin (red) reveal endothelial sprouts with single attached smooth muscle- or pericyte-like cells. Pericyte attachment forming endothelial tubes have been observed in vivo and contribute to vessel remodeling, maturation and stabilization.
(B) Detail of two crossing endothelial sprouts. Deconvolved confocal image, maximum intensity projection of in-gel-staining with FITC-coupled lectin G. simplicifolia (green fluorescent). Arrow points to filopodia arising from the endothelial cells. Dimensions of stack 100 m (x/y) and 10.5 m (z).



(A) (B)

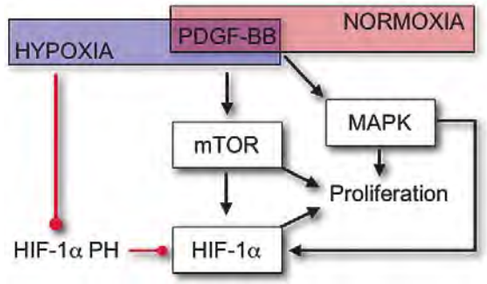


Fig. 2: Hypoxia response is regulated at different levels Hypoxia increases mTOR activity in dependence of growth factor stimulation via PI3K. This increase in mTOR activity increases angiogenesis via (1.) induction of vascular cell proliferation and (2.) the induction of HIF-1α, that induces angiogenic genes such as VEGF. Under conditions of normoxia, PDGF- and bFGF- induced signaling shifts to the MAPK pathway. HIF-1α Prolylhydroxylase (HIF-1α PH) is inhibited under hypoxia and independently contributes to HIF-1α stabilization.

Clinics

Treatment of hypertension and other cardiovascular risk factors is crucial for preventing coronary heart disease, heart failure, dementia, and stroke. The main focus of our studies is to improve treatment of patients at cardiovascular risk.
In series of studies we have assessed and plan to further assess the role of different antihypertensive drugs in reducing left ventricular hypertrophy (LVH) and other hypertensive target organ damages. A lack of decrease in left ventricular mass following antihypertensive treatment is associated with a higher risk for cardiovascular events. In particular, we have been assessing drugs targeting angiotensin converting enzyme (ACE) and angiotensin II receptors. Angiotensin II, formed from angiotensin I in a reaction catalyzed by ACE, is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. Various prospective, randomized clinical trials are underway to prove whether ACE inhibitors or angiotensin II type 1 receptor antagonists are particularly capable of improving the prognosis of patients with LVH. We have found that different drugs act distinctly on end organs, even if reduction of blood pressure is identical. These might be due to additional protective effects of antihypertensive drugs such as angiogenesis (see our research part). Furthermore, we have initiated studies on the effects of antihypertensive drugs and investigative procedures on target organ damage in patients with hypertension.

Blutgefässbildung bei Bluthochdruck

Angiogenese ist die Bildung von neuen Blutgefässen. Wir sind insbesondere interessiert, die Kaskade von Signalen zu verstehen, die bei einer Unterversorgung von Sauerstoff (Ischämie) in einem Organ zur Angiogenese führt. Eine gezielte Förderung der Blutgefässneubildung würde es ermöglichen, die Folgen eines Herzinfarkts oder eines Schlaganfalls zu vermindern. Die Angiogenese wird von verschiedenen Stimuli reguliert. Das Renin-Angiotensin Aldosteron System (RAAS) – das Regulationssystem von Blutdruck, Plasmavolumen und Osmolarität – spielt hier eine entscheidende Rolle. Hemmt man das Enzym ACE (angiotensin converting enzyme), so führt dies über einen höheren Bradykinin (BK) und einen niedrigeren Angiotensin II Spiegel zur Blutdrucksenkung und zur Schonung des Herzes. Wir konnten zeigen, dass in der Klinik verwendete Blutdruck-Senker (ACE Hemmer) auch die Angiogenese fördern. Diese Förderung beruht auf höheren BK Mengen, Hypoxie (Sauerstoffmangel) und Stickstoff-Monoxid (NO) – Synthese. Bradykinin und Angiotensin II sind, mit gegensätzlicher Wirkung, die Hauptakteure in diesem Regulations-System. Wir untersuchen daher die Rolle von verschiedenen Bradykinin-Rezeptoren und Effektormolekülen in der Kette der Reaktionen, welche zur Angiogenese führen. Parallel hierzu untersuchen wir eine durch Hypoxie induzierte Reaktionskette welche über den Transkriptionsfaktor HIF-1α zur Ausschüttung von VEGF (vascular endothelial growth factor) führt – einem Stimulator der Angiogenese. Über diesen Weg erhöht sich die Teilungsbereitschaft von Blutgefässzellen welche nun schneller auf Wachstumsfaktoren reagieren.
Andererseits lassen sich für die Blutdrucksenkung nebst der Hemmung von ACE auch Angiotensin II Rezeptor Antagonisten einsetzen. In der Klinik untersuchen wir die Fähigkeit beider Molekültypen auch eine links ventrikuläre Hypertrophie signifikant zu verringern. Patienten bei denen trotz Bluthochdruck-Behandlungen eine Reduktion der Hypertrophie ausbleibt, haben ein erhöhtes Risiko für ein kardiovaskuläres Ereignis. Bei diesen Studien, an denen mehrere Zentren beteiligt sind, kommen wir zum Schluss, dass verschiedene Medikamente, obschon sie alle den Blutdruck senken, verschieden auf die Organe wirken. Es ist möglich, dass hierbei der Einfluss dieser Medikamente auf die Angiogenese eine Rolle spielt.

Selected Publications

- Humar, R., Kiefer, F. and Battegay, E.J. (2004) Formation of new blood vessels in the heart can be studied in cell cultures. 3R-Info Bulletin 25, www.forschung3r.ch/de/publications/bu25.html
- Kiefer FN, Neysari S, Humar R, Li W, Munk VC, Battegay EJ. (2003) Hypertension and angiogenesis. Curr Pharm Des. 9(21): 1733-44.
- Kiefer F. N., Misteli H., Kalak N., Tschudin K., Fingerle J., van der Kooij M., Stumm M., Sumanovski L. T., Sieber C. C., and Battegay E. J. (2002) Inhibition of NO biosynthesis, but not increased blood pressure, reduces angiogenesis in rat models of secondary arterial hypertension. Blood Pressure 11: 116-124.
- Humar, R., Kiefer, F.N., Berns, H., Resink, T.J. and Battegay, E.J. (2002) Hypoxia enhances vascular cell proliferation and angiogenesis in vitro via rapamycin (mTOR) dependent signaling. FASEB J. 16 (8): 771-780.

DKBW Schwerpunkt Onkologie

Professor
G. Christofori
Institut für Biochemie
und Genetik

Professor
R. Herrmann
Klinische Onkologie
Universitätsspital Basel

Definiertes Ziel dieses Schwerpunktes ist es, die Forschung auf dem Gebiet der Onkologie im Raum Basel zu fördern und weiter auszubauen. Insbesondere soll die molekular-onkologische und die klinisch-onkologische Forschung der Universität Basel und der im Raum Basel ansässigen Spitäler, Forschungsinstitute und Pharmafirmen vernetzt werden, um die Lücken zwischen Grundlagenforschung, angewandter Forschung und klinischer Forschung zu schliessen und innovative, gemeinsame Projekte zu ermöglichen. Offensichtlich lebt der Schwerpunkt vom Enthusiasmus und der Eigeninitiative der beteiligten Forscher. Langfristig soll die konzertierte Aktion in diesem Forschungsbereich zur Bildung eines regionalen Krebszentrums führen.

Der Schwerpunkt wird derzeit vom Leiter des Institutes für Biochemie und Genetik, Prof. Gerhard Christofori, und vom Leiter der Klinischen Onkologie des Universitätsspitals Basel, Prof. Richard Herrmann, koordiniert. In Zeiten beschränkter finanzieller Mittel, hat der Schwerpunkt Onkologie sich bisher hauptsächlich darauf konzentriert, die Kommunikation zwischen den Forschergruppen zu erhöhen und Plattformen für den wissenschaftlichen Austausch anzubieten. Insbesondere werden eintägige Symposien veranstaltet, bei denen sich die Forscher mit ihren Projekten vorstellen und gemeinsame Interessen diskutiert werden können. Desweiteren führt der Schwerpunkt – auch mit der dankenswerten Hilfe einer Reihe von externen Sponsoren – die "DKBW Schwerpunkt Seminare Onkologie" durch, in denen herausragende Krebsforscher aus aller Welt ihre Forschungsergebnisse präsentieren. Bisher haben sich aus diesen Aktivitäten einige hoffnungsvolle Kollaborationen zwischen den beteiligten Arbeitsgruppen entwickelt, die vor allem über Instituts- und Firmengrenzen hinweg neuartige Forschungsprojekte und Therapieansätze bearbeiten.

Der Schwerpunkt Onkologie ist in den letzten Jahren nicht zuletzt auch durch Neuberufungen in diesem Forschungsgebiet und durch den Neubau des Zentrums für Biomedizin an der Mattenstrasse gefördert worden. Eine wichtige Aufgabe der Zukunft wird es nun sein, den Schwerpunkt gezielt durch definierte Forschungsprogramme weiter zu stärken, sei es durch den Austausch von Forschern zwischen Labor und Klinik, durch die Bereitstellung von Laborraum und durch zusätzliche Finanzierungshilfen.

Symposien

2002	1st SPO Symposium	13.06.02	Schauenburg
	2nd SPO Symposium	03.12.02	Castelen
2003	3rd SPO Symposium	07.05.03	Castelen
	4th SPO Symposium	10.12.03	Castelen

Schwerpunkt-Seminare

2003	19. Juni	Wolfhard Semmler, Heidelberg
	25. September	Gernot Walter, San Diego
	16. Oktober	Mariano Barbacid, Madrid
	20. November	Kari Alitalo, Helsinki
	04. Dezember	Bernd Groner, Frankfurt
2004	07. Januar	Walter Birchmeier, Berlin
	22. Januar	Margot Zöller, Heidelberg
	11. Februar	Anton Berns, Amsterdam
	18. März	Alan Hall, London
	31. März	Curzio Rüegg, Lausanne
	21. April	Cathrin Brisken, Lausanne

Castelen

Genome Stability
DNA Damage
Cytosine Deamination
DNA Repair
Base Excision Repair
Double-Strand Break Repair

Molecular Genetics

Prof. Dr. Primo Schär
Institut für Biochemie und Genetik

Group members
Dr. Christophe Kunz
Dr. Yusuke Saito
Dr. Roland Steinacher
Barbara Grubeski (technician)
Daniel Cortazar (PhD student)
Frauke Focke (PhD student)
Sanja Kais (PhD student)
Marcel Locher (Diploma student)

Maintenance of Genome Stability through DNA Surveillance and Repair.

Reactive agents of endogenous and environmental origin pose a constant threat to the integrity of our genomic material, the DNA. DNA damage, if it goes unrepaired, destabilizes genomes and, thus, increases the risk of cancer. We explore biological processes that enforce genome stability at the level of DNA damage response and repair. The objective of our work is to provide a clear understanding of both, the molecular mechanisms involved in the repair of DNA base damage and broken DNA backbones, and the biological consequences of their dysfunction.

DNA base excision repair (BER)
A substantial fraction of p53 mutations found in colon tumors are C➔T transitions in CpG dinucleotides that have likely arisen through spontaneous deamination of 5-metyhylcytosine (5-mC). 5-mC deamination produces G•T mispairs that must be repaired to G•C, if C➔T mutation is to be avoided. Similarly, deamination of cytosine generates G•U mispairs that also produce C➔T transitions, unless repaired. The restoration of G•C pairs is accomplished by the BER pathway. The thymine DNA-glycosylase (TDG) was postulated to initiate this BER process by hydrolyzing the N-glycosidic bonds of mispaired T or Us in DNA (Fig. 1).
Towards clarifying the biological role of TDG, we launched a concentrated program of biochemical and genetic investigation. Systematic analyses of the substrate spectra of purified yeast, insect and human TDGs revealed that, rather than being specialized for the repair of cytosine deamination products, this family of DNA glycosylases fights a much wider spectrum of DNA base damage. Further biochemical work disclosed a role of SUMO (small ubiquitine-related modifier)-modification in coordinating the BER process. We observed that SUMOylation of human TDG modulates its interaction with AP-sites and, thus, provides a mechanism for the coordinated dissociation of the enzyme from the mutagenic repair intermediate. We made use of fission yeast as a genetic pilot model to address the biological role of TDG. Widespread phenotypic analyses of disruption mutants established that TDG and the functionally related uracil DNA glycosylase share the task of eliminating uracil from DNA and contribute significantly to the cellular response to 5-fluorouracil induced DNA damage. These studies also showed that BER of DNA base damage accounts for a substantial fraction of gross genomic instability. Work on mouse knockout models led to the finding that TDG is essential for embryonic development, an unexpected turn that warrants intense investigation.

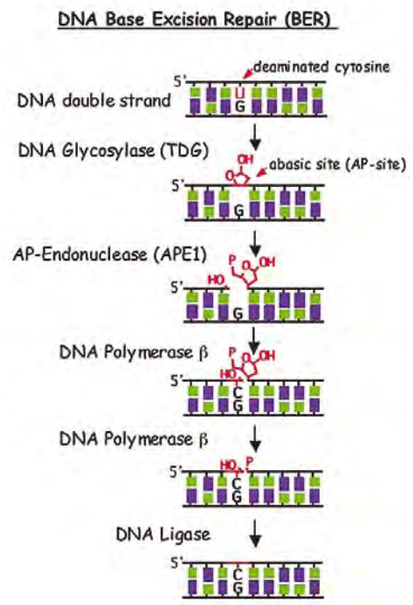


Fig. 1: The BER pathway fixes DNA base damage. First, a DNA glycosylase binds and releases the damaged base.
The resulting AP-site is then excised and replaced with the original nucleotide by the concerted actions of AP-endonuclease, DNA polymerase and DNA ligase activities.

Coordination of DNA double strand-break repair DSBR
DNA double-strand breaks (DSBs) represent the most severe form of DNA damage. Most frequently, they occur as a consequence of the DNA transactions involved in cell proliferation and differentiation. Eukaryotic cells utilize two distinct modes of DSBR – homologous recombination (HR) and non-homologous-end-joining (NHEJ), both of which are critical for genome stability and suppression of tumor development (Fig. 2).
We have been studying NHEJ in a yeast model with a particular interest in exploring regulatory components of DSBR. This led to the discovery of Nej1p and Nej2p that interact physically with Lif1p, an orthologue of human XRCC4. Lif1p also interacts with Dnl4p to constitute the DNA ligase complex required for NHEJ. Nej1p turned out to be an essential component of the NHEJ system, acting as key regulator of cell-type specific NHEJ activity in yeast. Nej2p is highly conserved from yeast to human and appears to have a negative regulatory role in NHEJ.

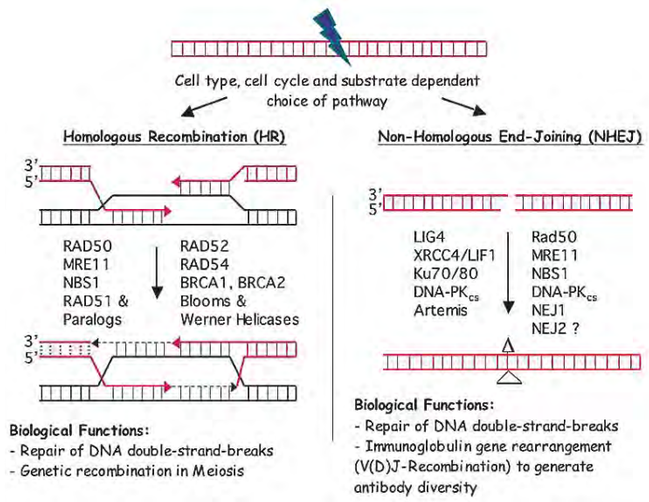


Fig. 2: Eukaryotic cells repair broken chromosomes by either of two pathways. HR is non-mutagenic and uses a homologous, undamaged partner molecule as a template for repair synthesis. The NHEJ pathway joins broken DNA ends in the absence of a homologous partner. This process may involve some DNA end-trimming and is therefore mutagenic. Defects in both pathways have been associated with cancer prone human disease.

Die Stabilität des Erbguts – Überwachen und Reparieren der DNA

Unsere Erbsubstanz, die DNA, ist konstant schädigenden Faktoren ausgesetzt. In jeder Zelle werden spontan verschiedene Arten von DNA Schäden generiert. Werden diese nicht durch die zelleigenen Systeme repariert, kann es zur genetischen Mutation und damit zu einem erhöhten Krebsrisiko kommen. Wir untersuchen die molekularen Mechanismen der DNA-Reparatur mit dem Ziel die biologischen Konsequenzen fehlerhafter Reparaturmechanismen zu verstehen.
Die häufigsten DNA Schäden betreffen die Purin- und Pyrimidin Basen. Fehlerhafte Basen werden durch die Basen-Exzisionsreparatur (BER) ersetzt. Hierbei schneidet zuerst eine DNA Glykosylase die beschädigte Base aus, wodurch eine basenlose Stelle entsteht (abasic site, AP), welche schliesslich über mehrere enzymatische Schritte durch ein intaktes Nucleotid ersetzt wird (Fig. 1). Die Thymin-DNA-Glykosylase (TDG) prozessiert spezifisch desaminierte Cytosin-Basen in der DNA und verhindert somit C➔T Transitionsmutationen. C➔T Mutationen sind unter anderem massgeblich an der Inaktivierung des p53 Tumorsuppressorproteins beteiligt. Mittels molekulargenetischer Studien untersuchen wir, inwiefern TDG – vermittelte Exzisionsreparatur zur Genomstabilität beiträgt und die Bildung von Tumoren unterdrückt. Die Entdeckung, dass die Funktion der TDG über SUMO – Modifikation moduliert und koordiniert wird bescherte uns neue Erkenntnisse über den Prozess der BER. Das Studium von Koordinationsmechanismen der DNA Reparatur ist von grosser Bedeutung, weil eine unkoordinierte Anhäufung mutagener Reparaturzwischenprodukte erheblich zur Instabilität unsrer Genome beiträgt.
Doppelstrangbrüche der DNA sind weitere, sehr ernsthafte Schäden. Diese entstehen meist während der normalen DNA-Replikation oder bei Zelldifferenzierungsvorgängen. Die Reparatur von Doppelstrangbrüchen kann entweder über homologe Rekombination (HR) oder über nicht-homologe End-zu-End Verbindung (NHEJ) repariert werden (Fig. 2). Wir untersuchen mit verschiedenen Modellen die NHEJ und interessieren uns insbesondere für die Komponenten der Regulation und Koordination dieser Reparaturvorgänge.

Selected Publications

- Schär, P., Herrmann, G., Daly, G. & Lindahl, T. (1997). A newly identified DNA ligase of Saccharomyces cerevisiae involved in RAD52-independent repair of DNA double-strand breaks. Genes Dev. 11, 1912-1924.
- Herrmann, G., Lindahl, T. & Schär, P. (1998). Saccharomyces cerevisiae LIF1: a function involved in DNA double-strand break repair related to mammalian XRCC4. EMBO J. 17, 4188-4198.
- Valencia, M.*, Bentele, M.*, Vaze, M.B., Herrmann, G., Kraus, E., Lee, S.E., Schär, P.* & Haber, J*. (2001). NEJ1 controls non-homologous end joining in Saccharomyces cerevisiae. Nature 414, 666-669. (*co-first and corresponding authorships).
- Hardeland, U., Steinacher, R., Jiricny, J. & Schär, P. (2002). Modification of the Human Thymine-DNA Glycosylase by Ubiquitin-Like Proteins Facilitates Enzymatic Turnover. EMBO J. 21, 1456-1464
- Hasan, S., El-Andaloussi, N., Hardeland, U., Hassa, P.O. Bürki, C., Imhof, R., Schär, P. & Hottiger, M.O. (2002) Acetylation Regulates the DNA End-Trimming Activity of DNA polymerase b. Mol. Cell 10, 1213-1222

Angiogenesis
Invasion
Lymphangiogenesis
Metastasis
Migration
Tumorigenesis

Tumor Biology

Prof. Dr. Gerhard Christofori
Institut für Biochemie und Genetik

Group Members
Dr. Fritz Brawand
Dr. Miguel Cabrita
Dr. Ugo Cavallaro
Dr. François Lehembre
Dr. Malte Lewerenz
Helena Antoniadis (technician)
Beat Hostettler (technician)
Roland Jost (technician)
Karin Strittmatter (technician)
Ursula Schmieder (technician)
Lucie Kopfstein (MD-PhD student)
Ivana Crnic (PhD student)
Stefan Grotegut (PhD student)
Fabienne Jäggi (PhD student)
Angelika Kren (PhD student)
Birgit Schaffhauser (PhD student)
Mahmut Yilmaz (PhD student)
Sandra Widjaja (MD student)
Christoph Caviezel (MD student)
Christoph Wunderlin (Diploma student)

Tumor Angiogenesis, Lymphangiogenesis and Metastasis

The major objective of our research is the identification and characterization of molecular events involved in late stage tumorigenesis. 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 a particular gene 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. E-cadherin is the main adhesion molecule of epithelia, and it has been implicated in carcinogenesis, because it is frequently lost in human epithelial cancers. Using transgenic complementation experiments in a transgenic mouse model of pancreatic cell carcinogenesis (Rip1Tag2), we have shown that the loss of E-cadherin-mediated cell-cell adhesion is causally involved in the transition from well-differentiated adenoma to invasive carcinoma. Currently, we are investigating the signal transduction pathways that are activated by the loss of E-cadherin function and that induce tumor cell migration and invasion.
During the development of many human cancers, expression of another cell-cell adhesion molecule, NCAM (Neural Cell Adhesion Molecule), is downregulated and, recently, we have demonstrated that in Rip1Tag2 transgenic mice the loss of NCAM function results in the formation of lymph node metastasis. NCAM is able to modulate integrin-mediated cell-matrix adhesion by binding and activating fibroblast growth factor receptors. The data suggest that abrogation of NCAM function results in the loss of signals that are required for the activation and maintenance of cell-matrix adhesion, thereby modulating the metastatic dissemination of tumor cells. Notably, the loss of NCAM function also correlates with upregulated expression of the vascular endothelial growth factor C (VEGF-C), which is a lymphangiogenic factor, and with a dramatic increase in lymphatic vessel density. Interfering with VEGF-C function by adenoviral expression of a soluble form of VEGF receptor 3, the cognate receptor for VEGF-C, resulted in the repression of lymphangiogenesis and in a reduction of lymph node metastasis. Conversely, transgenic expression of VEGF-C during Rip1Tag2 tumorigenesis induced lymphangiogenesis and the formation of lymph node metastasis, demonstrating that upregulated expression of VEGF-C is causally involved in lymph node metastasis.
Previous work in our laboratory has indicated that, besides VEGF, members of the fibroblast growth factor (FGF) family are involved in the onset and maintenance of tumor angiogenesis. Recently, an antagonist of FGF function has been identified in Drosophila development, named Sprouty. Subsequently, we have isolated cDNAs encoding four different mouse Sprouty proteins and investigated their role in the regulation of angiogenesis. We have found that Sproutys inhibit FGF- and VEGF-induced endothelial cell proliferation and differentiation by repressing the activation of mitogen-activated protein kinase (MAPK) pathway. Sproutys are anchored to membranes by palmitoylation and themselves are also a target of the MAPK signaling cascade, for example by regulation of their subcellular localization and by phosphorylation. Currently, we are investigating the mechanism by which Sproutys intersect tyrosine kinase

Fig. 1 In Rip1Tag2 transgenic mice, loss of E-cadherin-mediated cell-cell adhesion is causally involved in the transition from adenoma to carcinoma. In contrast, loss of NCAM cell adhesion is a rate-limiting event in the actual metastatic dissemination of tumor cells.

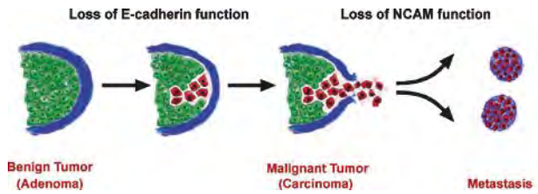
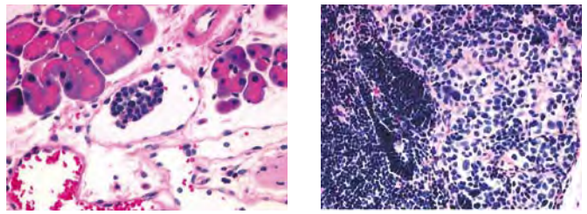


Fig. 2 Expression of the lymphangiogenic factor VEGF-C during cell tumorigenesis in Rip1Tag2 transgenic mice results in upregulated lymphangiogenesis in developing tumors. In these mice, circulating clusters of tumor cells are detected within lymphatic vessels (left panel), subsequently leading to the formation of lymph node metastasis (right panel).



Intravascular Tumor Cell

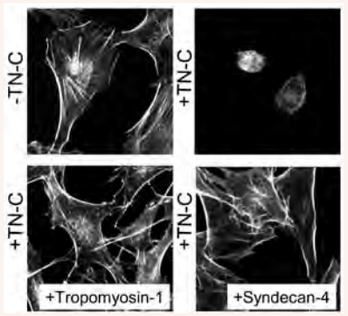
Lymph Node Metastasis

Signaling by Tenascin-C in Tumorigenesis

The high expression levels of the adhesion-modulatory extracellular matrix molecule tenascin-C in stroma of breast cancer and glioma inversely correlates with patient survival. Potential mechanisms for a tumorigenesis supporting effect of tenascin-C involve stimulation of tumor cell proliferation, promoting angiogenesis and suppression of the immune system. A major focus of the laboratory is the identification of tenascin-C-specific signal transduction pathways and their link to enhanced tumor cell proliferation. We identified syndecan-4, tropomyosin-1, and MAP kinase and Wnt signaling pathways as targets of tenascin-C and will address the effect of tenascin-C on these molecules and pathways in more detail. The in vivo function of tenascin-C is currently being investigated by its overexpression in transgenic mouse models of carcinogenesis.

Dr. Gertraud Orend
Institut für Biochemie und Genetik

Group members
Dr. Wentua Huang
Erika Fluri (technician)
Katrin Lange
(PhD student)



Whereas glioblastoma cells spread on fibronectin with actin stress fibers formed, they remain round in the presence of tenascin-C. Cell spreading is restored upon activation of syndecan-4 and tropomyosin-1, respectively.

Gefässbildung, Zell-Zell- und Zell-Matrix-Interaktion bei Krebs und Metastasen

Die Entwicklung eines bösartigen Karzinoms hängt weitgehend von der zellulären Umgebung des Geschwulstes ab. Bei der Entwicklung eines metastasierenden Tumors ist sowohl die Bildung neuer Blut- und Lymphgefässe, als auch der Verlust der Adhäsion zwischen den Zellen und der Adhäsion der Zellen zu ihrer Umgebung (Matrix) beteiligt. Diese Prozesse sichern die Versorgung des Tumors mit Nahrung und Sauerstoff, ermöglichen dessen Wachstum und erlauben das Loslösen von Krebszellen und ihre Invasion in das Nachbargewebe. Durch die neuen Gefässe können diese Krebszellen nun auch entferntere Gewebe erreichen und Metastasen bilden. Mit Hilfe von Zellkulturen und transgenen Maus-Modellen untersuchen wir die molekularen Mechanismen der Angiogenese und Lymphangiogenese (Blut- und Lymphgefässbildung) währen der Tumorentwicklung und während der Bildung von Metastasen.
In zahlreichen menschlichen Tumorkrankheiten zeigt sich der Verlust der Funktion von zwei «Ankermolekülen», E-cadherin und NCAM. Untersuchungen mit Mäusen welche spontane Pankreaskrebs ausbilden, zeigen, dass der Verlust von E-cadherin Krebszellen vom Tumor löst. Der Verlust von NCAM löst zusätzlich, durch eine indirekte Wirkung auf andere Moleküle, die Zellen von der Matrix ab (Abbildung 1). Somit ist der Verlust von NCAM einer der limitierenden Faktoren für die Bildung von Metastasen. Weiter induziert der Verlust von NCAM die Bildung von Wachstumsfaktoren welche die Lymphangiogenese fördern.
Unsere Partnergruppe befasst sich mit der Funktion eines Moleküls der Matrix, Tenascin-C. Tenascin-C beeinflusst sowohl die Haftung von Krebszellen an ihre Umgebung als auch die Geschwindigkeit des Tumorwachstums. Tenascin-C spielt vor allem in Gehirn- und Brusttumoren, sowohl bei der Zellteilung als auch bei der Angiogenese und in der Unterdrückung des Immunsystems eine entscheidende Rolle. Je höher die Tenascin-C Expression, desto geringer die Lebenserwartung der Patienten.

Selected Publications

- Cavallaro, U., Niedermeyer, J., Fuxa, M., and Christofori, G. (2001) N-CAM modulates integrin-mediated cell adhesion by activating FGF receptor signalling. Nature Cell Biol. 3, 650-657.
- Gannon, G., Mandriota, S., Pepper, M., and Christofori, G. (2002) Overexpression of human VEGF-A165 results in accelerated tumor angiogenesis but not metastasis during transgenic cell carcinogenesis. Cancer Research 62, 603-608.
- Christofori, G. (2003) Changing neighbors, changing behavior: cell adhesion molecule-mediated signalling during tumor progression. EMBO J. 22, 2318-2323.
- Orend, G., Huang, W., Olayioye, M.A., Hynes, N.E., and Chiquet-Ehrismann, R. (2003) Tenascin-C blocks cell-cycle progression of anchorage-dependent fibroblasts on fibronectin through inhibition of syndecan-4. Oncogene 22, 3917-3926.

Familial cancer
Hereditary colorectal cancer
Genomic instability
Cancer prevention
Presymptomatic genetic testing

Human Genetics

Prof. Dr. Hansjakob Müller
Abteilung Medizinische Genetik
UKBB / Departement Forschung
Universitätsspital Basel

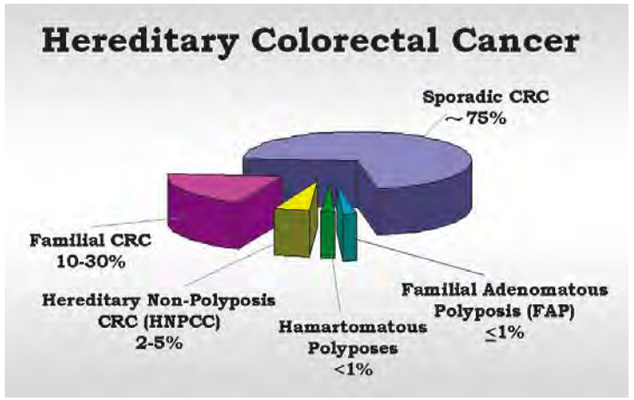
Group members
Prof. Walter Weber (external collaborator)
Dr. Ursula Albert
Dr. Nicole Bürki (external collaborator)
Dr. Karl Heinimann
Dr. Martina Plasilova
Marianne Häusler (family study professional)
Michèle Attenhofer (technician)
Sibylle Bertschin Woodtli (technician)
Carole Egenter (technician)
Thomas Woodtli (technician)
Judith Luz (PhD-student)
Jian Zhang (PhD-student)

Prevention of Colorectal Cancer through Genetics

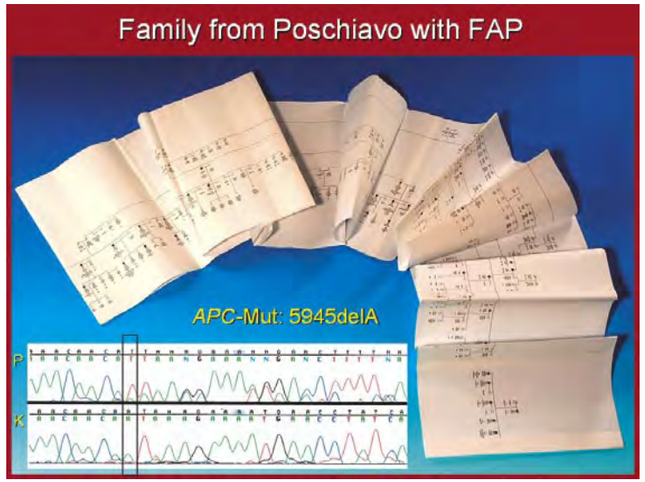
Since 1979 the activities of the research group Human Genetics have focused on the identification and characterization of predispositions leading to cancer with the goal of providing the most reliable genetic counseling and most effective medical care to affected patients and their relatives. Originally, several types of familial tumors, e.g. breast cancer and melanomas were included in these studies. During the recent years special attention has been given to genetic traits associated with a high risk of developing colorectal cancer (CRC) and other associated malignancies. Hereditary colorectal cancers are among the most suitable in vivo models for the study of the role of the underlying predispositions on the initiation and progression of carcinogenesis (adenoma-carcinoma sequence; well characterized histopathological changes related to a temporal order of several genetic events) as well as of the influence of proven and putative modifiers on this process. Germ line mutations of the APC-gene are found in the majority of patients with familial adenomatous polyposis coli (FAP). Their cancers exhibit chromosomal instability (CIN) characterized by bizarrely abnormal karyotypes whereas cancers caused by germ line loss of function mutations of DNA mismatch repair (MMR)- genes are characterized by the phenomenon of microsatellite instability (MSI or MIN). Germ line mutations with the base-excision repair gene MYH lead to the formation of multiple adenomas and cancer. Different types of genomic instability disorders have, therefore, the common feature of being able to increase the rate of progression along the path to CRC. The instability status of cancer cells offers new options for prediction of the outcome of therapy and the delineation of innovative therapeutic and preventive measures.

Our current main research projects concentrate on:

- Improvement of the individual risk assessment in familial adenomatous polyposis and in hereditary nonpolyposis colorectal cancer (HNPCC) as well as in hamartomatous polyposis syndromes by determining the genetic events occurring in the tumour cells.
- Identification of novel genetic pathways and genes predisposing to hereditary colon cancer



The "treasure chest" which provides the basis for these research activities is our cancer family registry which currently contains more than 300 well documented kindreds with hereditary colorectal cancer syndromes originating from all parts of Switzerland. Tumor samples were/are collected from affected family members with identified and yet unknown gene mutations.



Clinics

Five to ten percent of all colorectal cancers (CRCs) can be attributed to an ascertainable cancer predisposition, which can be subdivided into those that are related to a preexisting polyposis, either adenomatous or hamartomatous in nature and those that are not. Such inherited susceptibilities should be suspected if a patient is young and/or presents with synchronous or metachronous tumours or polyps with characteristic histological features. A strong family history of CRC and associated neoplasms also suggests a predisposition. However, a predisposition can also occur because of a de novo mutation affecting only one family member or can be inherited in an autosomal-recessive fashion such as MYH-mutations.
Mutated genes predisposing to CRCs exhibit considerable variation in penetrance and expressivity. This can create serious difficulties when an individual mutation carrier seeks medical help. It is often not possible to predict the occurrence of cancer in the colon and other organs at risk and to suggest the best kind of preventive measures and therapy, including heroic measures such as colectomy. Modifying factors, genetic and environmental in nature, that might influence the clinical consequences of a particular monogenic predisposition have yet to been defined.
Morbidity and mortality from hereditary CRCs can be considerably reduced by regular screening of the organs at risk and early treatment, mainly removal of developing tumours. Genomic instability could be a promissing target for new chemopreventive actions.
Many familial CRCs cannot be attributed to the already known predisposing genes. This causes frustration and uncertainty among patients, their relatives, and the responsible physicians. Further research is needed to clarify the genetic mechanisms responsible for a majority of familial CRCs.

Forschungsgruppen Humangenetik

5% – 10% aller Tumorkrankheiten entstehen auf dem Boden einer durchschlagskräftigen Veranlagung. Die Forschungsgruppe Humangenetik versucht seit 1979, solche zu erfassen und zu charakterisieren. Heute ist ihr erklärtes Ziel, Risikopersonen für gastrointestinale Tumoren, speziell solche für Kolorektalkarzinome (KRK), zuverlässig identifizieren und dann im Hinblick auf Präventionsmöglichkeiten individuell beraten zu können, stehen dabei doch heroische Massnahmen, wie die Entfernung des gesamten gefährdeten Organs, also die totale Kolektomie zu Diskussion. Vorerst wird bei Patienten aus Familien, in denen KRK und assoziiert auftretende Neubildungen gehäuft auftreten, respektive diese sich in ungewöhnlich frühem Alter und eventuell sogar mehrfach manifestieren, nach Keimbahnmutationen in bereits bekannten Krebsgenen gesucht. Lassen sich solche nicht entdecken, geht es darum, noch unbekannte Gene zu finden, deren Mutationen entsprechende Krebsveranlagungen darstellen können. Grosse Familien, in denen ein bekanntes "Krebsgen" weitervererbt wird, dienen dazu, die modifikatorischen genetischen und anderen Einflüsse zu erfassen, die das Ausbrechen eines Tumors im Gastrointestinaltrakt beeinflussen. Hereditäre Tumorkrankheiten erweisen sich als von der Natur gegebene Modelle, um die Mechanismen der Karzinogenese beim Menschen zu studieren. Aus den dabei gewonnenen Erkenntnissen lassen sich innovative Möglichkeiten der Vorbeugung, speziell der Chemoprävention ableiten.

Selected Publications

- Müller, Hj., Scott, R.J., Weber, W. Hereditary Cancer. (1996)
- Müller, Hj., Heinimann, K. (2003) Hereditary colorectal cancer: From bedside to bench and back. Advances in Colon Cancer 7, 11-14.
- Sieber, OM., Lamlum, H., Crabtree, MD., Rowan, AJ., Barclay, E., Lipton, L., Hodgson, S., Thomas, HJW., Neale, K., Phillips, RKS., Farrington, SM., Dunlop, MG., Müller, Hj., Bisgaard, ML., Bulow, S., Fidalgo, P., Albuquerque, C., Scarano, MI., Bodmer, W., Tomlinson, IP., Heinimann, K. (2002) Whole-gene APC deletions cause classical familial adenomatous polyposis, but not attenuated polyposis or "multiple" colorectal adenomas. Proc Natl Acad Sci USA 99, 2954-2958.
- Sieber, OM., Heinimann, K., Tomlinson, IP. (2003) Genomic instability – the engine of tumorigenesis? Nat Rev Cancer 3, 701-708
- Plasilova, M., Russell, AM., Wanner, A., Wolf, A., Dobbie, Z., Müller, Hj., Heinimann, K. (2004) Exclusion fo an extracolonic disease modifier locus on chromosome 1p33-36 in a large Swiss familial adenomatous polyposis kindred. European Journal of Human Genetics 12, 365-371.

AU-rich element
mRNA decay
Cytokines
AU-binding protein
Embryonal stem cells

Experimental Oncology

Prof. Dr. Christoph Moroni
Institut für Medizinische Mikrobiologie

Group members
Dr. Don Benjamin
Dr. Tobias Herzig
Dr. Ines Raineri
Marco Colombi (technician)
Brigitte Gross (technician)
Min Ji-Lu, (technician)
Sabrina Leuenberger (PhD student)
Bernd Rattenbacher (PhD student)
Martin Schmidlin (PhD student)
Daniel Wegmüller (PhD student)
Karin Kieser (diploma student)
Clelia Sasselli (diploma student)

mRNA Turnover and Oncogenesis

Synthesis, turnover and consequently the steady-state levels of mRNA are frequently perturbed in cancer cells. The malignant phenotype of a cell is due to a large part to over-expression of a set of genes collectively called oncogenes. While over-expression of these genes results mainly from increased transcription, the rate of mRNA turnover is another important parameter in setting the expression level of many genes related to growth control.

Our interest in mRNA turnover derived from the original observation that experimental mast cell tumors induced by the viral ras oncogene carried a defect in degrading the mRNA encoding interleukin-3 (IL-3), thus accumulating increased levels of IL-3 transcripts and protein leading to the establishment of autocrine growth and oncogenesis. The observation that the stable IL-3 mRNA could be destabilized by cyclosporinA, an inhibitor of the phosphatase calcineurin, provided an early indication that mRNA turnover is regulated by kinases and phosphatases through intra-cellular signalling networks. The intrinsic rapid decay of IL-3 mRNA is due to the presence in the 3'UTR of a so-called AU-rich element (ARE), a stretch of about 50 nucleotides containing several AUUUA pentamers. In TNFa, another cytokine of importance in the defense against tumors and microorganisms, we discovered a second element that we have termed the CDE (Constitutive Decay Element) as it promotes TNFa mRNA decay independently of the ARE. The ARE is present in the 3'UTRs of many growth factors, oncogenes, cell-cycle genes and other regulators of growth. When cells are physiologically activated by exogenous signals or become transformed into cancer cells, signaling pathways antagonize the rapid mRNA decay driven by the ARE resulting in mRNA stability and over-expression of the respective proteins. We have identified three signaling pathways, which upon activation stabilize mRNA: the c-jun N-terminal kinase pathway, the p38 MAP kinase pathway and the PI3-kinase/PKB pathway. Key to understanding how mRNA turnover is regulated is identification of the proteins binding the ARE and their expected role as phosphorylation targets of signaling pathways. Using a functional genetic screen, we have recently identified and cloned a gene called BRF1 that promotes the degradation of ARE-containing mRNA.

Our current work focuses on BRF1. Unpublished data show that phosphorylation at a specific serine residue of BRF1 inhibits BRF1 decay promoting activity and stabilizes mRNA. Phosphorylation occurs in response to insulin stimulation and is catalyzed by protein kinase B. Our current model (Fig. 1) postulates that the viral ras oncogene stabilizes ARE-mRNA via the PI3-kinase/PKB pathway, which leads (among other effects) to phosphorylation of BRF1 at a specific serine, thus inhibiting the basal decay promoting function of this protein. Our recent work suggests that the regulation of ARE-mRNA decay by BRF1 is not only important in cell activation and oncogenesis, but also in the differentiation of embryonal stem cells. In these, induction of differentiation led to rapid down-regulation of BRF1, and down-regulation of BRF1 by siRNA was conversely able to trigger morphological changes typical for ES-cell differentiation (unpublished observation). This indicates that the decision between cycling and differentiation of embryonal stem cells may be co-regulated by BRF1 and suggests that this model may provide a clue to studying "differentiation therapy" of cancer cells. We have also established a screening system for regulators of ARE-dependent mRNA turnover.

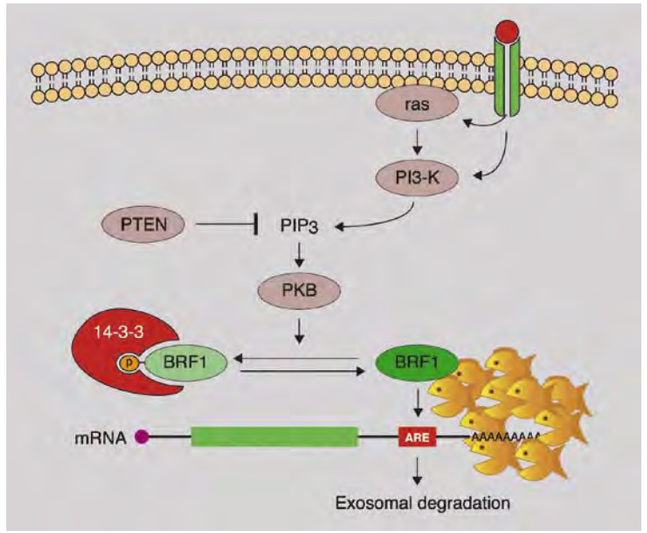


Fig. 1: ARE-containing mRNA is targeted by BRF1 to exosomal nucleases. Cell surface receptor activation, via ras, leads to PKB activation and phosphorylation of BRF1, which inactivates this protein, presumably by binding to the 14-3-3 protein, resulting in increased mRNA levels.

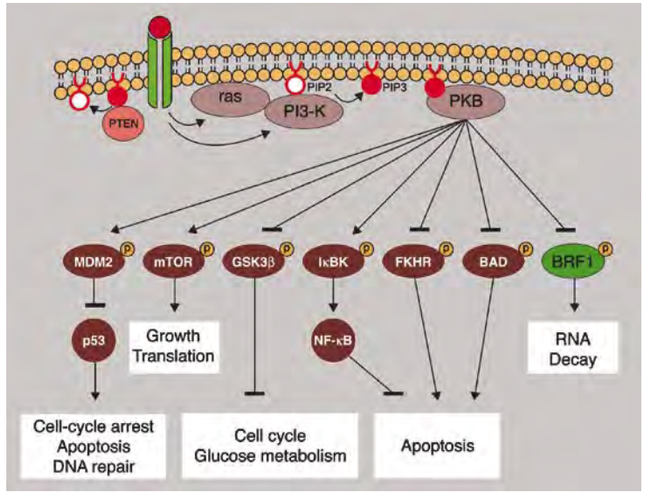


Fig. 2: Protein Kinase B (PKB) controls a membrane-activated, pleiotropic signalling pathway that affects – via several key proteins – multiple processes including cell cycle, growth, translation, metabolism and apoptosis. The novel finding that BRF1 is a target of PKB and that BRF1 phosphorylation leads to stability of ARE-containing transcripts links mRNA turnover to the pleiotropic PKB response. As the PKB pathway is frequently mutated in cancer cells, tumor cells are likely to have alterations in mRNA turnover rates.

RNA Stabilität und Krebs

Eine massiv erhöhte Menge einzelner kritischer Proteine liegt dem Phänomen Krebs zugrunde. Da Moleküle sowohl synthetisiert wie auch dynamisch wieder abgebaut werden, kann eine Überproduktion eines Proteins zwei Gründe haben: erhöhte Syntheserate oder verminderte Abbaurate. Unser Interesse in der Abbaurate von Genkopien (mRNA) und damit von Proteinen kam von unserer Beobachtung, dass sich in Tumorzellen der Maus ein Defekt im Abbau von Interleukin-3 mRNA fand. Dieser Abbaudefekt konnte durch das Medikament CyclosporinA korrigiert werden. Der Abbau selbst ist durch ein kurzes genetisches Element gesteuert, das sogenannte ARE (AU-rich element). Unsere Arbeiten zeigten, dass der ARE-gesteuerte Abbau von mRNA durch zwei gegenläufige Enzymsysteme gesteuert wird: durch Phosphokinasen (Enzyme, die Phosphatgruppen an Proteine binden), sie führen zur Stabilisierung und damit Ueberproduktion von mRNA, und von Phosphatasen, die Proteine die Phosphatgruppen abspalten. Das Verständnis dieser Mechanismen erfordert Wissen über die Proteine, die das ARE binden. Wir klonierten ein entsprechendes Gen (BRF1), und konnten zeigen, dass durch seine Phosphorylierung an einer bestimmten Aminosäure die mRNA Abbauaktivität von BRF1 beeinflusst wird. Wenn eine Zelle von aussen durch ein Signal, zum Beispiel ein Hormon, beeinflusst wird, kann sich der Phosphorylierungszustand von BRF1 verändern, und damit änderte sich die Abbaurate von ARE-haltigen mRNA Molekülen. Dies ist ein neuartiger Modus der Zellregulation und könnte in Krebszellen dazu führen, dass unerwünschte Produkte akkumulieren. Jüngste Daten zeigten, dass embryonale Stammzellen, wenn sie zur Differenzierung angeregt werden, die Menge an BRF1 drastisch reduzieren. Wir vermuten, dass damit spezifische ARE-mRNA gezielt angereichert wird, und dass BRF1 in der Entscheidung von Stammzellen, sich zu differenzieren oder nicht, eine Rolle spielt.

Selected Publications

- Nair, A. P. K., Hahn, S., Banholzer, R., Hirsch, H. H., and Moroni, C. (1994). Cyclosporin A inhibits growth of autocrine tumour cell lines by destabilizing interleukin-3 mRNA. Nature 369, 239-42.
- Stoecklin, G., Lu, M., Rattenbacher, B., and Moroni, C. (2003). A constitutive decay element (CDE) promotes TNFAlpha mRNA degradation via an ARE-independent pathway. Mol. Cell Biol. 23, 10:3506-15.
- Ming, X.-F., Looser, R., Stoecklin, G., and Moroni, C. (1999). Differential regulation of AUUUA-mediated mRNA turnover by the p38 MAPK and PI3-K pathways. EMBO J. 17, 6039-48.
- Ming, X. F., Stoecklin, G., Lu, M., Looser, R., and Moroni, C. (2001). Parallel and independent regulation of interleukin-3 mRNA turnover by phosphatidylinositol 3-kinase and p38 mitogen-activated protein kinase. Mol. Cell Biol. 21, 5778-89.
- Stoecklin, G., Colombi, M., Raineri, I., Leuenberger, S., Mallaun, M., Schmidlin, M., Gross, B., Lu, M., Kitamura, T., and Moroni, C. (2002). Functional cloning of BRF1, a regulator of ARE-dependent mRNA turnover. EMBO J. 21, 4709-18.
- Schmidlin, M., Lu, M., Leuenberger S.A., Stoecklin, G., Mallaun, M., Gross, B., Gherzi, R., Hess, D., Hemmings, B.A., and Moroni, C. (2004) The ARE-dependent mRNA destabilizing activity of BRF1 is regulated by protein kinase B. EMBO J, 2004, in press

Tumor immunology
Immunotherapy
Tumor antigens
Vaccination
Cytotoxic T lymphocytes

Oncology Surgery

Prof. Dr.
Giulio C. Spagnoli
Institut für Chirurgische Forschung und Spitalmanagement (ICFS)
Universitätsspital Basel
Stv. Leiter ICFS und Leiter Forschungsgruppe Onkologie

Prof. Dr.
Michael Heberer
Leiter Institut für Chirurgische Forschung und Spitalmanagement, ICFS
Universitätsspital Basel

Group members
Prof. Dr. Daniel Oertli
PD Dr. Walter W. Marti
Dr. Michel Adamina
Dr. Martin Bolli
Dr. Rachel Rosenthal
Dr. Walter Weber
Dr. Paul Zajac
Elke Schultz-Thater (technician)
Reto Schumacher (PhD student)
Celia Groeper (PhD student)
Chantal Feder (PhD student)
Anca Reschner (PhD student)
Sourabh Ghosh (PhD student)

Cancer Immunotherapy Between Laboratory and Bedside

The working hypothesis of our group is that, upon vaccination, the immune system might be able to react against antigens expressed in cancer cells. In particular, the generation of specific cytotoxic T lymphocytes (CTL) might significantly impact the clinical course of discrete tumors. A few years ago only, this hypothesis appeared to be highly speculative. However, in the past decade many tumor associated antigens (TAA) were identified and a series of clinical trials based were performed, with encouraging results.
We focused on (i) the clinical relevance of human TAA expression; on (ii) preclinical investigation of adjuvants and antigen formulations suitable for the immunization of cancer patients and on (iii) clinical active specific immunotherapy.

Characterization of the clinical relevance of human TAA expression
We generated monoclonal antibodies recognizing cancer/testis TAA (C/T TAA) also in paraffin embedded clinical specimens. They were successfully used to address C/T TAA expression in large series of patients (for a review: Juretic et al., 2003) (fig. 1). By using tumor microarrays, in collaboration with the Institute of Pathology of the University of Basel, we showed that in tumors of as high epidemiological relevance as bladder and lung cancers, C/T TAA expression is associated with a more severe prognosis as compared to negative cases (Kocher et al., 2002; Bolli et al., 2002). These data suggest that, in patients bearing these tumors, specific immunization procedures could be applied early during the clinical course of the disease, in stages not (yet) characterized by high neoplastic cell burdens.

Preclinical investigations on adjuvants and antigen formulations suitable for cancer patients immunization.
Synthetic class I restricted epitopes can be degraded by soluble peptidases in the plasma. Less explored is the role of cell associated peptidases. We used gp100 280-288 TAA epitope as a model to investigate degradation by cell associated enzymes. First, we showed that, in the presence of U937 monocytoid cell line but in the absence of sera, gp100 280-288 peptide is rapidly digested, with a <5 minutes half-life by cell associated amino- and carboxy-peptidases (Albo et al., 2003). We extended our research to enzymes associated to fibroblasts, a major cellular component of the dermis where immunogenic peptides are usually injected. In the absence of serum, gp100 280-288 peptide was found to be digested by fibroblast associated peptidases to a half life of about four minutes (Albo et al., 2004). These data indicate that synthetic class I restricted epitopes are characterized by extremely short lasting bio-availability, likely to severely jeopardize their immunogenic capacity.
We also explored the possibility to use adjuvants to complement our vaccinia virus based immunization procedures (fig. 2). Notably, adjuvants licensed for human use only include alum salts and virosomes (Gluck and Metcalfe, 2003). While the former do not to support CTL induction, we showed that the latter provide effective adjuvancy to the generation of CTL specific for HLA class I restricted epitopes "in vitro" (Schumacher et al., 2004).

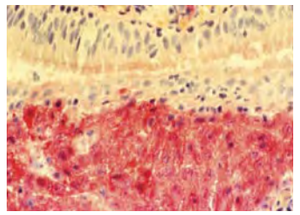


Fig. 1: A NSCLC section was stained with MAGE tumor associated antigen (TAA) specific monoclonal antibody 57B (red). Staining is only evident on tumor cells.

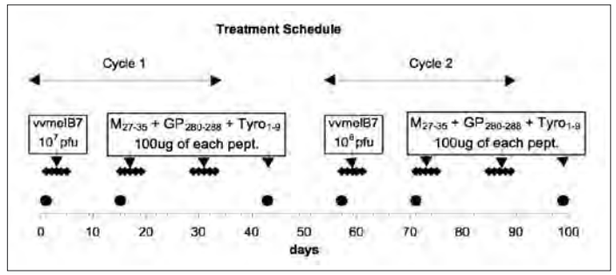


Fig. 2: Vaccination protocol; The immunization protocol consists of 2 cycles of 5 weeks separated by 3 weeks for a total duration of about 3 months. Each cycle is composed of 3 weeks of treatment, each separated by 1 resting week. For the immune monitoring during each cycle, blood samples (•) are obtained before,12 days after the virus injection and 12 days after the last peptide boost (thus on days 1, 15, 43, 57, 71 and 99). GM-CSF (®) is injected sub-cutaneously on each day of the vaccination weeks (5mg/kg.b.w./day). Non-replicative recombinant virus (vvmelB7), is delivered intra-nodally and represents the first antigenic formulation of each cycle at doses of 107 pfu on day 3 and 108 pfu on day 59. Soluble peptides boosts containing 100mg of $GP_{280-288}$, MART-1/Melan-A_{27-35} and Tyrosinase$_{1-9}$ are also provided intra-nodally on days 17 and 31 (cycle 1) and days 73 and 87 (cycle2). Peptides are also administered (in absence of GM-CSF) after each cycle (day 43 and 99) for DTH evaluation.

Active Specific Immunotherapy in Metastatic Melanoma Patients

We performed a phase I/II clinical trial based on the administration of a replication inactivated recombinant vaccinia virus encoding gp100 280-288, Melan-A/MART-1 27-35 and tyrosinase 1-9 HLA-A0201 restricted immunodominant TAA epitopes together with CD80 and CD86 (rVV-mel-B7) and boosts by synthetic peptides in stage III/IV metastatic melanoma patients (Oertli et al., 2002; Zajac et al., 2003, figure 2). Immunogens were injected intradermally in the context of a systemic GM-CSF treatment and monitoring was performed by tetramer staining and CTL precursors (CTLp) frequency analysis on "in vitro" restimulated CD8+ cells. Of 20 patients entering the protocol, 2 had to withdraw due to rapidly progressing disease. Immune responses were evaluated in 18 patients (stage III, n=5; stage IV, n=13) and increases in specific CTLp frequencies were observed in 15. In 16 patients, responsiveness against all antigens could be analyzed : 7 (43%) including all stage III cases showed evidence of induction of CTL specific for the three epitopes, 2 (12%) and 4 (25%) respectively, showed reactivity against two or one TAA. In 3 stage, IV patients no specific CTL reactivity was induced. Increases in CTLp frequency were mostly detected after rVV-mel-B7 injections. However, in a large majority of patients final CTLp levels were comparable to initial ones. Tetramer characterization of Melan-A/Mart-1 27-35 specific CTL also suggested a preferential expansion following recombinant virus administration. Vector specific humoral responses, frequently undetectable in stage IV patients did not prevent TAA specific CTL induction. Beside a single transient grade 3 leukopenia, no major clinical toxicity was reported. This study suggests that rVV-mel B7 is a highly effective inducer of specific CTL.Reactivity, however is not sustained and it is usually undetectable at the end of the immunization cycles. A lower responsiveness in stage IV as compared to stage III patients is also emerging. Indeed, among the former patients, over 50% did not respond to any of the three antigens or only responded to one of them (poor responders), whereas all stage III patients responded to all antigens. A further analogous trial based on intranodal immunization is currently under way.

Outlook
Clinical application of active specific immunotherapy is still in its infancy. In particular, regarding metastatic melanoma, due to the lack of specifically designed phase III clinical trials, its potential clinical impact cannot presently be evaluated on solid bases. However, improvements in the immunogenicity of CTL inducing vaccines and in immunization protocols, rise high hopes in the scientific community. An early application of immunotherapy, possibly prior to the development of high metastatic tumor burdens would be most advantageous. On the other hand, encouraging data in melanoma suggest that other tumor types of high epidemiological relevance, where TAA were also characterized, including lung and breast cancers, might represent targets of specific immunotherapy trials.

Immuntherapie gegen Krebs: Zwischen Labor und Klinik

Unsere Arbeitshypothese besagt, dass das Immunsystem des Menschen nach einer entsprechenden Impfung gegen gewisse Marker (Antigene) von Krebszellen reagieren kann. Viele tumor-assoziierte Antigene (TAA) wurden identifiziert, eine Reihe von klinischen Impfstudien mit ermutigenden Resultaten durchgeführt. Unsere Arbeit gliedert sich in drei Teile:
1. *Klinische Relevanz der menschlichen TAA*
Mit Hilfe eines eigens hergestellten Erkennungsproteins (monoklonaler Antikörper) konnten wir verschiedene Krebsarten auf TAA untersuchen. Tumoren der Harnblase und Lunge, die diese TAA exprimierten, waren mit einer deutlich schlechteren Prognose assoziiert. Dies suggeriert eine Impftherapie im frühen Verlauf der Erkrankung.
2. *Antigenformulierungen/Hilfsmittel (sog. Adjuvantien)*
Hauptproblem von synthetischen TAA ist deren geringe Bioverfügbarkeit aufgrund rascher Degradierung. Als kompetentes Adjuvans haben wir rekonstruierte Hüllen des Grippevirus (Influenza-Virosomen) untersucht.
3. *Aktive spezifische Immuntherapie bei Patienten mit malignem Melanom*
Mit einem gentechnisch hergestellten, inaktivierten Vacciniavirus, das 3 TAA und kostimulatorische Moleküle exprimiert, und synthetischen TAA zur Auffrischung (Boost) haben wir eine Impftherapie bei Patienten mit metastasierendem Melanom durchgeführt. Eine erkennbare Immunantwort ohne relevante Toxizität wurde in der Mehrheit vorübergehend erreicht. In unserer aktuellen Studie wird der Impfstoff nicht mehr in die Haut, sondern in die Lymphknoten verabreicht.
Aufgrund fehlender Phase III Studien kann über die allgemeine Ansprechrate von Melanompatienten auf Impftherapien noch keine Aussage gemacht werden. Neue Impfprotokolle mit verstärkter Wirksamkeit geben Anlass zur Hoffnung.

Selected Publications

- Oertli D, Marti WR, Zajac P, Noppen C, Kocher T, Padovan E, Adamina M, Schumacher R, Harder F, Heberer M, Spagnoli GC. (2002) Rapid induction of cytotoxic T-lymphocytes against melanoma associated antigens by a recombinant vaccinia virus vector expressing immunodominant epitopes and costimulatory molecules "in vivo". Hum Gene Ther, 13: 569-575.
- Bolli M, Kocher T, Adamina M, Guller U, Dalquen P. Haas P. Mirlacher M, Gambazzi F, Harder F, Heberer M, Sauter G, Spagnoli GC. (2002) Tissue microarray evaluation of MAGE tumor associated antigens expression: potential indications for specific immunotherapy and prognostic relevance in squamous cell lung carcinoma. Ann Surg, 236:785-793.
- Juretic A, Spagnoli GC, Schultz-Thater E, Sarcevic B. (2003) Cancer/testis tumour associated antigens: immunohistochemical detection with monoclonal antibodies. The Lancet Oncology, 4:104-109.
- Zajac P, Oertli D, Marti W, Adamina M, Bolli M, Gueller U, Noppen C, Padovan E, Schultz-Thater E, Heberer M, Spagnoli G (2003) Phase I/II clinical trial of a non replicative vaccinia virus expressing multiple HLA-A0201 restricted tumor associated epitopes and costimulatory molecules in metastatic melanoma patients. Hum Gene Ther, 14:1497-1510.

Immunoliposomes
EGFR
Targeted Therapies
Dendritic Cells
Tumor Vaccination

Medical Oncology

Prof. Dr.
Christoph Rochlitz
Departement Forschung
und Abteilung für Onkologie
Universitätsspital Basel

Dr. Miklos Pless

Group Members
Dr. Christoph Mamot
Dr. Willy Küng
Brigitte Vogel (technician)
Jürgen Reuter (technician)
Reto Ritschad (technician)
Mathias Irouschek (technician)

Molecular Approaches to the Treatment of Cancer

Our group has a long-standing interest in molecular approaches to the diagnosis and treatment of cancer. In previous studies, we have defined genetic factors helping to predict chemotherapy benefit in colorectal and other cancers, and we have performed numerous clinical trials of gene therapy and other experimental treatments in cancer patients. Recently, we have focussed our interest on two new approaches to cancer treatment, i.e. immunoliposomal targeting and vaccination strategies, which will be described in more detail below.

Immunoliposomal targeting
Immunoliposomes combine the pharmacokinetic and drug delivery advantages of long circulating, sterically stabilized liposomes with targeting receptor-specific properties of monoclonal anti-EGFR antibodies. Already, we have described the development of immunoliposomes (ILs) that bind EGFR or mutant EGFRvIII and internalize in target tumor cells, enabling intracellular delivery of potent anticancer agents in vitro and in in vivo tumor xenograft models.
Anti-EGFR ILs are constructed modularly with Fab' fragments of cetuximab (IMC-C225) or EMD 72000, covalently linked to liposomes containing various drugs, such as anthracyclines (doxorubicin or epirubicin), or the vinca alkaloid vinorelbine.
In vitro studies using various EGFR or EGFRvIII-overexpressing cell lines indicated that anti-EGFR ILs produced highly efficient binding and internalization, resulting in selective intracellular delivery of various drugs including doxorubicin (dox) and others. In each case, ILs were markedly more cytotoxic than the corresponding liposomal drug in target cells (Fig. 1). In vivo, ILs loaded with dox (anti-EGFR ILs-dox) showed extended circulation time after i.v. administration, with an 18 h terminal half-life in rats and 90% drug retention at 48h. Therapy studies with anti-EGFR ILs-dox given i.v. showed potent anticancer activity in EGFR-overexpressing MDA-MB-468 breast cancer and U87 glioma xenograft models. In each study, anti-EGFR ILs-dox produced significantly superior efficacy to all other treatments, including free dox and liposomal dox.
In summary, anti-EGFR ILs provide efficient and targeted drug delivery of anticancer compounds and may be applicable to a variety of EGFR- or EGFRvIII-overexpressing tumors. Clinical studies using immunoliposoml targeting are currently prepared.

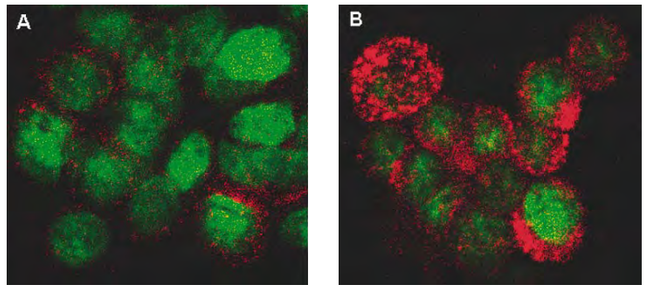


Fig. 1: In vivo uptake of non-targeted liposomes (a) and immunoliposomes (b) in an U87vIII xenograft model.

Hybrid cell cancer vaccine for renal cell cancer
Minimal requirements for a tumor vaccine are that it contains tumor-specific antigens which enables the immune system to mount a protective immune response, that these antigens are present in the tumor to be treated, and that the immune system is fully activated upon antigen recognition. These conditions are not easy to meet: in our study a simple strategy is used by electrofusing the tumor cells with antigen presenting dendritic cells (DC). With this method, an artificial "hybrid-cell" is created, expressing all relevant tumor antigens and all necessary costimulatory molecules (Fig. 2). While the tumor cells need to be autologous, the DC can either be derived from the patient or from an unrelated donor (allogeneic DC). We employ this method in a clinical trial with patients with metastatic renal cell cancer (RCC). As of now, 20 patients, all with progressing renal cell cancer have been treated and are evaluable. We found no severe side effects of the vaccine. Nine patients had a tumor progression, in 10 patients the tumor stabilized (for 4-17 months) and in 2 patients there was tumor regression (Fig. 3). A specific immune monitoring was set up for patients with RCC and HLA-A2: it focuses on CTL detection against the tumor associated antigens MUC1, HER2 and G250, concurrently attempted by surface staining and limiting dilution analysis of specific precursor frequency. Specific reagents for phenotypic studies are constructed by loading soluble HLA-A2.1 based fusion molecules with the peptides under investigation. In one of three patients studied so far we could detect a significant induction of CTLs against HER2, this patient had a disease stabilization of 12 months.

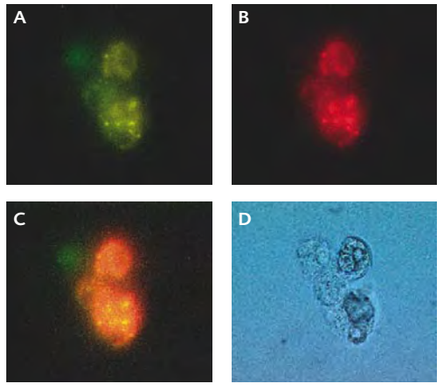


Fig. 2: Fluorescence-microscopy of hybrid cells using a membrane dye: green for dendritic cells (a), red for U266 cells (myeloma cell line) (b), yellow denotes fused cells (c), direct-Phase Microscopy shows two nuclei in hybrid cells(d).

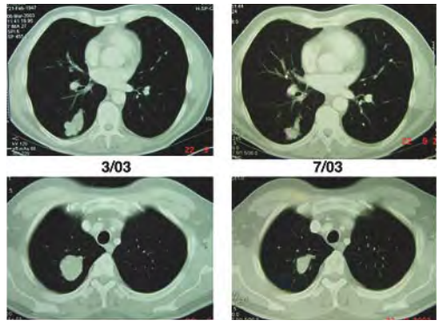


Fig. 3: Regression of lung metastases in a patient with renal cell cancer after hybrid cell vaccine.

Molekulare Krebstherapien

Unsere Gruppe befasst sich mit neuen Methoden der Therapie und Diagnostik für Krebs. Bislang haben wir unter anderem molekulare Marker identifiziert, mit denen sich die Effizienz einer Chemotherapie abschätzen lässt und verschiedene Formen der Gentherapie klinisch getestet. Im Fokus stehen zurzeit die immunoliposomale Krebstherapie und Vakzinationsstrategien. Immunoliposome sind Liposome, denen Teile von Antikörpern aufgesetzt werden. Damit wird erreicht, dass die Liposome spezifische Zellen erreichen, welche die entsprechenden Oberflächenantigene tragen. Krebszellen tragen häufig typische Proteine (Antigene), die sie von anderen Zellen unterscheiden. Ein Beispiel hierfür sind Krebszellen, welche EGFR (epidermal growth factor receptor) – einen Wachstumsfaktor-Rezeptor – an ihrer Oberfläche tragen. Werden nun Liposome mit Antikörperteilen, die EGFR spezifisch erkennen, ausgerüstet, so lagern diese sich an die Krebszellen an. Bei der Verschmelzung der Liposome mit der Membran der Krebszellen wird der Inhalt der Liposome, sehr wirksame Chemotherapeutika, in die Zelle geschüttet. Diese Strategie ermöglicht eine sehr gerichtete Behandlung mit geringeren Risiken und Nebenwirkungen. Wir werden die Immunliposom-Therapie demnächst in klinischen Studien testen. Die Effizienz von Anti-Karzinom-Vakzinen hängt davon ab, ob die Tumorzellen die Antigene, mit denen immunisiert wird, tatsächlich exprimieren und ob eine Immunreaktion erfolgt. Um dies sicherzustellen, haben wir Tumorzellen mit dendritischen Zellen fusioniert, welche nun dem Patienten injiziert werden. Dendritische Zellen sind Zellen des Immunsystems, welche Antigene präsentieren und dadurch die zelluläre Immunantwort stimulieren. Eine Dendrit-Tumor Fusionszelle wird nun die tumor-spezifischen Antigene selbst enthalten und die Immunantwort einleiten. Klinische Tests an Patienten mit Nierenkrebs-Metastasen zeigen uns, dass diese Methode Erfolg versprechend ist.

Selected Publications

- Schuler, M. et al. and Rochlitz, C.F. (2001) Adenovirus-Mediated Wild-Type p53 Gene Transfer in Patients Receiving Chemotherapy for Advanced Non–Small-Cell Lung Cancer. J. Clin. Oncol., 19, 1750.
- Mamot, C., Mild, G., Reuter, J., Laffer, U., Metzger, U., Terracciano, L., Boulay, J.-L., Herrmann, R., Rochlitz, C. (2003) Infrequent mutation of the tumor suppressor gene Smad4 in early stage colorectal cancer. Brit. J. Cancer, 88, 420-423.
- Rochlitz, C., Figlin, R., Squiban, P., Salzberg, M., Pless, M., Herrmann, R., Tartour, E., Zhao, Y., Bizouarne, N., Baudin, M. Acres, B. (2003) Phase I immunotherapy with a modified vaccinia virus (MVA) expressing human MUC1 as antigen-specific immunotherapy in patients with MUC1-positive advanced cancer. J. Gene Medicine, 5, 690-699.
- Jantscheff, P. et al. and Rochlitz, C. (2003) Expression of CEACAM6 in Resectable Colorectal Cancer: A Factor of Independent Prognostic Significance. J. Clin. Oncol., 21, 3638-3646.
- Mamot, C., Drummond, D.C., Greiser, U., Hong, K., Kirpotin, D.B., Marks, J.D. & Park, J.W. (2003) EGFR-targeted immunoliposomes mediate specific and efficient drug delivery to EGFR- and EGFRvIII-overexpressing tumor cells. Cancer Res., 63, 3154.

DKBW Schwerpunkt Immunologie

Professor A. Rolink
Roche Professur
für Immunologie

Professor
G. A. Holländer
Universitätskinderspital
Beider Basel
Departement Forschung
Universitätsspital Basel

Mit der Evolution vom Einzeller zu einem mehrzelligen Lebewesen hat sich auch die lebenswichtige Fähigkeit entwickelt, den Körper vor schädigenden Infektionserregern und maligne transformierten Zellen zu schützen. Diese essentielle Funktion wird durch das angeborene und erworbene Immunsystem sicher gestellt. Die zelluläre und molekulare Komplexität des Immunsystems birgt aber auch die Gefahr, dass Fehler in der Reifung von Effektorzellen beziehungsweise in der Funktion von an der Abwehr beteiligten Molekülen zu Immunpathologischen Zuständen wie Immundefizienzen und Autoimmunerkrankungen führen können.

Vier Forschungsgruppen des Departementes für Klinisch-Biologische Wissenschaften beschäftigen sich mit zellulären und molekularen Aspekten der Organogenese primärer und sekundärer lymphatischer Organe. Diese spezifischen anatomischen Orte stellen die geeignete Mikroumgebung zur Ausreifung und Selektion von Lymphozyten bereit. Hierbei ist von Interesse, unter welchen Bedingungen diese Effektorzellen des erworbenen Immunsystems für ihre unterschiedlichen Funktionen selektioniert werden. Bei angeborenem, erworbenem und therapeutisch induziertem Immunmangel sind virale Infekte von spezieller Gefahr. Drei DKBW-Forschungsgruppen untersuchen deshalb Möglichkeiten, virale Infekte (HIV, EBV, und Poliomavirus) früh im Ablauf einer Infektion zu diagnostizieren, zu quantifizieren und mittels immunologischer Effektormechanismen zu beseitigen. Die Infektabwehr des Immunsystems bedient sich ebenfalls entwicklungsgeschichtlich gut konservierter Mechanismen, welche gesamthaft als natürliche Immunität umschrieben werden. Hierzu zählt auch die Möglichkeit, gegen bakterielle Zellwandbestandteile über die Vermittlung von Membran-ständigen und löslichen Effektormolekülen effizient reagieren zu können. Zwei Forschungsgruppen innerhalb des Schwerpunktes Immunologie beschäftigen sich mit diesem Aspekt des Immunsystems. Zusätzlich richtet sich das Immunsystem auch gegen transformierte Zellen im Kontext maligner Erkrankungen, doch sind die spezifischen Mechanismen dieser Form der Abwehr noch unvollständig bekannt und die Kenntnis zu ihrer therapeutischen Nutzung noch nicht ausreichend untersucht. Ein Teil der immunologischen Forschung am DKBW geht deshalb der Frage nach, wie sich Hauttumoren der Erkennung durch das Immunsystem entziehen können und wie das Immunsystems durch Impfung zu einer gezielten Abwehr von Tumorzellen stimuliert werden kann. Schliesslich führt eine Immunantwort gegen körpereigene oder transplantierte Zellen zu einem Funktionsverlust und gelegentlich zu deren vollständiger Destruktion, eine Pathologie, wie sie bei der Graft-versus-Host-Disease, bei der Transplantatabstossung und bei Autoimmunität beobachtet werden kann. Fünf Forschungsgruppen innerhalb des Schwerpunktes Immunologie beschäftigen sich mit den molekularen und zellulären Grundlagen für diese ungewollte Immunreaktion.

Die Forschung im Bereich «Immunologie» am Departement für Klinisch-Biologische Wissenschaften bietet eine bedeutsame Plattform für die Interaktion zwischen klinischer und Labor-orientierter Forschung und ermöglicht Interaktionen mit den anderen Schwerpunkten des Departements. Bereits heute sind wesentliche Kooperationen zwischen den einzelnen Forschungsgruppen etabliert und ermöglichen so den wissenschaftlichen Austausch und die Realisation gemeinsamer Projekte. Schliesslich bietet der Schwerpunkt Immunologie auch die einmalige Chance, Aktivitäten in Lehre und Forschung der medizinischen und naturwissenschaftlichen Fakultäten konstruktiv zu integrieren.

Hematopoietic stem cells

Early hematopoietic progenitor cells

Pax-5

Stromal cells

Growth factors

Developmental and Molecular Immunology

Prof. Dr. Antonius Rolink
Roche Professur für Immunologie

Group members
Prof. Dr. Jan Andersson
Dr. Rod Ceredig
Dr. Gina Balciunaite
Dr. Steffen Massa
Corinne Démollière (technician)
Giuseppina Capoferri (technician)
Hannie Rolink (technician)
Ernst Wagner (technician)
Angèle Bénard (PhD student)
Annalisa Camporeale (PhD student)
Lukas Flück (PhD student)
Evita Harfst (PhD student)
Melanie Rauch (PhD student)
Lee Kim Swee (PhD student)
Maja Brenner (MD student)
Sarah Märki (diploma student)
Patrick Flückiger (diploma student)

Molecular Mechanisms Guiding the Development of Cells of the Immune System

Practically all mature blood cells have a limited lifespan. Hence, to maintain their peripheral pools, they have to be generated throughout life. A rare cell found in the bone marrow, called hematopoietic stem cell (HSC), is responsible for the lifelong production of the blood cells.
Much progress has been made in the phenotypic characterization of this rare HSC and of early hematopoietic precursor cells. However, at both the molecular and the cellular level, the mechanisms that guide the differentiation of these into the various blood cells are still poorly understood. We aim at a better understanding of the mechanisms underlying these differentiation processes.

Early hematopoietic progenitor cells with multi-lineage developmental potential *in vitro* and *in vivo*
We have shown earlier that pre-B cells derived from Pax-5 deficient mice possess the potential to differentiate into practically all cells of the blood. Recently, we have identified a similar cell type in bone marrow of normal mice. The summary of the multi-lineage development potential of this cell type in vitro and in vivo is shown in Fig. 1. Thus, $B220^+$, c-kit^+, $CD19^-$ cells isolated from bone marrow of normal mice differentiate into macrophages when cultured on OP9 stromal cells and M-CSF. The culture of these same cells on OP9 stromal cells in the presence of IL-7 results in the formation of pre-B cells. These ones can be maintained and expanded long-term in vitro. Most interestingly, transplantation of these cells into immunodeficient mice results in the establishment of a small but significant and functional B cell compartment.
In marked contrast, $B220^+$, c-kit^+, $CD19^-$ bone marrow cells cultured on OP9 stromal cells expressing the Notch ligand delta-1 like in the presence of IL-7 differentiate into pre-T cells. These pre-T cells as well, can be maintained and expanded long-term in culture and, upon transplantation into immunodeficient mice, can reconstitute the thymus and the peripheral T cell compartment. Currently, we use this as well as the Pax-$5^{-/-}$ pre-BI cell differentiation system for the identification of genes guiding the development of the various cells of the immune system. We are looking for a human cell type with a similar developmental potential. Such a cell might, in future, be used in therapy for patients with defects in the immune system.

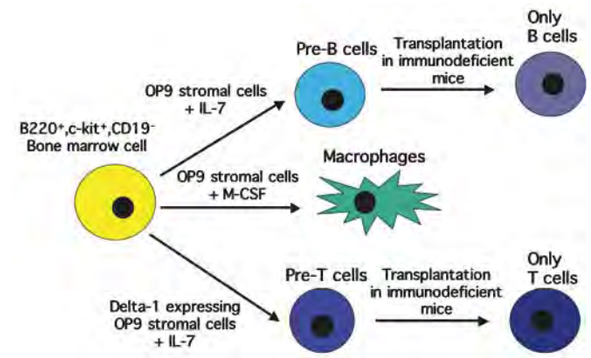


Fig. 1: In vitro and in vivo differentiation potential of an early hematopoietic progenitor cell found in mouse bone marrow
About 0.1% of mouse bone marrow cells are $B220^+$, c-kit^+, $CD19^-$. Under various culture conditions these cells can differentiate into pre-B cells, pre-T cells and macrophages. Pre-B cells and pre-T cells can be maintained in culture and can be used to reconstitute the B- and T-cell compartments in immunodeficient mice.

Late stages of B cell development (Fig. 2)
In the bone marrow of young adult mice, 1-2 x 10^7 immature B cells are generated per day. For so far largely unknown reasons, only 10–20% of these migrate to the spleen. In there, the immature B cell compartment can be subdivided into three populations called: Transitional B cell 1 (T1), 2 (T2) and 3 (T3). All three immature B cell populations are still sensitive for negative selection since they go into apoptosis upon cross-linking of their antigen receptor. Nevertheless, the very vast majority of immature B cells that reach the spleen will differentiate into mature B cells. The TNF family member BAFF plays a crucial role in this differentiation process.
The mature B cell compartment in the spleen comprises follicular and marginal zone B cells. The immature splenic B cells (T1-3) are precursors that give rise to follicular B cells, while the precursor for marginal zone B cells has not yet been identified.
We have found several genes that are differentially expressed in these splenic B cell sub-populations and we are testing their roles in this differentiation process, using transgenic and "knock-out" approaches. Moreover, a detailed analysis of the role of BAFF in late stages of B cell development is in process.

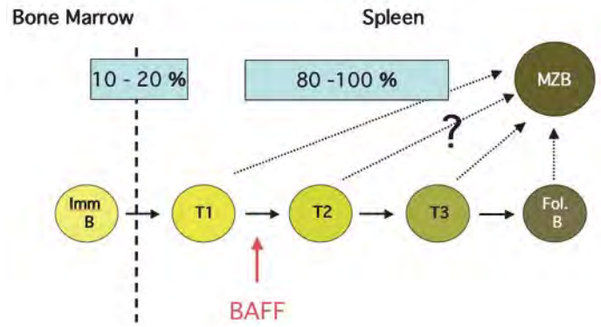


Fig. 2: Late stages of B cell development
Of the immature B cells produced in the bone marrow only a minor fraction migrates to the spleen. In the spleen the immature B cells go through three developmental stages before they enter the mature B cell compartment. The TNF family member BAFF plays a crucial role in this immature-mature B cell transition. The immature splenic B cells are the precursors of the mature follicular B cells. The precursors of the marginal zone B cells have not yet been identified.

Die molekulare Entwicklung der Zellen des Immunsystems

Blutzellen haben eine beschränkte Lebensdauer und müssen daher konstant durch die sogenannte Hämatopoese erneuert werden. Diese Erneuerung wird durch Stammzellen im Knochenmark gewährleistet. In unserem Labor untersuchen wir die molekularen Mechanismen, die die Differenzierung in die verschiedenen Zelltypen, insbesondere die Zellen des Immunsystems steuern. Dies letztlich mit dem Ziel, therapeutische Anwendungen zu finden.
Vorstufen von B Zellen (prä-B Zellen) aus Mäusen, die Pax-5 nicht exprimieren, können sich praktisch zu allen Blutzelltypen differenzieren. Von einem ähnlichen Zelltyp in genetisch unveränderten Mäusen entstehen Makrophagen, prä-B Zellen oder prä-T Zellen. Diese prä-B und prä-T Zellen können in Kultur gehalten und vermehrt werden und dienen zur Identifikation von Genen, die die weiteren Differenzierungsvorgänge der Zellen des Immunsystems steuern.
Im Knochenmark von adulten Mäusen entstehen täglich 10–12 Millionen prä-B Zellen. Nur 10–20 % davon wandern in die Milz. In der Milz kann man drei Entwicklungsstufen von unreifen B Zellen unterscheiden (T1, T2, und T3), die alle drei ihren Entwicklungsvorgang noch abbrechen können. Eine grosse Mehrheit dieser Zellen werden sich in der Milz jedoch zu reifen B Zellen differenzieren. Somit sind alle unausgereiften B Zellen in der Milz (T1-3) potentielle Vorstufen von follikulären B Zellen. Unklar hingegen bleibt, welches die Vorstufen der B Zellen der marginalen Zone sind. Wir untersuchen eine Reihe von Genen, die in den verschiedenen B Zell-Subpopulationen unterschiedlich exprimiert werden, um deren Rolle bei den Differenzierungsprozessen zu verstehen.

Selected Publications

- Rolink, A. G., Nutt, S. L., Melchers, F. and Busslinger, M. (1999) Long-term in vivo reconstitution of T-cell development by Pax5- deficient B-cell progenitors. Nature 401, 603-606.
- Nutt, S. L., Heavey, B., Rolink, A. G. and Busslinger, M. (1999) Commitment to the B-lymphoid lineage depends on the transcription factor Pax5. Nature 401, 556-562.
- Schaniel, C., Bruno, L., Melchers, F. and Rolink, A. G. (2002) Multiple hematopoietic cell lineages develop in vivo from transplanted Pax5-deficient pre-B I-cell clones. Blood 99, 472-478.
- Rolink, A. G., Tschopp, J., Schneider, P. and Melchers, F. (2002) BAFF is a survival and maturation factor for mouse B cells. Eur J Immunol 32, 2004-2010.
- Rolink, A. G., Andersson, J. and Melchers, F. (2004) Molecular mechanisms guiding late stages of B-cell development. Immunol Rev 197, 41-50.

Lymphoid organs
Autoimmunity
Fetal development
Chemokines
Lymphotoxin

Developmental Immunology

Prof. Dr. Daniela Finke
Institut für Immunologie

Group members
Caroline Bornmann (technician)
Dominik Meier (PhD student)
Sandrine Schmutz (PhD student)
Stephane Chappaz (PhD student)
Alan Valaperti (diploma student)

The Development of Secondary Lymphoid Organs

Lymphoid organs harbor hematopoietic cells in a framework of mesenchymal cells. Adaptive immune responses are generated in secondary lymphoid organs such as lymph nodes (LN), spleen and intestinal Peyer's patches (PP). Secondary lymphoid organs are not only important for anti-viral and anti-bacterial defense reactions but also for anti-tumor immune responses. Individuals who fail to develop organized lymphoid organs have a severe immunodeficiency.

1) Role of fetal hematopoietic cells in Peyer's patch and lymph node development. PP organogenesis starts around embryonic day 15.5 with the clustering of $LT\beta R^+VCAM\text{-}1^+$ mesenchymal cells in the proximal small intestine that extends until birth to the distal gut (Fig. 1a and b). One of the earliest hematopoietic cells colonizing the developing gut and fetal spleen expresses IL-7Rα and CD4 but lacks CD3 expression (Fig. 1d). RAG-2-/-γc-/-mice, which generate $CD4^+CD3^-$ cells without a functional IL-7R, fail to develop inguinal LN and PP (Fig. 1c). We have shown that the cellular interaction of mesenchymal and hematopoietic $CD4^+CD3^-$ cells is critical for PP formation during ontogeny (Fig. 2). The chemokine CXCL13 (BLC), which is expressed in the follicles of secondary lymphoid organs, interacts with CXCR5 receptors expressed by $CD4^+CD3^-$ cells. This induces both $LT\alpha1\beta2$ expression and $\alpha4\beta1$ integrin activation on $CD4^+CD3^-$ cells followed by high affinity attachment to $VCAM\text{-}1^+$ mesenchymal cells. Adhesion to mesenchymal cells via $\alpha4\beta1$/VCAM-1 is critical for efficient transmission of the lymphotoxin (LT)βR signal via $LT\alpha1\beta2$, a key step in tissue differentiation and lymphoid organ formation.

2) Crosstalk between epithelial and hematopoietic cells. The follicle-associated epithelium (FAE) that overlies PP expresses distinct features, when compared to the adjacent villus epithelium. Besides the presence of antigen-sampling M cells, the FAE constitutively expresses the chemokine CCL20. CCL20 is responsible for the recruitment of dendritic cells to the subepithelial region of PP. The mechanisms that induce FAE differentiation and CCL20 expression are poorly understood. We tested whether LTβR signaling mediates FAE differentiation and CCL20 expression. LTβR and LTa1β2 as well as CCL20 expression were monitored during embryonic development by *in situ* hybridization. CCL20 is expressed in the FAE before birth at the time the first hematopoietic $CD4^+CD3^-LT\beta^+$ cells are found in the gut. Gene expression studies following agonistic anti-LTβR antibody treatment *in vivo* and *in vitro* by laser micro-dissection and quantitative RT-PCR revealed that LTβR signaling can induce CCL20 expression in intestinal epithelial cells, suggesting that this pathway triggers constitutive production of CCL20 in the FAE.

3) Role of activated B cells in lymphoid tissue neoformation. There is strong evidence that the mechanism for lymphoid organogenesis in embryos and ectopic lymphoid tissue formation during chronic inflammation is similar. We tested the role of activated lymphocytes in neoformation of lymphoid tissue. Wild type B cells were adoptively transferred into neonatal LTα-/- mice, which are unable to form PP or LN. Subsequent activation of B cells in recipient mice by MAb treatment caused the neoformation of lymphoid follicles in the small intestine of LTα-/- mice. In addition, the development of mesenteric LN anlage was observed. The Ab-cocktail alone or non-activated B cells failed to induce lymphoid tissue. Our data suggest that the infiltration of activated B cells into inflamed tissues as observed in autoimmune diseases and chronic inflammations can initiate a cascade of interactions resulting in lymphoid follicle and tissue formation.

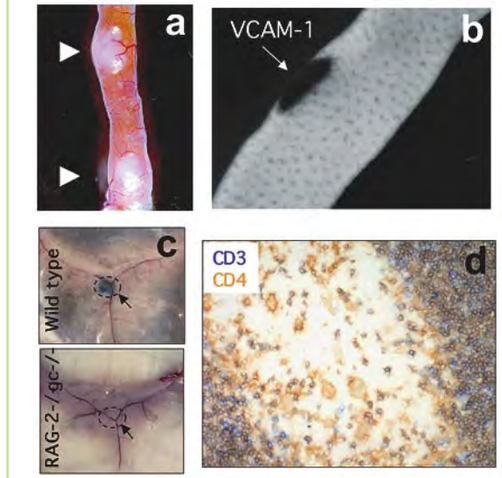


Fig. 1: Peyer's patch and Lymph node development. (a) Peyer's patches in mouse small intestine (b) Whole mount immunohistochemistry with anti-VCAM-1 MAb shows PP anlage (c) In contrast to wild type animals (top), RAG-2-/-γc-/- mice (bottom) lack inguinal lymph nodes (d) $CD4^+CD3^-$ cells in lymph node.

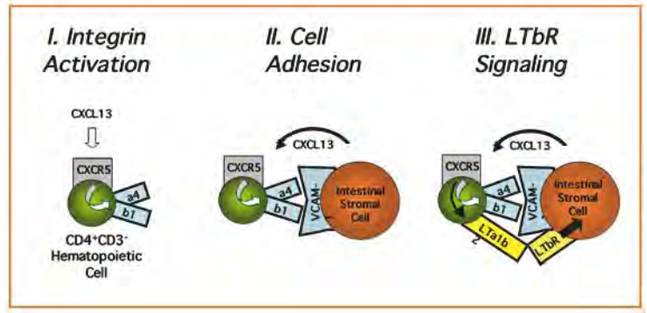


Fig. 2: Peyer's patch development during ontogeny.
Integrin activation by chemokines, adhesion and LTβR engagement are crucial steps.

Die Entwicklung sekundärer lymphatischer Organe

Das Vorhandensein von Lymphknoten, Milz und Peyer'schen Platten im Darm (sogenannten sekundären lymphoiden Organen) ist wichtig für die Ausbildung einer normalen Immunantwort und Abwehr von Viren, Bakterien oder Tumorzellen. Die Faktoren, die die Entwicklung von lymphatischem Gewebe während der embryonalen Organogenese regulieren, sind wenig bekannt. Es wird vermutet, dass molekulare Mechanismen eine Rolle spielen, die auch während einer chronischen Entzündung (z.B. Darmentzündung) wirksam sind. Wir haben gezeigt, dass hematopoietische $CD4^+CD3^-$ Zellen lymphoides Gewebe induzieren können. Diese Zellen kommunizieren mit anderen Zelltypen, z.B. Epithelzellen und Mesenchymalzellen und binden an den Lymphotoxin β Rezeptor (LT)βR, einem Schlüsselmolekül bei der Reifung und Differenzierung von lymphatischem Gewebe. Das Chemokin CXCL13 (BLC) induziert $LT\alpha1\beta2$, den Liganden für (LT)βR und aktiviert a4β1 Integrin. Die Adhesion von hematopoietischen $CD4^+CD3^-$ Zellen auf Mesenchymalzellen via $\alpha4\beta1$/VCAM-1 ist entscheidend für die effiziente Signalübertragung von Lymphotoxin (LT)βR. Es ist uns gelungen, Chemokine zu identifizieren, die durch LTβR induziert und ausschliesslich von Epithelzellen in Peyer'schen Platten gebildet werden. Das erklärt, wie hematopoietische Zellen, die ein LTβR-Signal auf Epithelzellen induzieren, gewebsspezifische Differenzierung und Chemotaxis erzeugen können. Darüber hinaus konnten wir zeigen, dass ähnlich wie in einer chronischen Immunantwort, aktivierte B Lymphozyten die Entwicklung von follikulären dendritischen Zellen und lymphoiden Follikeln im Darm unterstützen. Damit haben wir ein Modell entwickelt, mit dem wir die Entstehung von lymphatischem Gewebe während einer chronischen Entzündung untersuchen können.

Selected Publications

- Rumbo, M., F. Sierro, N. Debard, J.P. Kraehenbuhl, D. Finke (2004) Lymphotoxin b receptor signaling induces the chemokine CCL20 in intestinal epithelium. Gastroenterology, 127, 213-223
- Finke. D., S. Luther, H. Acha-Orbea (2003) The role of neutralizing antibodies for mouse mammary tumor virus transmission and mammary cancer development. PNAS, 100, 199-204.
- Finke, D., H. Acha-Orbea, A. Mattis, M. Lipp, J.P. Kraehenbuhl (2002) $CD4^+CD3^-$ cells induce Peyer's patch development: role of _4_1-integrin-activation by CXCR5. Immunity, 17, 363-373.
- Finke, D. and J.P. Kraehenbuhl (2001) Formation of Peyer's Patches. Curr. Opin. Gen. Develop. Biol., 11, 561-567
- Wehrli, N., Legler, D.F., D. Finke, K.-M. Toellner, P. Loetscher, M. Baggiolini, J.C.M. MacLennan, H. Acha-Orbea (2001) Changing responsiveness to chemokines allows medullary plasmablasts to leave lymph nodes. Eur. J. Immunol. 31, 609-616.

Sepsis
Myocarditis
Cardiomyopathy
Atherosclerosis
Inflammation
Autoimmunity

Experimental Critical Care Medicine

Prof. Urs Eriksson
Departement Forschung
Departement für Innere Medizin
Universitätsspital Basel

PD Dr. Patrick. Hunziker (guest scientist)

Group members
Dr. Julia Burian
Dr. Przemyslaw Blyszczuk
Dr. Peter Burger
Dr. Marc Wolf
Heidi Bodmer (Technician)
Nora Mauermann (PhD student)
René Marty (PhD student)

Targeting Inflammatory Heart Disease

Viral infections triggering autoimmunity have been implicated in the pathogenesis of certain dilated cardiomyopathy, the commonest cause of heart failure in young patients. We have shown that dendritic cells loaded with heart specific self-peptides induce T-cell mediated myocarditis in naïve, non-transgenic mice (Fig. 1). After resolution of acute myocarditis, mice develop heart failure. This model of autoimmune myocarditis (EAM) reflects a unifying theory as to how tissue damage and activation of Toll-like receptors (TLRs) during infections can induce autoimmunity, autoimmune relapses, and cardiomyopathy (Fig. 2) and offers a nice approach to study inflammatory mechanisms and the pathophysiological response of the failing ventricle to volume or pressure overload. It will be of help in the development of novel treatment strategies and will be of help in refining current therapeutic options for inflammatory heart disease and heart failure.
In particular, induction of autoimmune myocarditis requires priming of autoreactive T-cells that migrate to the heart and interact with resident tissue cells expressing self-antigen. Expression of activation markers on tissue resident dendritic cells expressing MHC class II always precedes inflammation in the course of autoimmune myocarditis. As antigen-presenting cells, they are involved in the generation or aggravation of autoimmune responses upon activation. Furthermore, these cells might be critical for the attraction and recruitment of T-cells, as well as other inflammatory cells. Various chemokines and cytokines are capable of fine-tuning the functional role of heart resident dendritic cells. TNF-α for example, has been recognized as a key cytokine mediating activation of tissue resident dendritic cells. It also promotes apoptosis of cardiomyocytes, and directly impairs cardiac contractility. Our research focuses on the role of specific mediators and cytokines that activate tissue resident dendritic cells. We take advantage of knockout mice lacking specific cytokines, chemokines and/or their receptors. We hope that this approach will allow us to develop novel treatment strategies based on *in vivo* blocking of specific proinflammatory mediators. Possible target cytokines include IL-1β, TNF-α, and IL-6 (Fig. 2). Inflammatory mechanisms are also critically involved in the pathogenesis of atherosclerosis and coronary heart disease the most prevalent heart disease worldwide. We are also interested in inflammatory aspects of atherosclerosis (the "vulnerable plaque") and our research focuses on the exploration of nanoscience tools for diagnostic and therapeutic purposes in this area.
Our working hypotheses are guided by clinical observations. In turn, we are interested in a straight transfer of our experimental findings to clinical practice. Therefore, our group established close local, national and international collaborations with both clinicians and basic researchers.
Our current and future projects focus on the autoimmune myocarditis model while studying the mechanisms involved in induction and healing of inflammatory heart disease, as well as in mediation of tolerance. Focusing on the vulnerable plaque leading to acute coronary syndromes, Patrick Hunziker's projects involve imaging of the vulnerable plaque by atomic force imaging, bedside diagnosis of coronary syndromes by novel microfluidics-based immunoassays, and therapeutic targeting of the vulnerable plaque by nanocontainer targeting (Fig. 3).

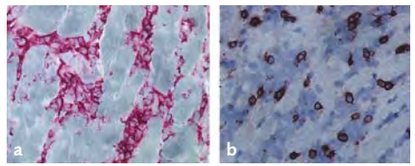


Fig. 1: Inflammatory infiltrates include macrophages and dendritic cells expressing MHC class II molecules (a), and lymphocytes. CD4+ T lymphocytes (b) are critical for disease development.

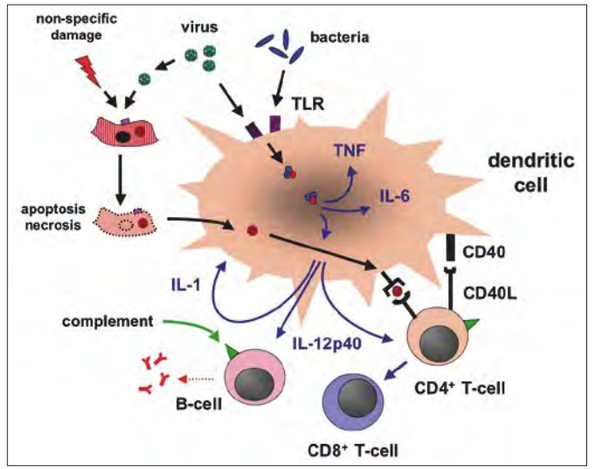


Fig. 2: Dendritic cells scavenging apoptotic and necrotic heart tissue after virus infection, express self antigen, and prime autoreactive T cells if activated through Toll-like receptors (TLR). TLR activation results in production of proinflammatory cytokines. Activated complement contributes to the development of myocarditis.

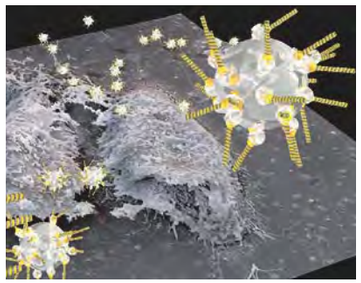


Fig. 3: Targeting of activated plaque macrophages by functionalized polymer nanocontainers

To Recognize and Understand Heart Failure

The laboratory of Experimental Critical Care Medicine focuses on the pathogenesis of inflammatory mechanisms in heart failure and atherosclerosis. At the bench, we are developing novel treatment strategies and diagnostic approaches. Our partners at the Division of Medicine A (Head Prof. A.P. Perruchoud), Department of Internal Medicine are directly transferring our research progress "bedside" to the patients of the University Hospital. Prof. Christian Müller and his team at the Division of Medicine A are taking advantage of the so-called B-type natriuretic peptide (BNP) as a specific marker for volume overload of the heart. Prof. Müller recently showed that BNP measurement clearly discriminates between heart failure and other causes of acute dyspnea. At the moment several studies addressing the relevance of neuroendocrine and inflammatory mediators as diagnostic and prognostic markers in patients with proven or suspected heart diseases are under way.

Prof. Dr.
Christian Müller
Medizinische Klinik A
Universitätsspital Basel

Entzündung und Herzkrankheit

Zusammen mit der genetischen Prädisposition sind autoimmune Prozesse dafür verantwortlich, dass Infektionen mit kardiotropen Viren gelegentlich in der Entstehung der dilativen Kardiomyopathie münden, der häufigsten Form der Herzschwäche bei Kindern und Jugendlichen. Um diese Autoimmunprozesse, d.h. die gegen das eigene Herz gerichteten Entzündungsvorgänge zu verstehen, verwenden wir ein Mausmodell. In diesem Modell wird durch Immunisation mit körpereigenem Herzmuskelmyosin in empfindlichen Mäusen eine schwere Herzmuskelentzündung ausgelöst, die schliesslich zur Herzinsuffizienz fortschreitet. Durch Verwendung von genetisch veränderten Tieren, denen spezifische Entzündungsmediatoren (Botenstoffe) fehlen, kann eruiert werden, welche Mediatoren für die Krankheitsentstehung notwendig sind. Auf diese Weise kann die Basis zur Entwicklung neuartiger Therapiestrategien gelegt werden. Ein weiterer Schwerpunkt ist das Verständnis der entzündlichen Prozesse die der Entstehung der Koronaren Herzkrankheit zugrunde liegen. In diesem Zusammenhang nutzt PD Dr. Hunziker die Fortschritte der Nanotechnologie zur Entwicklung neuer und revolutionärer diagnostischer und therapeutischer Verfahren.
Die Forschung des Labors für experimentelle Intensivmedizin ist innerhalb des DKBW mit dem Schwerpunkt Immunologie vernetzt. Zudem bestehen Kollaborationen mit den Abteilungen für Kardiologie, Hämatologie, Intensivmedizin, und der Allgemeinen Inneren Medizin des Universitätsspitals Basel. National und international bestehen "joint-ventures" mit dem Institut für Molekulare Biotechnologie der Österreichischen Akademie der Wissenschaften in Wien (Prof. J. Penninger), sowie mit der ETH Zürich.

Selected Publications

- Eriksson U, Ricci R, Hunziker L, Kurrer MO, Oudit GY, Watts TH, Sonderegger I, Bachmaier K, Kopf M, Penninger JM (2003) Dendritic cell-induced heart failure requires essential cooperation between adaptive and innate immunity. Nat Med; 9:1484-1489
- Oudit GY, Crackower MA, Eriksson U, Sarao R, Kozieradzki I, Sasaki T, Irie-Sasaki J, Gidrewicz D, Rybin VO, Wada T, Steinberg SF, Backx PH,Penninger JM (2003) Phosphoinositide 3-Kinase g-deficient mice are protected from isoprotenerol-induced heart failure. Circulation; 108:2147-2152
- Eriksson U, Kurrer MO, Sonderegger I, Iezzi G, Tafuri A, Hunziker L, Suzuki S, Bachmaier K, Bingisser RM, Penninger JM, Kopf M (2003) Activation of dendritic cells through the IL-1 receptor 1 is essential for the induction of autoimmune myocarditis. J Exp Med; 197(3):323-331
- Eriksson U, Kurrer MO, Schmitz N, Fontana A, Marsch SC, Eugster HP, Kopf M (2003) IL-6 deficient mice resist development of autoimmune myocarditis associated with impaired upgulation of Complement C3. Circulation; 107:320-325

T Lymphocyte
Antigen Presentation
Tuberculosis
Vaccine
Infection
Autoimmunity

Experimental Immunology

Prof. Dr. Gennaro De Libero
Department Forschung, Universitätsspital Basel

Group Members
Dr. Lucia Mori De Libero
Dr. Sabrina Mariotti
Dr. Emmanuel Rossy
Lena Angman (technician)
Sebastiano Sansano (technician)
Anthony Collmann (PhD student)
Hans-Jürgen Gober (PhD student)
Magdalena Kistowska (PhD student)
Marco Cavallari (PhD student)

Recognition of Non-peptidic Antigens by T Lymphocytes

Antigen recognition by T cells is a central event in the initiation of acquired immune responses. The capacity of T cells to recognize a large variety of antigens, including peptides, glycolipids, and phosphorylated metabolites has been recently appreciated.
We are studying the recognition of non-peptidic ligands by T cells with special attention on the following two topics.

1) Recognition of glycolipid antigens and role of this recognition in autoimmunity and infection.
In Multiple Sclerosis patients we have described T cells specific for self glycosphingolipids presented by CD1 molecules. Crystal structure analyses of CD1-glycolipid complexes have shown that the lipid tails are embedded in hydrophobic pockets within CD1 molecules, whereas the hydrophilic parts are exposed on CD1 surface. We have investigated how the hydrophilic moieties of glycolipids are correctly positioned for T cell receptor (TCR) recognition. CD1a site directed mutagenesis and binding assays of fluorescent glycolipids to synthetic CD1a molecules have revealed amino acids which hold and orient the hydrophilic part of bound glycolipids. This interaction stabilizes the highly flexible sugar moiety of glycolipids, thus contributing to the formation of immunogenic CD1-lipid complexes.
The immunogenicity of glycolipids is also affected by the acyl chain structure, which indirectly influences the position of hydrophilic parts as demonstrated by studying binding of anti-glycolipid monoclonal antibodies to soluble CD1-glycolipid complexes and investigating the response of glycolipid-specific T cell clones to synthetic glycolipids differing only in the length of one acyl chain.
This is important in light of the different types of acyl chains added during synthesis of glycosphingolipids in different tissues in physiological conditions or during the inflammatory response.
In another series of studies we have found that in patients with active tuberculosis a large number of T cells recognize a novel mycobacterial lipid (Ac2SGL). Ac2SGL is presented by CD1b and stimulates T lymphocytes with the T helper 1 functional phenotype. The Ac2SGL-specific T cells recognize macrophages infected with Mycobacterium tuberculosis and show bactericidal capacities. Ac2SGL is currently being tested as a novel anti-tuberculosis vaccine in guinea pigs.

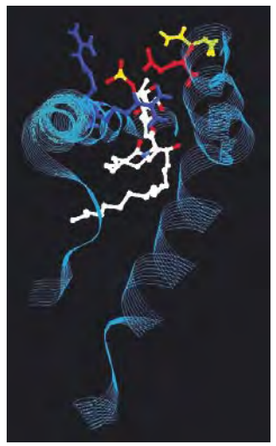


Fig. 1: Structure of the CD1a-sulfatide complex. Only the alpha 1 and alpha 2 helices of CD1a are shown (blue ribbons). The CD1a aminoacids interacting with the hydrophilic part of sulfatide are shown in blue, yellow and red. Sulfatide is shown in white with colored sulfur (yellow) and oxygen atoms (red).

2) Recognition of phosphorylated mevalonate metabolites by human TCR gamma/delta T cells
We have shown that a major population of human T cells expressing the TCR gamma/delta recognizes as antigens small phosphorylated non-peptidic metabolites generated in the mevalonate pathway. Recognition of these antigens is dependent on presentation on the cell surface by dedicated ubiquitous and non-polymorphic antigen-presenting molecules.
Tumor cells, such as Burkitt's lymphoma cells, accumulate large amounts of the stimulatory mevalonate metabolites and thus are potent stimulators of TCR gamma/delta T cells.
This feature has been exploited to target tumor cells from different human tissues for TCR gamma/delta T cell recognition. When tumor cells are incubated with aminobisphosphonate drugs, they accumulate the stimulatory mevalonate metabolites and acquire the capacity to be recognized and killed by TCR gamma/delta cells.
These studies indicate that tumor delivery of these drugs may represent a novel approach to immunotherapy of tumors.

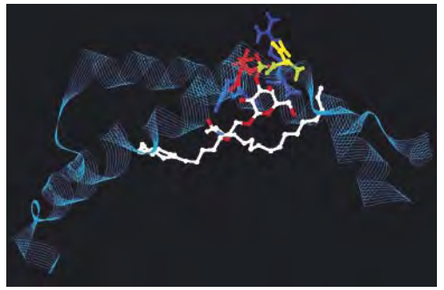


Fig. 2: The same CD1a-sulfatide complex as in Fig.1 tilted 45° on the horizontal plane. Colors as in Fig. 1.

Tuberculosis, the Infection Causing the Largest Number of Deaths

Tuberculosis, a major cause of death in developing countries, is caused by Mycobacterium tuberculosis, an obligately aerobic intracellular bacterium.
M. tuberculosis survives and grows in resting alveolar macrophages. Thus, the ability of a person to mount a rapid and effective immune response determines whether the outcome of exposure will be symptomatic disease or not.
Initial interaction between M. tuberculosis-infected macrophages and T cells elicits a helper (CD4) and a cytotoxic (CD8) T cell response. The main contribution of the CD4 T cells is the release of IFN gamma, which activates macrophages. CD8 T cells kill and disrupt infected phagocytes that have not succeeded in stopping bacterial growth together with intracellular pathogens. Both aspects are of main importance in the contribution to immunity. An effective vaccine must stimulate the right type of immune response if it is to provide long lasting immunity to Tuberculosis.
Identification of T cells specific for mycobacterial lipids has opened new perspectives to generation of novel vaccines for two major reasons. First, because lipids are presented to T cells by non-polymorphic CD1 antigen-presenting molecules. This allows the entire human population to react to immunogenic lipids. Second, because unlike proteins, lipids cannot be modified under selective pressure in bacteria. Therefore, the lipid specific immune responses reduce the risk to select bacterial mutants not expressing that particular lipid.
Our experimental observation that T cells specific for mycobacterial lipids release large amounts of IFN gamma and also kill infected phagocytes, is a strong indication to further investigate lipids as subunit components of a anti-tuberculosis vaccine.

Die T Lymphozyten erkennen ein reiches Repertoire an Antigenen

Das Erkennen von Antigenen durch T Lymphozyten ist ein äusserst wichtiger Schritt in der Entwicklung der Immunantwort. T Lymphozyten erkennen verschiedene Klassen von Antigenen: Peptide, Glykolipide und phosphorylierte Metabolite. Wir untersuchen die Mechanismen und die physiologische Bedeutung der Erkennung der letzteren zwei Antigenklassen.
Aus dem Blut von Patienten, die an Multipler Sklerose leiden, lassen sich T Zellen isolieren, welche körpereigene Glykolipide erkennen. Glykolipide gehören zu den häufigsten Bestandteilen der Myelinscheide im Gehirn. Die Zerstörung dieser Myelinscheide führt zum Zerfall der Nerven bei der Multiplen Sklerose. T Zellen mit körpereigenen Glykolipidspezifizität sind im Blut von Patienten mit Multipler Sklerose häufiger als im Blut von gesunden Probanden. Da zudem diese T Zellen entzündungsfödernde Zytokine ausschütten, liegt die Vermutung nahe, dass sie an der Autoimmun-Reaktion beteiligt sind, welche zu den verheerenden Läsionen im Gehirn führten. Diese Hypothese wollen wir überprüfen.
Wir untersuchen andererseits, die Immunantwort von T Zellen gegen Lipide aus Mycobacterium tuberculosis, dem Bakterium, das für die Tuberkulose verantwortlich ist. Im Blut von Patienten, welche an Tuberkulose erkrankt sind aber auch im Blut von gesunden Probanden mit vorausgegangener Infektion, sind die Titer von lipid-spezifischen T Zellen sehr hoch. Dies zeigt, dass dieser Typ von Immunantwort sehr häufig ist. Wir haben ein hoch immunogenes Glykolipid von Mycobakterien isoliert und dessen Struktur bestimmt. Gegenwärtig prüfen wir dieses Glykolipid als möglichen Bestandteil

Selected Publications

- De Libero G. 2004. The Robin Hood of antigen presentation. Science. 303, 485-487.
- Gilleron M., Stenger S., Mazorra Z., Wittke F., Mariotti S., Bohmer G., Prandi J., Mori L., Puzo G., De Libero G. 2004. Diacylated sulfoglycolipids are novel mycobacterial antigens stimulating CD1-restricted T cells during infection with Mycobacterium tuberculosis. J. Exp. Med. 199, 649-659.
- Gober H.-J., Kistowska M., Angman L., Jenö P., Mori L., De Libero G. 2003. Human TCR gamma/delta cells recognize endogenous mevalonate metabolites in tumor cells. J. Exp. Med. 197, 163-168.
- Shamshiev A., Gober H.-J., Donda A., Mazorra Z., Mori L. and De Libero G. 2002. Presentation of the same glycolipid by different CD1 molecules. J. Exp. Med. 195, 1013-1021.
- Shamshiev A., Donda A., Prigozy T.I., Mori L., Chigorno V., Benedict C.A., Kappos, L., Sonnino S., Kronenberg M., and De Libero G. 2000. The alpha-beta T cell response to self-glycolipids shows a novel mechanism of CD1b loading and a requirement for complex oligosaccharides. Immunity 13, no. 2:255-64.

Skin Cancer
UV Damage
Apoptosis
Immune Escape
RNA Interference

Experimental Immunology

Prof. Dr.
Peter Erb
Institut für Medizinische Mikrobiologie

PD Dr.
Ursula Günthert

Group Members
Dr. Ji Jinming
Andrea Glaser (technician ATA)
Marion Wernli (technician ATA)
Jacqueline Samaridis (technician)
Karsten Stauffer (technician)
Erwin Kump (PhD student)
Ainhoa Mielgo (PhD student)

The Role of an Apoptosis-Inducing Regulator in Nonmelanoma Skin Tumors (Prof. Dr. P. Erb)

Long-term UV-light exposure of human skin epidermis is associated with an increased risk for the development of skin cancers. UV radiation not only induces DNA damage in epidermal cells, it also interferes with skin homeostasis, which is maintained by a unique distribution pattern of apoptosis-inducing and –preventing molecules. If the DNA damage is not repaired or the damaged cells are not eliminated by apoptosis, this can lead to cell transformation, uncontrolled proliferation and eventually to tumor formation (Fig. 1).
Apoptosis is induced by Fas-ligand (FasL) or TRAIL upon interaction with their corresponding receptors, Fas or TRAIL-receptors (TRAIL-R). FLIP or certain members of the bcl-2 family can prevent apoptosis. We are investigating the role of several cell death-inducing and -preventing molecules in the formation of nonmelanoma skin tumors, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), but also in the escape of these tumors from the recognition by the immune system.
In normal, UV-protected skin epidermis, FasL but not Fas is expressed (Fig. 2a). FasL functions as a sensor, i.e. it not only prevents the influx of inflammatory cells, but also controls cell transformation. Exposure of the skin to UV-light upregulates Fas and downregulates FasL. In chronic sun-exposed skin FasL cannot be detected anymore at all, neither at the protein nor mRNA level (Fig. 2b). Thus, the sensor function of FasL is lost, transformed cells cannot be efficiently eliminated and the risk of tumor formation is increased. Indeed, in actinic keratosis, a precancerous stage, which can develop into SCC, FasL is not expressed. In addition, TRAIL-R are downregulated and apoptosis induction via the alternative TRAIL – TRAIL-R pathway is prevented as well.
However, as soon as BCC or SCC have formed a complete turn-around becomes manifest, FasL, but not Fas is now strongly expressed in the tumor cells (Fig. 2c). Thus, FasL behaves like a double-edged sword. On the one hand, it protects the skin from tumor formation, on the other hand, once a tumor has formed it presumably protects the tumor from the attack of the immune system. While ample evidence for such an immune escape mechanism is available in vitro, this has not as yet been proven in vivo. Therefore, we devised experiments to directly downregulate FasL expression in tumor tissue. Two approaches were chosen, FasL gene silencing via specific phosphorothiated antisense oligonucleotides (ASO) or by RNA interference using synthetic short interfering RNA duplexes (siRNA). With both, FasL-specific ASOs as well as siRNAs we successfully downregulated FasL expression not only in cell lines but also in normal skin epidermis and in BCC tissue. Thus, it is not only possible to transfect tumor tissue with ASOs or siRNAs, but also to silence the gene of interest. These experiments now provide the basis to test the immune escape hypothesis in vivo.

Fig. 1 Sun-light (UV) exposure of the skin can induce basal cell or squamous cell carcinoma formation.

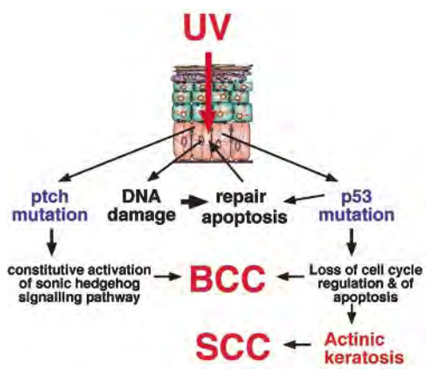
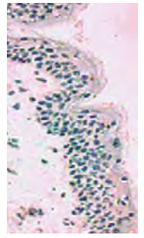
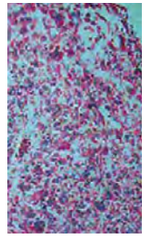


Fig. 2 FasL expression in skin epidermis and SCC.

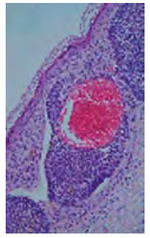
(a) Sun-protected skin, FasL is expressed (red cells)



(b) Sun-exposed skin, FasL is not detectable



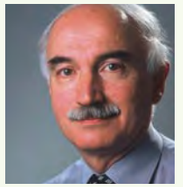
(c) strong FasL expression in SCC



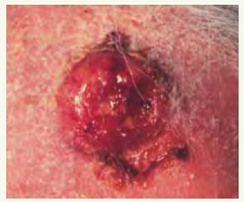
(d) Histological section of BCC

Clinics

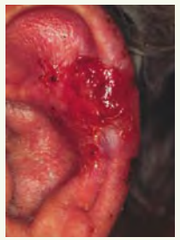
Skin cancers are by far the most frequent human malignancy . In the USA, every third cancer diagnosed is a skin cancer. These tumors include malignant melanomas and nonmelanoma skin cancers that are neoplasms of epithelial origin such as the basal cell carcinoma (BCC) and the squamous cell carcinoma (SCC). BCC is the most common cancer in humans. It is estimated that more than 1 million new cases occur per year in the United States. In central Europe, the incidence of BCC is around 30/10'000 per year and the incidence of SCC is around 15/10'000. An epidemiological survey in Switzerland has shown that the incidence of BCC has risen between 1976 and 1998. Exposure of the skin to UV radiation along with decreaseing ozon levels are thought to be responsible for the increase of the cases. Nonmelanoma skin cancers occur predominantly in patients with pale skin, red-blond hair and blue eyes. Moreover, 80% of the tumors are located on sun-exposed skin, i.e. the face and neck for BCCs and the back of the hand and the face for SCCs. Most of the nonmelanoma skin cancers are due to mutations in the PTCH and p53 genes. Nodular BCC is the dominant clinical variant of BCC. This tumor has an infiltrating and destructive growth but in contrast to SCC usually does not metastasize.



Prof. Dr.
Stanislaw Büchner
Dermatologische Universitätsklinik
Universitätsspital Basel



BCC



SCC

Weichen Hauttumorzellen dem Immunsystem aus? – Kann man dies verhindern?

Zuviel Sonne ist ein Hauptgrund für die Bildung von Hauttumoren wie Melanom, Plattenepithelkarzinom und Basaliom. Die UV-Strahlen im Sonnenlicht können DNA in der Zelle mutieren. Solche Zellen müssen durch programmierten Zelltod (Apoptose) eliminiert werden, sonst besteht das Risiko, dass sie sich zu Tumoren entwickeln. Ein Hauptmechanismus der Apotpose geschieht via Interaktion zweier Moleküle, des Fas-Liganden (FasL) mit seinem Rezeptor Fas. In normaler, lichtgeschützter Haut wird FasL exprimiert. Dieser verhindert, dass Entzündungszellen in die Epidermis eindringen und eliminiert transformierte Zellen. UV-Licht bewirkt nun, dass FasL nicht mehr exprimiert wird, dadurch geht die «Schutzfunktion» gegen transformierte Zellen verloren und das Risiko der Tumorbildung ist stark erhöht. Sobald sich aber ein Basaliom oder Plattenepithelkarzinom gebildet hat, wird FasL wieder exprimiert. Seine Funktion ist jetzt aber eine andere, er schützt vermutlich den Tumor vor dem Angriff des Immunsystems («Immune Escape»). Um dies zu beweisen haben wir eine Strategie entwickelt, um die Bildung von FasL im Tumorgewebe zu verhindern. Mittels spezifischen Antisense-oligonukleotiden oder sog. «short interfering RNA» (siRNA) Molekülen blockieren wir in den Zellen die mRNA, welche das FasL Protein herstellt. Es ist uns gelungen, nicht nur diese Moleküle in das Tumorgewebe zu bringen, sondern auch die Expression des FasL im Tumor zu unterdrücken. Damit sind die Voraussetzungen geschaffen, die «Immune Escape» Hypothese zu prüfen. Bewahrheitet sich diese Hypothese, so ergeben sich mit siRNA Molekülen neue mögliche Therapieformen für diese Hauttumoren.

Selected Publications

- Buechner, S. A., Wernli, M., Harr, T., Hahn, S., Itin, P., and Erb, P. (1997). Regression of basal cell carcinoma by intralesional interferon-alpha treatment is mediated by CD95 (Apo-1/Fas)-CD95 ligand-induced suicide, J Clin Invest 100, 2691-2696.
- Bachmann, F., Buechner, S. A., Wernli, M., Strebel, S., and Erb, P. (2001). Ultraviolet light downregulates CD95 ligand and trail receptor expression facilitating actinic keratosis and squamous cell carcinoma formation, J Invest Dermatol 117, 59-66.
- Buechner, S. A., Wernli, M., Bachmann, F., Harr, T., and Erb, P. (2002). Intralesional interferon in basal cell carcinoma, Recent Results in Cancer Research 160, 246-250.
- Ji, J. M., Wernli, M., Buechner, S., and Erb, P. (2003). Fas ligand downregulation with antisense oligonucleotides in cells and in cultured tissues of normal skin epidermis and basal cell carcinoma, J Invest Dermatol 120, 1094-1099.
- Ji, J. M., Wernli, M., Klimkait, T., and Erb, P. (2003). Enhanced gene silencing by the application of multiple specific small interfering RNAs, FEBS Lett 552, 247-252.

CD44 variant isoforms

Apoptosis

Autoimmune diseases

Colorectal cancer

Haematological tumors

Protection against Apoptosis is Mediated by CD44 Variant Isoforms (PD Dr. U. Günthert)

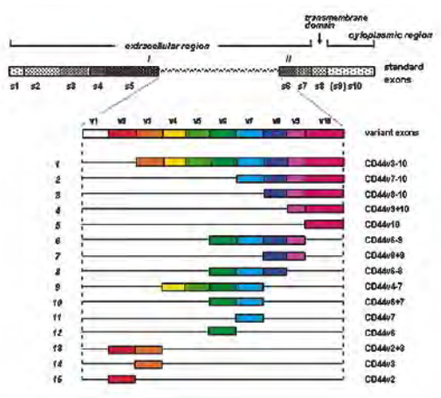
The transmembrane glycoprotein CD44 and its many isoforms are adhesion molecules, which are functionally involved in haematopoiesis, immune pathology, embryonic development and neoplastic transformation. Although only encoded by one gene, CD44 isoforms represent a large family of molecules that differ in the primary structure. These differences are produced by alternative splicing of at least ten unique exons, encoding extracellular regions out of a total of twenty exons (see scheme). We have generated genetically modified mice in which exons of the variant region are deleted without affecting the expression of the remaining exons. These exon-specific k.o. mice allowed for the functional analysis of these regions in haematologic malignancies, in colon carcinogenesis and in autoimmune diseases.The role of CD44 as a survival factor, especially in autoimmune diseases and in colon carcinogenesis is a central project. Our goal is to find out which apoptotic pathways are involved, how they are regulated and how the CD44 variant isoforms functionally block apoptosis in these diseases.

1. Function of CD44v in autoimmunity

A. *In experimental autoimmune encephalomyelitis (EAE), a model for Multiple Sclerosis (MS).* CD44v isoforms are required for the onset and maintenance of EAE – mice with deficiencies of these isoforms display reduced incidence and severity of EAE. With active and passive immunisation protocols we are evaluating whether CD44v deletions cause increased apoptosis of leukocytes in the central nervous system (CNS), altered cytokine profiles, and reduced migration to the target organ (CNS) resulting in fewer infiltrates. Expression studies are also performed in human MS brains, which showed CD44v presence in inflamed lesions.

B. *In experimental colitis, a model for human inflammatory bowel disease (IBD).* In mice, CD44v deletion results in reduced incidence and severity of colitis, increased apoptotic capacity in the inflammatory lesions and reduced ability to develop CD4 transfer-induced colitis. Furthermore, in the chronically diseased IL-10 k.o. mice, the deficiency for CD44v reduced substantially inflammatory lesions in the lamina propria. Comparative studies are performed with cells from patients with Crohn's disease.

C. *In collagen II induced arthritis (CIA), a model for human rheumatoid arthritis (RA).* CD44v deletion in mice results in reduced incidence and severity of arthritis (CIA and genetic model), increased production of CD4/CD44v cells in the spleen of arthritogenic mice (genetic model), increased apoptotic capacity in the inflammatory lesions of the joints (both models) and serum transfer from arthritogenic mice (KRNxNOD) results in reduced RA in CD44v k.o. recipient mice.



Organization and nomenclature of CD44v isoforms

2. Function of CD44v in tumour progression:
Initiation of neoplastic alterations in colorectal tumors – the role of CD44 variant isoforms in interaction with adenomatous polyposis coli (APC) in the wnt signaling pathway. Mice carrying an APC mutation called Min (multiple intestinal neoplasia), and that are, in addition, deficient for CD44v isoforms, develop considerably fewer polyps and survive much longer than APC/Min mice, which carry the CD44 wildtype gene. The concomitant truncation of the APC protein and the overexpression of CD44v isoforms are seemingly linked in the earliest stages of colon carcinogenesis. We are interested to find out how these molecules interact and which mechanisms lead to resistance of the tumour cells against programmed cell death.

3. Function of CD44v in apoptosis blockade:
CD44 variant isoforms interfere with Fas mediated cell death. CD44v transfected Jurkat cells are strongly protected against Fas-mediated apoptosis. Furthermore, CD44v9 transfected XG-1 plasmacytoma cells are protected against Fas-mediated apoptosis. CD44v co-localises with Fas on the surface of Jurkat cells and implicates a functional correlation.
Anti-CD44v therapeutic approaches could be an intriguing novel potential for the treatment of autoimmune diseases and tumourigenesis by specifically inducing cell death in these CD44v positive regions.

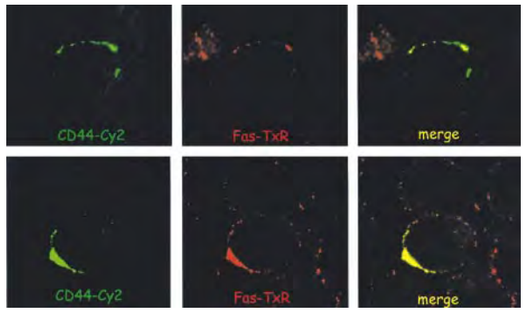


Fig. 1 Colocalization of CD95 and CD44v on the surface of Jurkat cells.

Clinics

We have a long-standing collaboration on haematological tumours with haematologist Prof. Dr. **Reinhard Stauder**, University Hospital Innsbruck, Austria.
The specific upregulation of CD44 variant isoforms in Non-Hodgkin lymphoma (NHL) cells and Multiple myeloma (MM) cells is an independent indication for an adverse prognosis of the patient. Protection of the tumour cells against Fas mediated cell death is another cause for tumour progression and hence poor prognosis. The upregulation of CD44v isoforms in haematological tumours and the resistance to undergo cell death appear to be directly and functionally linked. Understanding the mechanisms how CD44v isoforms interfere with Fas mediated cell death may lead to the development of new strategies for diagnosis and treatment of NHL and MM patients. The insensitivity to cell death induction is a major enigma in haematological diseases resulting in accumulation of malignant cells in the specific sites. Moreover, defects in the apoptosis pathways may lead to resistance towards chemotherapy and irradiation, pointing out the need for specific diagnostic approaches (to distinguish susceptible patients groups) as well as apoptosis-based therapies. Despite numerous efforts to elucidate the mechanisms of resistance to apoptosis in tumourigenesis, no conclusive results were obtained so far. Crohn's disease, a human inflammatory bowel disease, is characterised by strong expression of CD44v in the lamina propria of inflamed lesions. Therapeutic strategies for apoptosis induction of the CD44v expressing cells is evaluated in collaboration with gastroenterologist PD. Dr. **Bianca Wittig**, University Hospital Benjamin Franklin, Charité Berlin, Germany.

CD44 Isoformen schützen vor Programmiertem Zelltod

Das transmembranäre Gykoprotein CD44 existiert in vielen Formen. Diese verschiedenen Formen sind Adhäsionsmoleküle, welche bei der Hämopoiese (der Erneuerung der Blutzellen), bei Immunkrankheiten, während der embryonalen Entwicklung und bei der Krebsentstehung eine wichtige Rolle spielen. Ein einziges Gen ist für die verschiedenen Formen verantwortlich. Die Unterschiede entstehen durch sogenanntes alternatives Splicing, eine unterschiedliche Zusammensetzung von Genstücken, welche dann auch zu unterschiedlichen Proteinen führt (siehe die schematische Darstellung). Um die Funktionen dieser verschiedenen CD44 Formen zu studieren, haben wir genetische Konstrukte generiert, welche, wenn sie einer Maus eingesetzt werden, die Herstellung gewisser spezifischer Zusammensetzungen von CD44 Einheiten (gewisse Isoformen) nicht mehr erlauben. Damit untersuchen wir nun die Rolle von CD44 Isoformen als zelluläre Überlebensfaktoren, insbesondere in Autoimmunkrankheiten und bei Darmkrebs. Es gibt transgene Mäuse, welche gewisse Krankheiten (verschiedene Krebsarten, Autoimmun- od. Verdauungskrankheiten) schneller ausbilden und so als Modellsysteme dienen, in denen wir spezifisch die Rolle unserer Konstrukte testen. Unsere Resultate zeigen, dass in Mausmodellen ohne gewisse CD44 Isoformen ,sich eine autoimmune Form der Enzephalomyelitis, gewisse Darmkrankheiten und Arthritis weniger, weniger oft oder weniger gravierend entwickeln. Wenn man umgekehrt in Zelllinien gewisse CD44 Isoformen einbringt so zeigt sich, dass diese vor dem programmierten Zelltod schützen. Das Absterben fehlerhafter Zellen ist jedoch für die Gesundheit und das Überleben des ganzen Organismus Lebenswichtig. Zusammengefasst können wir mit den erlangten Erkenntnissen neue Immuntherapieformen gegen spezifische CD44 Isoformen schon im Mausmodell testen und für menschliche Anwendungen ins Auge fassen.

Selected Publications

- Günthert, U., Hofmann, M., Rudy, W., Reber, S., Zöller, M., Haußmann, I., Matzku, S., Wenzel, A., Ponta, H., Herrlich, P. (1991) A new variant of glycoprotein CD44 confers metastatic potential to rat carcinoma cells. Cell 65, 13-24.
- Stauder, R., Eisterer, A., Thaler, J., Günthert, U. (1995) CD44 variant isoforms in non-Hodgkin's lymphoma: A new independent prognostic factor. Blood 85, 2885-2899.
- Wittig B., Johannson, B., Zöller M., Schwärzler C., Günthert U. (2000) Abrogation of experimental colitis correlates with increased apoptosis in mice deficient for CD44v7. J. Exp. Med., 191, 2053-2063.
- Eisterer W., Bechter O., Hilbe W., van Driel M., Lokhorst H.M., Thaler J., Bloem A.C., Günthert U., Stauder R. (2001) CD44 isoforms are differentially regulated in plasma cell dyscrasias and CD44v9 represents a new independent prognostic parameter in multiple myeloma. Leuk. Res. 25, 1051-1057.
- van Driel, M., Günthert, U., van Kessel, A.C., Joling, P., Stauder, R., Lokhorst, H.M., Bloem, A.C. (2002) CD44 variant isoforms are involved in plasma cell adhesion to bone marrow stromal cells. Leukemia 16, 135-143.

Kidney transplantation

Epstein-Barr virus (EBV)

Post-transplant lymphoproliferative disorder (PTLD)

CD8 T cells

Quality and quantity of the immune response

Immuno-biology

Dr. Christoph Hess
Departement Forschung
Universitätsspital Basel

Group members
Dr. Olivier Gasser
Dr. Anna Missiou

Impact of Post Kidney-allograft Immuno-suppression on the Host Immune Response to Epstein-Barr Virus

Abstract
The newly formed Immunobiology lab aims at investigating the impact of iatrogenic immuno-suppression (IS), as established in kidney allotransplantation, on the Epstein-Barr virus (EBV)-specific CD8 T cell response. The transplant setting offers a unique window into in vivo-strategies utilized by the immune system to efficiently control lytic EBV infection, and prevent malignant transformation of latently infected B cells. Furthermore, an improved knowledge of EBV-specific immunity may allow identification of individuals at risk for developing EBV-associated pathology.

Background
Renal transplantation is the therapy of choice for end-stage renal disease. In Switzerland around 200 kidney transplants are performed yearly, 60–70/year in Basel. Cyclosporine, tacrolimus or sirolimus combined with mycophenolate mofetil (or azathioprine) and prednisone, are the mainstays of IS. Induction therapies include T cell antibodies and, more recently, interleukin-2 receptor blockers. Complications include infection, rejection, and malignancy. Chronic allograft failure remains the main problem limiting long-term success.
Viral pathogens are an important cause of morbidity following transplantation. Viruses playing prominent roles in the post-transplant setting include (i) herpes viruses (EBV, cytomegalovirus, herpes simplex virus, varizella zoster virus, human herpes viruses 6-8), (ii) hepatitis viruses (hepatitis C virus, hepatitis B virus), (iii) the papillomavirus (JC virus), (iv) the polyomavirus (BK virus) as well as (v) influenza/parainfluenza viruses.
EBV infection or reactivation is thought to play a major role in the genesis of post-transplant lymphoproliferative disorder (PTLD), one of the most life-threatening complications of IS in allograft recipients. Most PTLD tumor cells present an activated B-cell phenotype and an unrestricted pattern of latent EBV gene products. The overall incidence of this malignancy in renal transplant recipients is 1–2%, but varies with the nature and severity of the immunosuppressive regimen.
HLA class I restricted CD8 T cells are an essential component of the protective immune response against a variety of viral infections, including EBV. The outcome of EBV-infection is containment rather than eradication. An effective host response to infection depends on production of (i) functional CD8 T cells and (ii) their attraction to sites of viral replication.

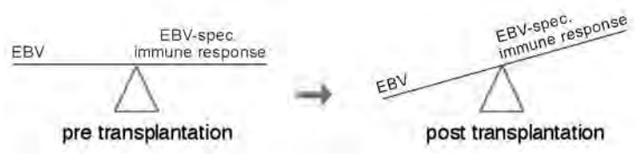


Fig. 1: Immuno-suppression, as initiated at the time of kidney transplantation, indicates a shift in the balance between EBV and the EBV-specific immuneresponse.

IS, as initiated with kidney allotransplantation, alters the balance between the host immune response and EBV. Breadth, magnitude, immune-phenotype, and ex-vivo function of EBV-specific CD8 T cells will be monitored through longitudinal ELISpot analyses, flow-cytometry based phenotypic characterization, cytotoxicity assays and proliferation assays.
Attraction of leukocytes to tissues is essential for inflammation and the host response to infection. This process is controlled by chemokines, which are chemotactic cytokines . Regulation and function of chemokines/chemokine receptors involved in controlling trafficking of EBV-specific CD8 T cells in kidney allograft recipients will be studied prior and sequentially under IS. To this aim, quantitative PCR, flow-cytometry based chemokine/chemokine receptor analyses, chemotaxis assays, calcium-flux assays, internalization-studies and western-blot analyses will be used.
Together these data will monitor *quantitative* as well as *qualitative* changes of the EBV-specific CD8 T cell response following transplantation, and may allow insight into both basic and clinical aspects of the EBV-specific immune response.

Virusinfekte nach Nierentransplantationen

Die Nierentransplantation ist das Nierenersatz-Wahlverfahren bei chronischem Nierenversagen.
Um Transplantatabstossungen zu verhindern, ist eine unspezifische medikamentöse Schwächung des Immunsystems nötig. Durch diese Schwächung kann es dazu kommen, dass bestimmte Viren die bei normalem Immunsystem problemlos in Schach gehalten werden, sich unkontrolliert vermehren und dadurch krankmachend werden.
Im kürzlich gegründeten Immunobiologie Labor versuchen wir die immunologische Grundlage von Problemen mit dem Epstein-Barr Virus (EBV) nach Nierentransplantation zu beleuchten. Ziel unserer Forschung ist es, Mechanismen der immunologischen Kontrolle von viralen Infekten besser verstehen zu lernen. Schlussendlich hoffen wir dadurch Patienten bei welchen EBV ausser Kontrolle zu geraten droht frühzeitig nach Transplantation indentifizieren zu können.

Selected Publications

- Hess C., S. Sadallah, A. Hefti, R. Landmann, J.A. Schifferli (1999) Ectosomes Released by Human Neutrophils are Specialized Functional Units. J. Immunol. 163:4564-73.
- Hess C., S. Sadallah, J.A. Schifferli (2000) Induction of neutrophil responsiveness to myeloperoxidase antibodies by their exposure to supernatant of degranulated autologous neutrophils. Blood 15; 2822-7.
- Hess C., Th. Klimkait, L. Schlapbach, V. Del-Zenero, S. Sadallah, G. Ballestra, V. Werder, C. Schaefer, M. Battegay, J.A. Schifferli (2002) HIV-1 is associated with erythrocytes in vivo. Lancet 359: 2230-34.
- Hess C., M. Altfeld, S.Y. Thomas, M.M. Addo, E.S. Rosenberg, T.M. Allen, R. Draenert, R.L. Eldridge, J.v. Lunzen, H.J. Stellbrink, B.D. Walker, A.D. Luster (2004) HIV-1-specific CD8 T-cells with an effector-phenotype and control of viral replication. Lancet 363:863-6.

Ectosome
Neutrophil
Inflammation
Complement
CRIT

Immuno-nephrology

Prof. Jürg A. Schifferli
Departement Forschung Universitätsspital Basel

Group members
Dr. Marten Trendelenburg
Dr. Olivier Gasser
Dr. Jameel Inal
Dr. Salima Sadallah
Brigitte Schneider (Technician)
Kwok Min Hui (PhD Student)
Ceylan Eken (PhD Student)
Sigrun Lange (PhD Student)

Characteristics and Functions of Ectosomes released by Human Polymorphonuclear Neutrophils

Upon activation, human polymorphonuclear neutrophils (PMN) release microvesicles, called ectosomes, directly from the cell surface. This release occurs in vitro as well as in vivo at sites of inflammation but also in blood when the activation of PMN is generalized as in sepsis. Ectocytosis is known to include the loss of cellular phospholipid-asymmetry, a process triggered by intra-cellular calcium influx. As a consequence, ectosomes bear phosphatidylserine on their outer membrane leaflet. Ectosomes express at their surface a series of proteins as well, including receptors and active enzymes, such as elastase and myeloperoxidase. Some of the proteins present on ectosomes are acquired from plasma. For instance ectosomes bind C1q, the first component of the complement cascade. The binding of C1q is followed by activation of the classical pathway of complement, leading to the opsonisation of PMN-ectosomes with C3- and C4-fragments. Complement-opsonisation of PMN-ectosomes is of prime importance for their fate in the circulation, since it drives their immune-adherence to erythrocytes (Fig. 1), similarly to immune complexes. The biological significance of this observation is unknown, however it might be suggested that this binding contributes to the clearance of ectosomes by fixed macrophages and may prevent unwanted interactions with endothelial cells. Indeed, we could show in vitro that ectosomes bind specifically to endothelial cells. Interestingly, monocytic/macrophages (MM) bind and phagocytose ectosomes rapidly. However, these reactions do not activate MM to become more aggressive. To the contrary, this phagocytosis modifies the programme of MM so that they release anti-inflammatory cytokines such as TGFb1. This property of ectosomes is not without some resemblance to properties of cells undergoing apoptosis, which die and are phagocytosed "in silence". Whether the expression of phosphatidylserine is the main mediator of such effects is under investigation.
In sum, and as a general biological observations, cells – here PMN – communicate with other cells not only via soluble mediators or cell/cell contact, but also by the release of ectosomes which are capable of transmitting signals.

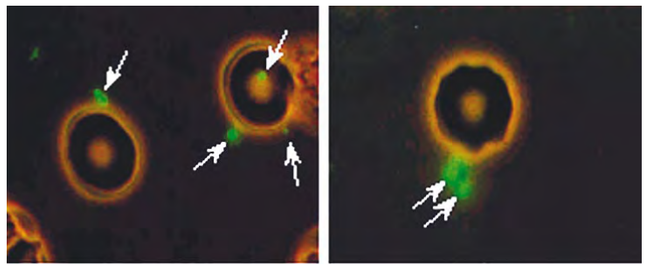
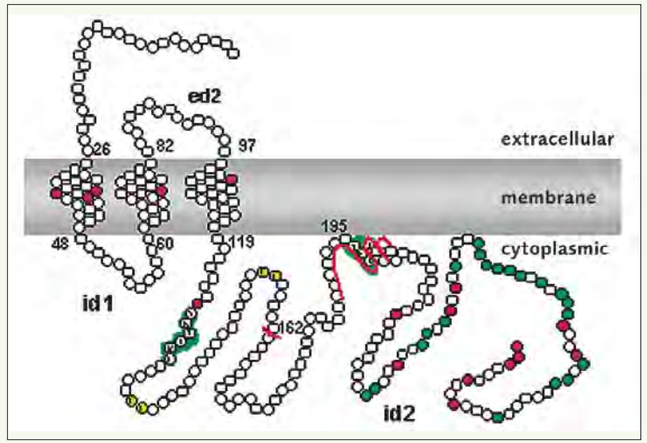


Fig. 1: Fluorescence microscopy of the binding of labeled ectosomes (arrows) to purified erythrocytes in the presence of complement

Clinics

The human Schistosome parasite lives in human blood vessels and has very efficient defence mechanisms against the attack of the human immune system, in particular against the enzymes of the complement cascade. One of the parasite proteins involved in this defence is CRIT (Complement Receptor Inhibitory Trispanning, Fig. 2), which is capable of blocking complement. We now found that humans have a protein highly similar to parasite CRIT, suggesting that the Schistosome may have acquired CRIT from humans, thereby gaining an evolutionary advantage. In humans, CRIT controls excessive activation of complement, suggesting that CRIT-based therapies could one day control diseases where complement attacks the body in an unregulated manner.

Fig. 2



Ectosome als interzelluläre Signalüberträger / Complement C2 Receptor Inhibitor Trispanning (CRIT)

Die grösste Gruppe der weissen Blutkörperchen sind die Granulozyten, auch polymorphonukleäre Zellen genannt. Die neutrophilen polymorphonukleären Zellen (PMN) scheiden Mikrovesikel aus, wenn sie aktiviert werden. Sie tun dies an entzündeten Stellen im Körper aber auch im Blut selbst im Falle von Infektionen. Das Ausscheiden der Mikrovesikel (auch PMN Ectosomen genannt) geschieht durch Ectozytose. Diese Mikrovesikel tragen an ihrer Oberfläche zahlreiche Proteine, wovon einige aus dem Plasma stammen. Von besonderem Interesse ist, dass sie das Protein C1q binden. C1q ist der erste Bestandteil im sogenannten Komplementsystem, einem wichtigen Bestandteil des Immunsystems. Sobald C1q gebunden ist, wird das Komplementsystem in klassischer weise aktiviert, wodurch die PMN Ectosome opsoniert werden. Unter Opsonisation versteht man eine Protein-Ummantelung welche die Phagozytose erleichtert. Dies führt nun dazu, dass die PMN Ectosome an Erythrozyten binden (Fig. 1) und durch Makrophagen verschlungen werden. Die biologische Bedeutung dieser Beobachtung ist unbekannt, wir vermuten jedoch, dass dadurch eine schädliche Interaktion der PMN Ectosome mit Endothelialzellen verhindert werden soll. Erstaunlicherweise werden durch diese Phagozytose die Makrophagen – ähnlich wie bei der Phagozytose apoptotischer Zellen – nicht aggressiver, sondern scheiden entzündungshemmende Zytokine wie TGFb1 aus.
Wir widmen unsere Forschung auch einem menschlichen Protein, CRIT (Fig. 2). Ein Schistosom Parasit der Blutbahnen hat auch ein CRIT Protein und ist gegenüber dem Immunsystem äusserst resistent. Wir vermuten, dass das Parasit dieses Protein vom Wirt übernommen hat um der Abwehr auszuweichen. CRIT verhindert eine Überreaktion des Komplementsystems und wir hoffen mit CRIT Therapieformen für gewisse Autoimmunreaktionen zu entwickeln.

Selected Publications

- Hess, C., Sadallah S., Hefti A., Landmann R., and Schifferli J.A. (1999) Ectosomes released by human neutrophils are specialized functional units. J Immunol. 163:4564-73.
- Gasser, O., Hess C., Miot S., Deon C., Sanchez J.-C., Schifferli J. A. (2003) Characterisation and properties of ectosomes released by human polymorphonuclear neutrophils. Exp Cell Res. May 1;285(2):243-57.
- Gasser, O., Schifferli J. A. (2004) Activated polymorphonuclear neutrophils disseminate anti-inflammatory microparticles by ectocytosis. Blood, in press
- Inal, J., Schneider, B., Armanini, M., and Schifferli, J.A. (2003) A peptide derived from the parasite receptor, Complement C2 Receptor Inhibitor Trispanning, CRIT, suppresses immune complex-mediated inflammation in mice. J. Immunol 170, 4310.
- Inal, J. and Schifferli, J.A. (2002) Complement C2 receptor inhibitor trispanning (CRIT) and the _-chain of C4 share a binding site for complement C2. J. Immunol. 168, 5213.

Staphylococcus Aureus
Infection
Nosocomial Disease
Toll-like Receptor 2
Virulence Factor

Infectious Diseases

Prof. Dr. Regine Landmann
Departement Forschung
Universitätsspital Basel

Group members
Dr. Sascha Kristian
Dr. Anne Stalder
Dr. Andrea Steinhuber
Fabricia Ferracin (technician)
Zarko Rajacic (technician)
Hakim Echchchannaoui (PhD student)

Molecular Mechanisms of Host Defense and Virulence Factor Regulation in *S. pneumoniae* and *S. aureus* Infection.

Host defense via Toll-like receptor 2 against *S. pneumoniae* and *S. aureus*
Toll-like receptors and CD14 are host pattern recognition receptors, which mediate innate immune responses to pathogen-derived molecules. TLR2 and CD14 specifically respond to teichoic acids and other cell wall and membrane components from gram-positive bacteria. Teichoic acids are positively charged polysaccharides intercalated in the cell wall; they contribute to virulence by determining the surface charge and thus the resistance against host-derived cationic peptides. In isolated form, the wall components elicit an inflammatory response in host cells via TLR2/CD14. The responses include cytokines, chemokine, nitric oxide in phagocytes, maturation in dendritic cells and defensin release in epithelial cells. The function of these cell wall components in the interaction with host TLR2/CD14 is however unknown, if they are exposed as part of live pathogens such as *Streptococcus (S.) pneumoniae*, which is the major agent responsible for adult meningitis and in *Staphylococcus (S.) aureus*, which causes device-related infections, pneumonia and sepsis. Therefore we are investigating the impact of TLR2 and CD14 on infection in mice with either of these bacteria and of their isogenic mutants expressing altered TLR2/CD14 ligands. *S. pneumoniae* meningitis is a severe disease with a 30% mortality. The pathogenesis is due to bacteria-induced inflammation, which leads to vascular and neuronal damage. TLR2 and CD14 modulate the disease course, since TLR2$^{-/-}$ and CD14$^{-/-}$ mice are more severely sick and die earlier than wild type mice. Yet their mechanism of action differs; TLR2$^{-/-}$ mice have early enhanced bacterial load (Fig. 1 and 2), delayed phagocytosis and bacterial killing of granulocytes and CD14$^{-/-}$ mice have early accelerated leukocyte immigration; both mouse strains have consequently enhanced inflammation, measured as leukocyte-derived TNF in infiltrating cells, which is the cause of death. Our future studies aim at unravelling the mechanism how TLR2/CD14 affect bacterial killing and leukocyte migration.Staphylococci are the cause of device-related infections. A mouse tissue cage infection model, in which low inocula of *S. aureus* or *S. epidermidis* cause a persistent local infection, exactly reproduces orthopedic implant infection. Persistence is explained by the absence of vessels and opsonins and the presence of functionally weak leukocytes undergoing apoptosis. Virulence is dependent on the staphylococcal susceptibility to extracellular bactericidal activity in an immunocompetent host. Therefore this model serves to test *S. aureus* mutants, which are altered in susceptibility to any of the bactericidal mechanisms. The host response is mediated by phagocytes exclusively and comprises defensins, reactive oxygen species, cytokines, chemokines, leukocyte infiltration and apoptosis. *S. aureus* expressing mutant teichoic acids, which lack positively charged alanine, are virulence-attenuated in cage infection in wild type mice, because they are more susceptible to host cationic antimicrobial peptides. Virulence is restored in the same infection in TLR2$^{-/-}$ mice, most likely because defensin production is TLR2-dependent. In future, the impact of other mutations in peptidoglycan and lipoproteins on *S. aureus* virulence in intact and TLR-deficient mice is studied.

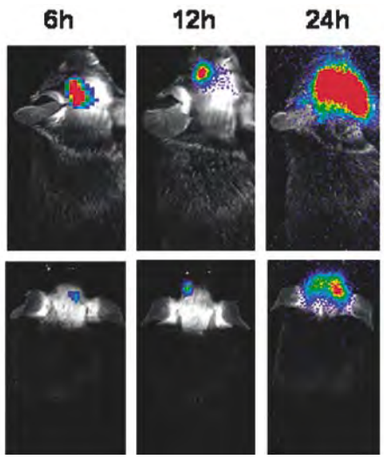


Fig. 1: Visualization of luciferase-tagged *S. pneumoniae* with a CCD camera in live anaesthetized mice 6 to 24 h after subarachnoidal infection.Bacterial load is higher in TLR2$^{-/-}$ (upper row) than in wild type mice (lower row).

Regulation and expression of virulence factors in *S. aureus*
The tissue cage infection also serves to study gene expression of staphylococcal virulence factors. *S. aureus* expresses multiple surface adhesins, which participate in colonization and invasion. Among them clumping factor A, a fibrinogen binding protein is important for adherence to extracellular matrix coated surfaces. It is modulated by host factors, since its gene expression is higher in vitro than in vivo, it is upregulated late in infection and is higher in adherent than in planktonic bacteria in tissue cages. In future the regulation and function of virulence factor genes and products, which affect biofilm, is followed in vivo (Fig.3).

Fig. 2: Scanning electron micrograph of *S. aureus* grown under aerobic (left) and unaerobic (right) conditions. Under unaerobic conditions the procution of slime (polysaccharide adhesin) is strongly enhanced

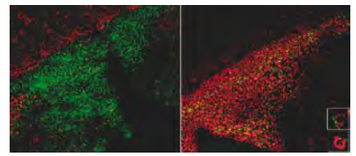


Fig. 3: Green fluorescent protein-tagged *S. pneumoniae* (green in left picture) in ventricles of mice with pneumococcal meningitis, surrounded by GFAP-stained astrocytes (red in left picture) and are associated with leukocytes stained with an antigranulocyte antibody (red in right picture). Insert: Larger magnification of leukocyte-associated *S. pneumoniae*

Clinics

Research concentrates on *Staphylococcus aureus* infections, infections in the transplant patients and HIV-infection. All areas are related to research within the DKBW. *Staphylococcus aureus* infections are among the most serious bacterial infections. We examine the epidemiological relevance of severe *S. aureus* infections and colonization as well as predictors of severe *S. aureus* infection. Infections in the transplant patient are a focus of our team. We are particularly interested in fungal infections and in BK virus nephropathy which represents in renal-transplant recipients a secondary infection. Clinical research of HIV infection has concentrated on the natural disease course and the immune recovery of CD4-T-lymphocytes after start of highly potent antiretroviral therapy. Immune recovery is strongly dependent on the degree of viral load reduction, individual factors such as age and pre-therapy baseline values such as immune status. Other clinical studies are directly related to clinical work such as a newly proposed algorithm for the management of tuberculosis in refugees.

Prof. Dr.
Manuel Battegay

PD Dr.
Ursula Flückiger
Infektiologische Klinik
Universitätsspital Basel

PD Dr. Stefano Bassetti
Dr. Luigia Elzi
Dr. Gilbert Kaufmann
Dr. Gerd Laifer
Dr. Pedram Sendi
Dr. Maja Weisser
Prof. Dr. Hans Hirsch

Staphylokokkeninfekte an Fremdkörpern – wie passen sich der Wirt und das Bakterium an?

Staphylokokkeninfekte sind die häufigste Komplikation von Prothesen- und Katheter-Implantationen. Der Wirt verfügt über natürliche Abwehrmechanismen, die – nach Stimulation durch Zellwandbestandteile des Staphylokokken – zur Bakterienabtötung und Entzündung führen können, im Fremdkörperinfekt aber oft nicht genügen. Wir zeigten die Rolle des "Toll-like Rezeptors-2" für die Abwehr gegen Staphylokokken und untersuchen weitere molekulare Mechanismen der natürlichen Immunantwort in einem Mausfremdkörperinfektmodell.
Staphylokokken verfügen ihrerseits über Oberflächenstrukturen (Adhesine) und Toxine, die die Fähigkeit eine Infektion zu verursachen d.h. die Virulenz beeinflussen. Das obige Mausinfektmodell eignet sich hervorragend zur Untersuchung der Virulenzfaktoren. Wir zeigten, dass Gene, welche Virulenzaktoren kodieren in vivo und in vitro unterschiedlich exprimiert und reguliert sind. Weitere Analysen der molekularen Anpassung von Staphylokokken im Fremdkörperinfekt sind von Bedeutung für die Erkennung der Faktoren, welche therapeutische Ziele in S. aureus darstellen könnten.

Selected Publications

- Echchannaoui H., K. Frei, C. Schnell, S. Leib, W. Zimmerli, R. Landmann (2002). Toll-like receptor 2-deficient mice are highly susceptible to *Streptococcus pneumoniae* meningitis due to reduced bacterial clearing and enhanced inflammation.J Infect Diseases 186:798-806.
- Wolz C., C. Goerke, R. Landmann, W. Zimmerli, U. Flückiger (2002). Transcription of clumping factor A in attached and unattached *Staphylococcus aureus* in Vitro and during device related infection. Infect. Immun, 70: 2758-2762.
- Hirsch HH., W. Knowles, M. Dickenmann, J. Passweg, T. Klimkait, MJ.Mihatsch, J. Steiger (2002). Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med, 347: 488-496.
- Kristian S., X. Lauth, V. Nizet, F. Goetz, B. Neumeister, A. Peschel, R. Landmann (2003) Alanylation of teichoic acids protects *Staphylococcus aureus* against Toll-like receptor 2-dependent host defense in a mouse tissue cage infection model. J Infect Diseases, 188: 414-423.
- Dory D., M Letiembre, H. Echchanaouui, F. Ferracin, J. Pieters, Y. Adachi, S. Akashi, R. Landmann (2003). Generation and functional characterization of a clonal murine periportal Kupffer cell line from H2Kb –tsA-58 transgene mice. J Leukoc. Biol. 74: 49-59.

Quantitative PCR
Phenotyping
Treatment resistance
Reporter systems
HIV
Oncology

Molecular Research for Diagnostics

PD Dr. Thomas Klimkait
Institut für Medizinische Mikrobiologie

Group Members
Dr. Vincent Brondani
Dr. François Hamy
Claudia Jörg (Technician)
Stéphane Hubert (Technician)
Séverine Louvel (PhD Student)
Daniela Kenzelmann (Diploma Student)

Phenotyping for Molecular Diagnosis of Therapy Resistance

In 2003 the research group Klimkait ("Molecular Research for Diagnostics (MRD)") focused its anti-HIV activities on aspects of the co-existance of clinically relevant virus variants. The basis for this focus was the clinical observation that even during highly effective therapy several viruses can co-evolve in the same patients. This phenomenon can occur quite rapidly (within months) and poses a significant complication in the diagnosis of therapy-escaping viruses that carry resistances to specific drugs. In addition viral recombination has now been demonstrated for retroviruses, another effective route for viral treatment-escape. The research group MRD has developed a phenotyping system, which functions quite analogous to the well-established antibiogram for microbes. This new diagnostic tool has been designed to detect and characterize HIV-resistance in clinical samples; it is in Switzerland currently the only system of its kind and is reimbursed by the Swiss health care system.
In the year 2003 MRD has invested in a second, concept-expanding development, which originated in the concept of phenotyping resistance to antiviral drugs. The adaptation will lead to an application in drug resistant cancers by targeting the molecular cause of chronic myeloid leukemia, the Philadelphia-chromosome-linked BCR-ABL. A reliable reporter system is being established for the assessment of Gleevec resistance as well as a patient's genetic predisposition linked to treatment failure with this novel drug.
Aside from research towards diagnostics systems with direct utility, MRD invested research into treatment applications of oligonucleotides, to be used either as DNA- or small interfering RNA molecules. Using cell culture models in the context of cell functions (CXCR4 and the androgen receptor) these approaches might have a direct bearing for cancer strategies (metastasis and prostate cancer, respectively).
In June 2003 the group received, upon assistance by the University's technology transfer office (WTT), a patent on an HIV inhibitor, which follows the unique concept of simultaneously blocking viral gene activation and secondary events on the target cell, triggered by HIV.

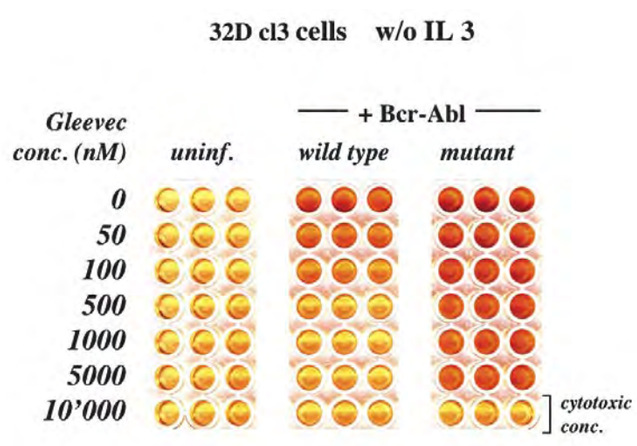


Fig. 1: deCIPHR system for the phenotypic assessment of therapy resistance. The idea behind this approach was to establish a test-system analogous to the well-established "antibiogram", which is widely used in microbiology and apply it to novel therapeutic areas such as in the fields of virology and oncology.

Partners for our research on molecular aspects of viral human pathogens are Prof. Dr. H. Hirsch on topics related to transplantation virology, Prof. M. Battegay in the context of clinical HIV-research, particularly therapy resistance, and Prof. M. Heim on hepatitis-associated virology. Additional research projects are ongoing with Prof. J. Schifferli (University Hospital) and Prof. J. Pieters (Biocenter). In the center of these collaborations are ex vivo evaluations and RNA and DNA quantification of central pathogens relevant in the respective clinical context.

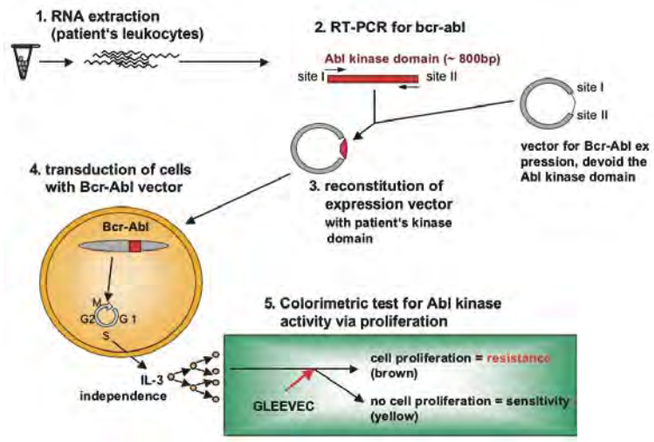


Fig. 2: Establishment of a phenotypic assessment scheme for testing susceptibility or resistance in CML to treatment with Gleevec. The underlying principle is to link the therapeutic target function (Bcr-Abl hybrid kinase) to a reporter read-out (white → yellow; yellow → brown). This way a genetic predisposition for therapeutic failure can be detected with high precision and sensitivity.

On page 127 we introduce our spin-off company InPheno.

Phänotypisierung als "Molekulares Diagnostikum" von Therapieresistenzen

Im Jahr 2003 konzentrierte die Forschungsgruppe Klimkait (MRD) ihre ani-HIV Aktivitäten auf Aspekte der Ko-Existenz verschiedener klinisch relevanter HIV-Varianten im Patienten. Diese Fokussierung entstand aus der Beobachtung, dass selbst unter Therapie im Patienten zeitgleich mehrere HIV-Mutanten evolvieren können. Dies kann innert weniger Monate geschehen, und solche resistente Viren stellen inzwischen ein sehr ernstes Problem für das klinische Management einer HIV-Infektion dar. Die Entdeckung, dass Retroviren ihr Erbgut rekombinieren können, erklärt ausserdem ein beschleunigtes Therapieversagen. Das in der Gruppe MRD entwickelte Phänotypisierungssystem "PhenoTecT" weist Ähnlichkeiten zum "Antibiogramm" auf, welches in der Mikrobiologie längst breite Anwendung gefunden hat, und wurde so konzipiert, dass es für die Routineanwendung an Plasmaproben sowie für Medikamentenprofilierungen in der Entwicklung ideal ist; in der Schweiz ist es zurzeit das einzige solche System, das über die Analysenliste abgerechnet werden kann.
Ein zweites Projekt der Gruppe MRD erweitert das an HIV validierte Konzept in ein neues Anwendungsgebiet: die Krebstherapie. Gegen chronisch myeloische Leukämie wird heute Glivec erfolgreich eingesetzt, welches gezielt das mit dem Philadelphia-Chromosom assoziierte Bcr-Abl Gen blockiert. Ein zuverlässiges Phänotypisierungssystem ist in der Gruppe MRD in Entwicklung. Es soll Glivec-Resistenz und eine ungünstige genetische Prädisposition in betroffenen Patienten detektieren, ohne dass ganze Chromosomenabschnitte sequenziert werden müssen.
Weitere Forschungsprojekte befassen sich mit der Funktion der zellulären Co-Rezeptoren von HIV, Oligonukleotidanwendungen und neuen Diagnostik-Strategien in Virologie und Onkologie. Im Jahr 2003 erhielt die Gruppe unter Mithilfe der WTT der Universität Basel ein Patent auf ein neues Konzept der HIV-Hemmung, bei welchem "Entry" und Genaktivierung blockiert werden.

Selected Publications

– Suñé, C.; L. Brennan; D.R. Stover; and T. Klimkait (2003) Effect of polymorphisms on the replicative capacity of protease inhibitor-resistant HIV-1 variants under drug pressure. Clin.Microbiol.Inf. 10: 119-126
– Hamy, F.; V. Brondani; R. Spoerri; S. Rigo; C. Stamm; and T. Klimkait. (2003) Blocking Androgen Receptor Activity in LNCaP cells by Antisense Oligonucleotides. Prostate Cancer and Prostatic Diseases 6 (1), 27-33
– Hess, C.; T. Klimkait; L. Schlapbach; V. Del Zenero; S. Sadallah; E. Horakova; G. Balestra; V. Werder; C. Schaefer; M. Battegay; and JA. Schifferli (2002) Association of a pool of HIV-1 with erythrocytes in vivo: a cohort study. Lancet 359, 2230-2234
– Hirsch, HH.; M. Mohaupt; and T. Klimkait (2001) Prospective Monitoring of BK Virus Load in a Patient with BK Virus Allograft Nephropathy under Sirolimus. Journal of Infectious Diseases 184, 1494-1495

Vascular Endothelium

Cytotoxic T Lymphocytes

Arteriosclerosis

Graft vs Host Disease.

Molecular Nephrology

PD Dr. Barbara Biedermann
Departement Forschung
Universitätsspital Basel

Group Members
Dr. Marco Kummer
Dr. Christine Stegmann
Denise Wittwer (technician)

Anti-endothelial Cytotoxic T-lymphocytes in Human Disease

Vascular integrity is required for tissue homeostasis. Cytotoxic T lymphocytes are important effector cells of antigen-specific immune responses. We have shown that vascular endothelial cells can activate CD8 T lymphocytes to differentiate into endothelial-selective cytotoxic T lymphocytes. In addition, vascular endothelial cells regulate T-lymphocyte differentiation in a complex way. The balance of activating and suppressing signals is playing a decisive role in the evolution of immune-mediated vascular disease.

After allogeneic stem cell or solid organ transplantation, vascular endothelial cells are the first cell type which is met by circulating, blood-borne alloreactive T-lymphocytes. Under these circumstances, endothelial cells are gate-keepers but also activators and potential targets of antigen-specific T lymphocytes. Endothelialitis, the subendothelial accumulation of cytotoxic T lymphocytes is the histopathological hallmark lesion of vascular rejection after solid organ transplantation. We have shown that endothelialitis also occurs after allogeneic stem cell transplantation. Endothelial injury by cytotoxic T lymphocytes leads to microvessel loss in this classical, antigen-mediated human disease: graft versus host disease.

Arteriosclerosis is an inflammatory lipid storage disease of large arteries. The inflammatory infiltrate consists of antigen presenting cells (macrophages and dendritic cells) and T lymphocytes, predominantly CD8 T lymphocytes. Molecular mediators of the innate immune system (e.g. Toll receptors, chemokines, adhesion molecules) are critically involved in the initiation and progression of arteriosclerosis. The role of an antigen-specific, acquired immune response in this context is still ill defined. In apolipoprotein E knock-out mice, an animal model of arteriosclerosis, anti-vascular cytotoxic T-lymphocytes accelerate the formation of atherosclerotic lesions. We hypothesize that sustained, chronic vascular injury by activated cytotoxic T lymphocytes causes symptomatic arteriosclerosis in man. We characterize the type of endothelial injury caused by cytotoxic T lymphocytes in cell culture experiments and in an animal model of arteriosclerosis. We have developed a human arterial tissue array to systematically examine the arterial wall in different stages of arteriosclerosis. The tissue array is an important and valid tool to confirm the relevance of in vitro observations and results obtained from animal experiments for the pathogenesis of arteriosclerosis in man.

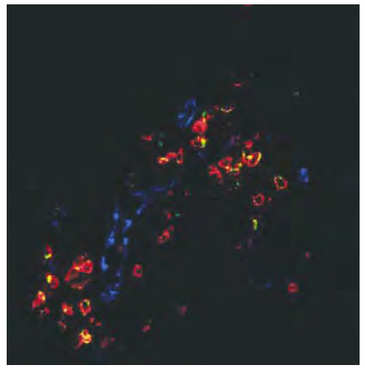


Fig. 1: Activated cytotoxic T lymphocytes (red cells with yellow granules) attack vascular endothelial cells (blue).

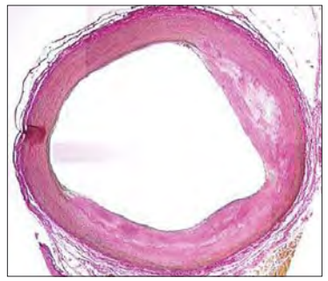


Fig. 2: Arteriosclerosis is an inflammatory lipid storage disorder of large arteries.

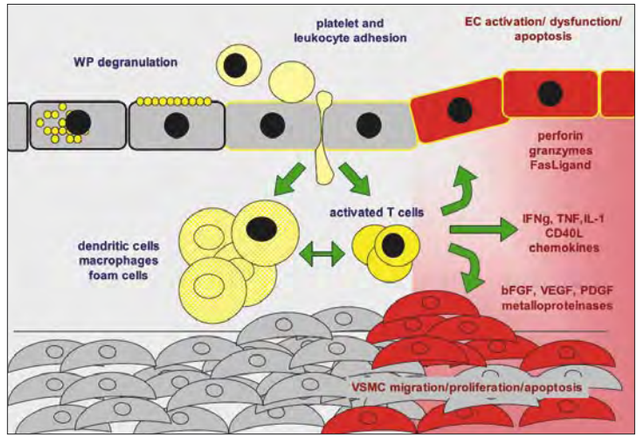


Fig. 3: Cellular and molecular events involved in chronic vascular inflammation, e.g. in transplant-associated vasculopathy or arteriosclerosis.

Molecular Medicine of Arteriosclerosis

Arteriosclerosis is a very common disease in civilized countries. About half of the patients treated at our Department (Medizinische Universitätsklinik, Kantonsspital Bruderholz) suffer from arteriosclerosis. Arteriosclerosis can be asymptomatic or symptomatic. In asymptomatic arteriosclerosis, the arterial lesion does not compromise the aterial flow in an organ. In symptomatic arteriosclerosis, the arterial perfusion of organs is critically impaired. Depending on the organ involved by symptomatic arteriosclerosis, a myocardial infarction, a stroke or other cardiovascular events occur. At present, the most efficient interventions to treat symptomatic arteriosclerosis are percutaneous transluminal angioplasty or bypass surgery. However, since arteriosclerosis is a panarterial disease, the therapy should not exclusively focus on culprit lesions but rather be systemic. Since life-time incidence of symptomatic arteriosclerosis is 40-50%, treatment should induce sustained remission of the disease after a limited period of time. The focus of our clinical research is to develop non-invasive, molecular concepts to diagnose and to identify novel drug targets to treat arteriosclerosis. Novel diagnostic and therapeutic approaches are tested and validated in clinical trials.

Prof. Dr. Reto Krapf
Kantonsspital
Bruderholz

Zytotoxische T Lymphozyten bei Blutgefässerkrankungen

Die einwandfreie Funktion von Blutgefässen ist eine Voraussetzung für die Gewebe-Homöostase. Bestimmte weisse Blutkörperchen (CD8-positive T Lymphozyten) können sich in Gegenwart von als fremd erkannten Endothelzellen (Innenschichtzellen der Blutgefässwand) zu endothel-spezifischen, zytotoxischen T Lymphozyten entwickeln. Letztere spielen bei Immunreaktionen gegen Blutgefässe eine wichtige Rolle.

Nach Organ- oder Stammzell-Transplantationen sind die Endothelzellen die ersten fremden Körperzellen, welche mit zirkulierenden T Lymphozyten in Kontakt treten. Die Ansammlung von zytotoxischen T Lymphozyten unmittelbar unter dem Endothel (Endothelialitis) ist bei der histopathologischen Untersuchung das typische Anzeichen für ein gefässbedingtes Abstossen eines Organs nach einer Transplantation. Wir konnten aufzeigen, dass eine Endothelialitis auch nach Knochenmarks-Transplantationen entstehen kann. In diesem Fall ist sie ein Anzeichen für die Graft versus Host («Transplantat gegen Wirt») Reaktion. Im Labor untersuchen wir mit Tiermodellen und in Gewebekulturen die molekularen Mechanismen, die zur Aktivierung der T-Lymphozyten durch Endothelzellen führen. Diese Mechanismen sind nicht nur bei Gefässentzündungen nach Transplantationen wichtig, sondern spielen vermutlich auch eine wesentliche Rolle bei der Entstehung der Arteriosklerose.

Die Arteriosklerose (Arterienverkalkung) entsteht durch eine chronische Entzündung der Arterienwand, bei der es zur Verengung dieser Blutgefässe, der Arterien, kommt. Durch die schlechte Durchblutung kann diese Krankheit sich als Hirnschlag und Herzinfarkt äussern. Die Arteriosklerose ist sehr verbreitet, nahezu die Hälfte unserer Patienten sind davon betroffen. Ist eine Organfunktion durch die Arteriosklerose beeinträchtigt, hilft meistens nur noch die Gefässoperation. Da die Arteriosklerose jedoch eine Erkrankung aller Arterien im Körper ist, sollte sich die Behandlung eigentlich nicht ausschliesslich auf die am meisten betroffene Stelle beschränken. Unsere klinische Forschung befasst sich mit der Entwicklung von neuen, nicht-invasiven Diagnose- und Behandlungsmöglichkeiten der Arteriosklerose.

Selected Publications

- B. C. Biedermann, J. S. Pober (1998) Human endothelial cells induce and regulate cytolytic T cell differentiation. J Immunol; 161:4679-4687.
- B. C. Biedermann, J. S. Pober (1999) Human vascular endothelial cells favor clonal expansion of unusual alloreactive cytolytic T lymphocytes. J Immunol; 162: 7022-7030.
- B.C. Biedermann (2001)Vascular Endothelium checkpoint to control inflammation and immunity. News Physiol Sci; 16:84-88
- B.C. Biedermann, S. Sahner, M. Gregor, D.A. Tsakiris, C. Jeanneret, J.S. Pober, A. Gratwohl (2002) Endothelial injury mediated by cytotoxic T lymphocytes and loss of microvessels in chronic graft versus host disease. Lancet; 359:2078-83.
- B.C. Biedermann, D.A. Tsakiris, M. Gregor, J.S. Pober, A. Gratwohl (2003) Combining altered levels of effector transcripts in circulating T cells with a marker of endothelial injury is specific for active graft-vs-host disease. Bone Marrow Transpl; 32:1077-1084.

Thymus

Development

Gene Profiling Microenvironment

Autoimmunity

Aire

Graft-Versus Host Disease

Pediatric Immunology and Diabetology

Prof. Dr.
Georg A. Holländer
Universitätskinderspital Beider Basel
Departement Forschung
Universitätsspital Basel

PD Dr.
Urs Zumsteg

Group members
Dr. Marcel Keller
Dr. Werner Krenger
Dr. Luca Piali
Dr. Thomas Barthlott
Dr. Jason Gill
Dr. Elena Litvinova
Dr. Simona Rossi
Dr. Noriko Shikama-Dorn
Dr. Saulius Zuklys
Dr. Emanuela Burchielli (MD PhD student)
Dr. Mathias Hauri (MD PhD student)
Dr. Lukas Jeker (MD PhD student)
Thomas Boulay (technician)
Elli Christen (technician)
Katrin Hafen (technician)
Annick Peter (technician)
Yves Mathieu (PhD student)
Kyung-jae Na (PhD student)

Molecular and Cellular Mechanisms of Thymus Development and Function

With the development of higher organisms, the necessity evolved to establish a cellular system able to distinguish between vital Self and injurious Non-Self. From the perspective of the immune system, this essential task is achieved by a myriad of receptors and cells that belong either to the innate or to the adaptive immune system. However, the most elaborate, dynamic and effective defence strategies are carried out by the adaptive immune response. T lymphocytes orchestrate this immune response and thus represent a key component of the adaptive immune system.

The thymus provides the ideal microenvironment for the survival, expansion, and differentiation of precursor cells to fully functional T cells. This intrathymic maturation constitutes a process dependent on several non-lymphoid cell types and their membrane-bound and secreted molecules. Epithelial cells constitute the most important component of the thymic stroma and can be differentiated into functionally and phenotypically distinct subpopulations (Figure 1). Thymic epithelial cells are centrally involved in the active instruction of immature T cells to ignore Self antigens but to respond to Non-Self antigens.

Research in the laboratory of Pediatric Immunology is focused on the development and function of thymic epithelial cells. Although the principles of thymic organogenesis are well preserved throughout vertebrate evolution, the molecular mechanisms controlling this complex event are just beginning to be unravelled. The murine thymus emerges at day 10.5 post conceptionem (p.c.) as an epithelial anlage budding from the ventral endodermal lining of the third pharyngeal pouch. In the course of the next 12 hours, a thymic primordium is formed that is separate from the endodermal lining of the foregut and thus positioned in the mesenchyme of the third branchial arch. Immigration of lymphoid precursor cells occurs by day 12. p.c. and is paralleled by a rapid proliferation and differentiation among thymic epithelial cells (Figure 2).

We have started to dissect the genetic programs that control the commitment to a thymic epithelial cell fate, and that direct the functional maturation of thymic epithelial cells. For this purpose, we have physically isolated cells committed to a thymic epithelial cell fate from embryos as early as day 10.5 p.c. The mRNA expression profile of these cells was subsequently analysed for the presence of both new and known gene products that are preferentially expressed in endodermal cells with a thymic cell fate. Intriguingly, some of the identified gene products are directly related to the signalling pathways of Wnt, sonic hedgehog and the TGF-β family of molecules, which have been known to provide developmental cues critical for organ formation in organisms ranging from Drosophila to vertebrates. Mice deficient for a singular molecule in these pathways have now been generated to assess their specific role in thymic organogenesis. In this context, we have also identified a novel family of nuclear proteins, which have been termed "Shoca" based on their structure and function as **SH**2-d**o**main **c**ontaining **a**daptor molecules (Figure 3 and Figure 4). The *in vitro* biological function of Shoca has been linked to Wnt signalling and its *in vivo* role for thymic organogenesis is presently investigated in Shoca-deficient mice.

Although thymic epithelial cells instruct developing T cells to be tolerant to Self-Antigens, the molecular mechanisms operational in this process are only incompletely understood. However, rare autoimmune disorders have been observed that could reveal the precise molecular basis to thymic tolerance since these disorders are caused by a single gene defect. The Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy Syndrome (APECED) constitutes such a disorder. APECED is caused by a loss of function of the transcription factor **A**utoimmune **Re**gulator (AIRE) in thymic epithelial cells. By generating mice deficient for Aire, we have created a murine model of APECED that lends itself to the analysis of the molecular mechanisms by which AIRE controls the induction of T cell tolerance by thymic epithelial cells.

Type I diabetes mellitus constitutes one of the endocrine pathologies observed in the presence of AIRE-deficiency. This disorder is caused by the autoimmune destruction of insulin-secreting β-cells in the islets of Langerhans. Although this pathology is mediated by T cells reactive to Self, the mechanism by which these cytotoxic effector cells gain access to the islets has remained unknown. We have now elucidated that several chemokines expressed by β-cells are responsible for the attraction of harmful T cells to the islets (Figure 5). Importantly, mice deficient for the corresponding chemokine-receptor developed diabetes either much later or not at all. This mechanism is presently tested for its potential for pharmacological intervention.

The thymic function is maintained throughout life and new T cells are continuously generated. This capacity is particularly important for the swift repletion with naïve T cells. The kinetics by which donor-derived precursors repopulate the recipient decide on the efficiency by which a functional immune system is re-established after hematopoietic stem cell transplantation. We could now demonstrate that pre-transplant conditioning and graft-versus-host disease (GVHD) negatively affect thymic epithelial cell function and thus impair intrathymic maturation and selection of T-cells. While the precise molecular mechanisms responsible for this loss of thymic function are presently investigated, we could already reveal that fibroblast growth factor-7 serves a highly specific mediator of thymic epithelial cell proliferation and repair when given in vivo to mice conditioned by radiation and/or challenged by GVHD.

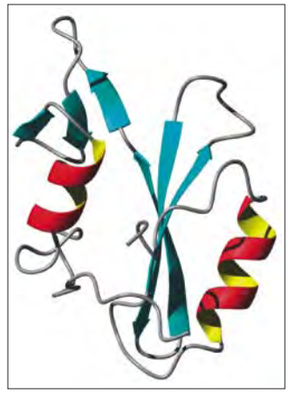


Fig. 3:
Computer model of the SH2 structure of Shoca.

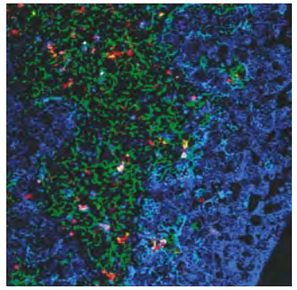


Fig. 1:
Subpopulations of adult thymic epithelial cells are characterized by differential gene expression. Cells are stained for cytokeratin 8 (blue), a marker for cortical epithelial cells, for cytokeratin 5 (green) detecting medullary epithelial cells, and for the cell surface antigen MTS24, which serves as a stem cell marker (red).

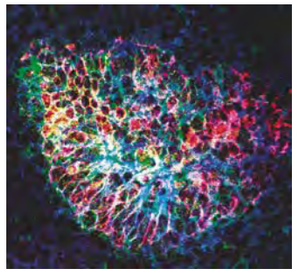


Fig. 2:
Thymic anlage of an embryo at day 12 of gestation (green: MTS24; red: cytokeratin 5; blue: cytokeratin 8)

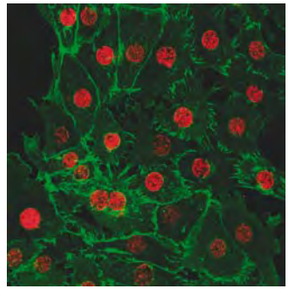


Fig. 4:
Shoca expression (red) in the nucleus of thymic epithelial cells (green).

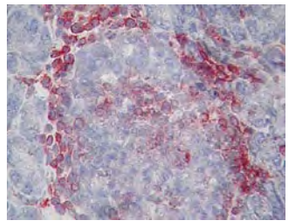


Fig. 5:
Islets of Langerhans infiltrated with cytotoxic T cells in the course of the immunopathology leading to Type I diabetes.

Clinics

Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases in childhood with a prevalence of about 1.7 per 1000 people aged 20 years. Worldwide prospective studies on the incidence have shown an increase in the past few decades and also in Switzerland a yearly average increase of 5.1% has been shown between 1991 and 1999. In the preschool age group a more than 4 fold increase has been recorded but the explanation for this shift towards younger age at diagnosis remains unclear. The trigger of autoimmune pancreatic beta-cell destruction in genetically prone children seems to be multifactorial and intervention strategies have not been successful so far. When a child gets T1DM, insulin dependency and the need for appropriate nutrition is the same as in diabetic adults. However, due to different stages of growth and development, there are major physiological, medical, psychological, social and emotional differences demanding a special approach and separate guidelines. Childhood diabetes has the potential to be profoundly destructive, both for the affected individual as for his family relationships. Despite of modern intensified insulin replacement therapy, the disease continues to be the leading cause of end stage renal disease, blindness and amputation, and still a major cause of cardiovascular complications and premature death. Prevention of T1DM must be a primary goal and research in the field of the immunopathogenesis as well as advances in the molecular and biological understanding of pancreatic beta-cell destruction are a prerequisite for clinical prevention trials.

Die Entwicklung des Immunsystems und Autoimmunität

Ein einwandfreies Funktionieren des Immunsystems ermöglicht die gezielte Abwehr gegenüber einer fast uneingeschränkten Vielzahl schädlicher Einflüsse. Das aus unterschiedlichen Zellen und Effektormolekülen zusammengesetzte Immunsystem besitzt hierzu die einmalige Fähigkeit, zwischen körpereigenen, harmlosen Selbst"Antigenen einerseits und potentiell schädigenden, so genannten «Fremd-» Antigenen andererseits genau unterscheiden zu können. Diese essentielle Funktion wird vor allem durch T Lymphozyten ermöglicht, die ihre Reifung und Selektion in direktem funktionellem Kontakt mit Epithelzellen und anderen Stromazellen des Thymus erfahren haben. Gegenwärtig ist aber noch wenig bekannt, wie Thymus Epithelzellen sich aus den entsprechenden Vorläuferzellen entwickeln können und in welcher Weise sie ihre für die Reifung des Immunsystems bedeutungsvollen Funktionen wahrnehmen.
Die Forschung im Labor der pädiatrischen Immunologie untersucht das genetische Programm, das für die Entwicklung und Funktion von Thymus Epithelzellen verantwortlich zeichnet. Hierzu wurde das Genexpressionsmuster von Thymus Epithelzellen untersucht, welche zu unterschiedlichen Stadien ihrer Entwicklung isoliert wurden. Dabei konnten wir aufzeigen, dass die Thymus Entwicklung durch ein umfassendes Netzwerk von unterschiedlichen Molekülen gesteuert wird, zu denen unter anderem auch die Wnt Glykoproteine, die Sonic Hedgehog Proteine und Mitglieder der grossen Familie der TGF- Moleküle gehören. Diese Wachstums- und Differenzierungsmoleküle sind bekannter Weise auch bei der Entwicklung anderer Organe mitbeteiligt. Zusätzlich zu diesen bereits bekannten Genprodukten haben wir auch in Thymus Epithelzellen Transkripte von bis anhin noch nicht identifizierten Genen isolieren können. Hierzu gehört die von uns als «Shoca» (SH2 domain containing adaptors) bezeichnete Molekülfamilie, welche die Signaltransduktion über den Wnt-vermittelten Aktivierungsweg moduliert.
Der Thymus kann durch unterschiedliche, schädigende Einflüsse in seiner Funktion wesentlich gestört werden. So können Thymus Epithelien durch die im Rahmen der Therapie von malignen und nicht malignen hämatologischen Erkrankungen verwendete Chemo- und Bestrahlungstherapie teilweise oder gar gänzlich zerstört werden. Die genaue Kenntnis der regulären Entwicklung der Thymus Epithelien ist deshalb förderlich, neue therapeutische Strategien zu entwickeln, wie die Thymusfunktion in solchen klinischen Situationen erhalten beziehungsweise umfassend wieder hergestellt werden kann.
In welcher Weise Epithelzellen unreife T Zellen während ihrer Entwicklung im Thymus selektionieren können, ist noch überwiegend unbekannt. Im Speziellen ist auf molekularer Ebene noch unaufgeklärt, wie ein Repertoire an immunologischen Effektorzellen im Thymus ausgewählt werden kann, das gegenüber Selbst-Antigenen tolerant ist, doch gegen Fremd-Antigene eine gezielte Abwehrantwort zulassen kann. Eine wesentliche Ausnahme hierzu ist die neuere Erkenntnis, dass der Mangel des Transkriptionsfaktors AIRE (autoimmune regulator) zu einem komplexen Autoimmunsyndrom Anlass gibt. Dieser Faktor kann unter physiologischen Bedingungen in einer kleinen Subpopulation von Thymus Epithelzellen nachgewiesen werden und sein Fehlen ist für die Entstehung einer komplexen Autoimmunerkrankung verantwortlich. Diese als autoimmune Polyendokrinopathie mit ektodermaler Dysplasie (APECED) bezeichnet Pathologie ist durch eine immunologische Zerstörung unterschiedlicher Organe und den damit verbundenen Funktionsverlust gekennzeichnet. Wir haben nun ein Mausmodel für diese Erkrankung geschaffen, welches uns erlaubt, gezielt der Frage nachzugehen, wie ein Defekt eines singulären Transkriptionsfaktors zu einem solch vielfältigen, autoimmunologischen Pathologie wie dem APECED Syndrom Anlass geben kann.
Schliesslich konnte in unserem Labor auch in den letzten Jahren aufgeklärt werden, wie autoreaktive T Zellen bei der autoimmunen Form des Diabetes mellitus die Zellen der Langerhansinseln auffinden und zerstören können. Diese Erkenntnis wird gegenwärtig dazu verwendet, in Zusammenarbeit mit einer Biotechnologie Firma, neue Ansätze zur Therapie des Diabetes mellitus auszutesten.

Selected Publications

- W. van Ewijk*, G. Holländer*, C. Terhorst, B. Wang (2000) Crosstalk regulates the organization of thymic microenvironments. Development, 127:1583-1591. (* contributed equally)
- S. Zuklys, G. Balciunaite, A. Agarwal, E. Palmer, P. Naquet, G. Holländer (2000) Differential thymic transcription of aire, the gene defective in the monogenic autosomal recessive autoimmune disease APECED. Journal of Immunology, 165:1976-1983.
- Rossi, B. R. Blazar, C. L. Farrell, D. M. Danilenko, D. L. Lacey, K. I. Weinberg, W. Krenger, and G. Holländer (2002) Keratinocyte Growth Factor Preserves Normal Thymopoiesis And Thymic Microenvironment During Experimental Graft-Versus-Host-Disease. Blood, 100: 682-91.
- J. Gill, M. Marlin, G. Holländer, R. Boyd (2002) A single precursor population is sufficient to reconstitute the complex epithelial microenvironment of the thymus. Nature Immunology, 3: 635-642.
- G. Balciunaite, E. Balciunaite, S. Zuklys, Y. D. Mathieu, J. Gill, R. Boyd, D. J. Sussman, G. Holländer (2002) Wnt glycoproteins regulate the expression of Foxn1, the gene defective in nude mice. Nature Immunology, 3: 1102-1108.
- S. Frigerio, T. Tobias Junt, Bao Lu, Craig Gerard, U. Zumsteg, G. Holländer*, L. Piali* (2002) In Insulitis, Beta Cells Are Responsible for CXCR3-Mediated T Cell Infiltration. Nature Medicine 8:1414-1420. (* contributed equally)

T cell
Signaling
Thymocyte selection
Transplantation
Tolerance

Transplantation Immunology and Nephrology

Prof. Dr. Ed Palmer
Departement Forschung
Universitätsspital Basel

Group Members
Dr. Mark Daniels
Dr. Diana Gil
Dr. Adam Schrum
Dr. Emma Teixeiro
Dr. Guy Werlen
Barbara Hausmann (technician)
Dominique Roubaty (technician)
Gideon Hönger (technician)
Denise Bielmann (technician)
Doris Lutz (technician)
Dieter Naeher (PhD student)

T cell Biology and Transplantation Rejection

While transplantation has been successfully used to treat many types of organ failure, it is limited in the long term by the immune system's intolerance of the graft. Graft rejection is initiated by T lymphocytes and reflects the immune systems' pre-occupation with eliminating cells, which are "non-self". Professors Palmer and Steiger have combined their scientific and clinical expertise to approach this difficult clinical problem. Their collaborative effort is based on the idea that controlling graft rejection depends on understanding how T cells recognize "non-self".

The T cell receptor: a decision maker for the T lymphocyte
T cells develop in the thymus, where thymocytes differentiate if their TCRs can recognize fragments of foreign proteins. This process is called positive selection and generates functional T cells, which are critical for defending the organism from infectious attack. A fraction of thymocytes has TCRs, which recognize normal body constituents (self proteins). These thymocytes are self-reactive and must be eliminated to maintain T cell tolerance. The removal of self-reactive thymocytes is known as negative selection and is a critical step in avoiding autoimmunity. The molecular bases of positive and negative selection are not understood. The question is how the TCR can deliver 2 different signals: one, which can lead to thymocyte differentiation and another, which can lead to thymocyte death. We have identified a motif in the TCR α chain called the α-CPM, which has been conserved for 500 million years. Thymocytes expressing mutant TCRs, which lack this motif fail to undergo positive selection, although they are competent to undergo negative selection. The existence of such a mutant implies that the TCR has distinct structural features, which control positive and negative selection signals. We are using a combination of genetic, biochemical and cell biological approaches to dissect these two kinds of signals, which are used to establish a functional T cell repertoire.
In the presence of foreign antigen, peripheral T cells divide, develop effector functions and eventually undergo activation induced cell death (AICD). A mutation in the transmembrane domain of the TCR β chain generates a TCR, which fails to transmit signals leading to AICD. The mutant receptor does not engage the signaling adaptor, Carma-1 and subsequently is defective in activating the NF-κB signaling pathway. Our current focus is to better define how the TCR independently signals T cell proliferation and AICD and how the ratio between division and death controls T cell homeostasis.
We have also developed a model of graft rejection by transplanting MHC-disparate skin onto mice, whose T cells express an allo-reactive TCR. This model allows one to follow the graft-rejecting T cells, through the activation and effector phases. These experiments will allow us to determine the lifespan of allo-reactive T cells under conditions of immunosuppression and to develop strategies for inducing peripheral tolerance to the grafted skin. Finally, we are trying to generate diagnostic tools to monitor the frequency of allo-reactive (graft-rejecting) T cells in transplant recipients. These types of reagents could be clinically useful in predicting the onset of a rejection reaction.

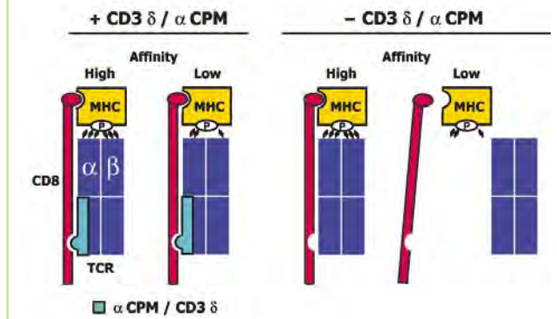


Fig. 1: T cell receptors containing the aCPM and CD3δ are able to co-operate with the CD8 co-receptor to generate a signal subsequent to pMHC ligand binding. Mutant T cell receptors that lack the αCPM or CD3δ fail to generate specific signals with low affinity pMHC ligands.

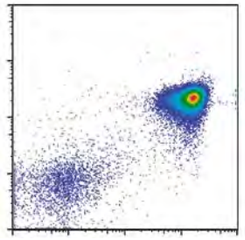
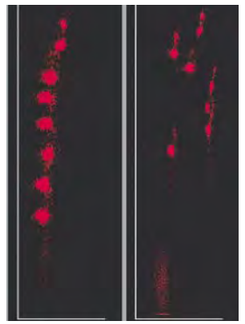


Fig. 2: Thymocytes from transgenic mice expressing a TCR lacking the αCPM are stained with anti-CD4 and CD8 antibodies. These mice are blocked in undergoing positive selection and fail to generate mature (single positive) T cells.

Fig. 3: Left panel: Cross-linking the TCR (yellow) on wild type T cells recruits and co-localizes the adaptor, Carma-1 (red). Right panel: T cells expressing a mutant T cell receptor can cross-link the TCR (green) but fail to recruit Carma-1 (red). This leads to a defect in AICD.



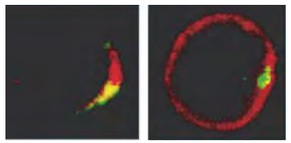


Fig. 4: Fluorescent beads coated with different HLA antigens have been incubated with patient sera to detect anti-HLA antibodies. The left panel shows the analysis of beads incubated with a negative serum, while the right panel shows the same beads incubated with serum that contains multiple anti-HLA antibodies.

Clinics

The Department of Transplantation Immunology and Nephrology co-ordinates one of the major centers for kidney transplantation in Switzerland and has been active in this area for over 40 years. The transplantation team carries out approximately 70 renal transplants per year and has published widely in the areas of renal physiology, infections of transplant patients and clinical management of immunosuppression. The Department oversees the Clinical Transplantation Laboratory, which is responsible for the immunological testing of donated organs, living donors and recipients on the waiting list. This clinical laboratory determines tissue and antibody compatibilities between donors and recipients and is one of the leading solid organ transplantation laboratories in Switzerland. As part of a novel concept, the Clinical and Research laboratories share the same laboratory space and work in concert, developing new diagnostic tests for the detection cross-matching antibodies. In 2004, the Clinical Laboratory offered a course in flow cytometric methods, which was attended by laboratory staff from solid organ transplantation centers all over Switzerland. One of the long-term goals is to establish techniques to monitor the immunological status of graft recipients, post-transplantation. The goal of post-transplantation monitoring is to extend the life-span of transplanted organs and the quality of life for the recipient.

Prof. Dr. Jürg Steiger
Abteilung Nephrologie
Universitätsspital Basel

T-Lymphozyten und Abstossungsreaktionen

Das Ziel des Labors für Transplantationsimmunologie und Nephrologie ist, die Abstossungsreaktion der transplantierten Organe zu erforschen und letztlich zu verhindern.
Da die eigenen T-Lymphozyten des Empfängers der Hauptgrund für die Abstossung sind, erforschen wir deren Aufgabe und Wirkung, sowie deren mögliche Behandlung und Veränderung, um diese Zellen dem Transplantat gegenüber tolerant zu machen.
Seit vielen Jahren forschen wir auf dem Gebiet der T-Lymphozyten und haben schon viel über ihre Wirkungsweise herausgefunden. T-Lymphozyten sind normalerweise gegenüber den eigenen Körperorganen tolerant, dennoch stossen sie ein gesundes transplantiertes Organ vehement ab. Warum das transplantierte Organ als fremd erachtet wird, und wie man die Abstossungsreaktion verhindern kann, darauf fokussieren wir unsere Forschungsarbeit.
Daneben entwickeln wir verschiedene klinische Tests, um den frühen Beginn einer Abstossung nachzuweisen, sowie zur Festlegung, welche Spender für einen möglichen Empfänger am besten geeignet sind.
Durch die enge Zusammenarbeit zwischen unserer Forschungsgruppe und der Nieren-Transplantationsabteilung des Universitätsspitals Basel haben wir die Gelegenheit, mit unserer Forschung die Qualität der Behandlung der Patienten positiv zu beeinflussen.

Selected Publications

- Teixeiro, E., Daniels, M.A., Hausman, B. Schrum, A.G, Naeher, D., Luescher, I., Thome, M., Bragado, R. and Palmer, E. T cell division and death are segregated by mutation of TCRβ chain constant domains, Immunity, in press (2004).
- Werlen, G., Hausmann, B.T., Naeher, D. and Palmer, E. Life and death decisions in the thymus: Timing is everthing. Science 199: 1859-63 (2003).
- Sayegh, M.H., Wu, Z., Langmuir, P.B., Sandner, S., Kishimoto, K., Palmer, E., Mitchell, R.N. and L.A. Turka. Allograft rejection in a new allospecific CD4+ TCR transgenic mouse. Am J Transplant. 4:381-9 (2003)
- Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, Steiger J: Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N.Engl.J.Med. 347:488-496, 2002
- Werlen, G., Hausmann, B. and Palmer, E. A motif within the T cell receptor controls positive selection by modulating the ERK pathway, Nature, 406: 422-426 (2000).

Polyomavirus

Cytomegalovirus

Adenovirus

Viral load

Cellular immunity

Adoptive T-cell transfer

Transplantation Virology

Prof. Dr. Hans H. Hirsch
Institut für Medizinische Mikrobiologie
und Infektiologische Klinik
Universitätsspital Basel

Group Members
Dr. Rainer Gosert
Dr. Adrian Egli (MD-PhD student)
Ariane Kaiser (research technician)
Beatrice Hess (research technician)
Vroni Del Zenero (research technician)
Simone Binggeli (PhD student)

Control of Viral Infections in Transplant Patients

Viral infections in transplant patients are associated with increased morbidity and mortality. A key reason for a pronounced vulnerability to viral infections resides in the impaired immune functions of transplant patients. In hematopoietic stem cell transplantation (SCT), immune effector cells are depleted following therapy and conditioning, but immune dysfunction may persist long after the engraftment, particularly in patients with "graft-versus-host" disease requiring the administration of immunosuppressive drugs. In solid organ transplantation (SOT), immune functions are deliberately suppressed by drugs to protect the transplant from "host-versus-graft" injury (rejection). Thus, a window of opportunity is opened leading unchecked viral replication and more severe disease after transplantation. Antivirals, if available at all, may reduce viral replication and disease, but are not sufficient to eradicate viral infections. This is particularly true for herpes-, polyoma- and adenoviruses, which may reactivate from latent infections. Thus, specific antiviral immune functions are required for termination and control of viral infection.

Polyomavirus hominis type 1, also called BK virus (BKV) infects up to 90% of the general population. Significant clinical manifestations are rare and limited to individuals with impaired immune functions. Since 1995, polyomavirus-associated nephropathy (PVAN) has been recognized as an emerging disease affecting 1-10% of renal transplant recipients with variable graft loss in 10-80% of cases. Intervention is difficult due to the lack of specific antivirals and relies mostly on improving immune control by decreasing the immunosuppressive load. Currently, three complementing areas of research are pursued:

Clinical studies

Quantification of BKV DNA load in plasma and urine has been introduced into the clinical routine in 2002-2003 after demonstrating its role in screening and monitoring of renal transplant patients at risk for PVAN (Hirsch et al. 2002). Screening for BKV replication identifies patients with earlier stages of limited focal involvement which may respond better to reduced immunosuppression. Studies from patients with PVAN undergoing allograft nephrectomy show that the BKV load in plasma instantaneously disappears (Fig. 1) indicating that the plasma BKV load is entirely derived from the renal transplant and hence an important surrogate marker of allograft involvement. Moreover, significantly higher BKV plasma viral load was observed in cases with persisting PVAN, as compared to cases with negative histology (P<0.001). Since the risk of false negative biopsies due to sampling errors increases with early focal PVAN, a new definition has been put forward: "Presumptive" PVAN is defined by high plasma BKV load (>10'000 copies/mL), but still negative or undetermined biopsy, and an intervention should be considered similar to histologically confirmed "definitive" PVAN. This approach requires validation in future clinical studies

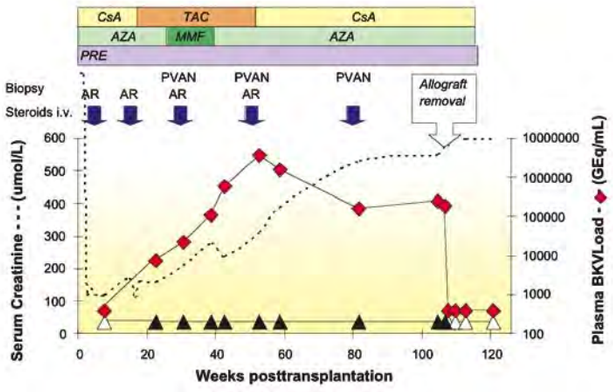


Fig. 1: Progressive renal transplant dysfunction (serum creatinine concentration) and increasing BK viral load (PVAN, Polyomavirus-associated nephropathy; AR, acute rejection; CsA, cyclosporine; TAC, tacrolimus; AZA,azathioprine, MMF, mycophenolate mofetil; PRE, prednisone)

Virological studies

The BKV genome is small with 5.3 kb of double-stranded DNA and can be divided in three regions of i) the noncoding control region (NCCR) containing the origin of replication and promoter/enhancer functions driving ii) the early gene (large and small Tumor antigen) and iii) the late gene expression (agnoprotein, capsid proteins VP1-3). Sequencing of the NCCRs isolated from the urine of renal transplant patients with PVAN demonstrated archetype (WW) NCCR architecture. In contrast, we found deletions, insertions, and rearrangements in NCCRs isolated from plasma of patients with PVAN. To investigate the functional consequences of these rearrangements, we constructed a bi-directional reporter with red and green fluorescent proteins indicating early and late expression and found that archetype and NCCRs containing insertions were associated with transcription mainly from the late region, whereas the NCCR with an extensive deletion of part of the Q-Block and most of the R-Block demonstrated a switch from late to early gene transcription. Importantly, expression of the large T-antigen induced a virologically expected shift towards increased late gene expression, irrespectively of the NCCR. The impact of immunosuppressive drugs on BKV expression is currently investigated.

Immunological studies

Viral load measurements for BK virus, cytomegalovirus, Epstein-Barr-virus and adenovirus correlate only to alimited extent with the risk for disease. The quantification and functional testing of virus-specific cellular immune effectors may provide complementing clinically relevant information in transplant patients. As demonstrated in Fig. 2, virus-specific interferon-γ-producing CD4 and CD8 T-cells can be detected in whole blood of patients by FACS analysis. Clearly, adoptive transfer of functional virus-specific immune effectors and corresponding monitoring at GLP-GMP level is within reach in the coming years.

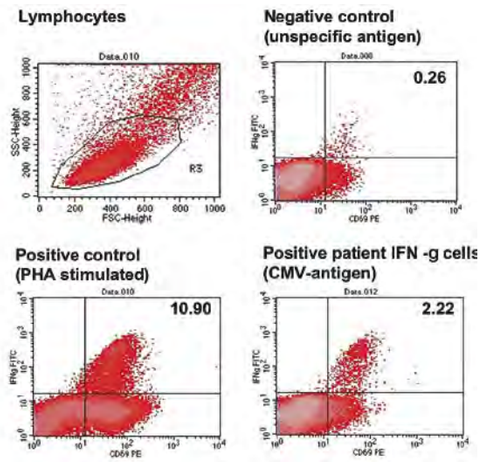


Fig. 2: CMV-specific interferon-γ (IFN-γ) producing CD4-cells in whole blood.

Virusinfektionen bei Transplantationspatienten

Virusinfektionen bei Transplantationspatienten sind mit erhöhter Morbidität und Mortalität assoziiert, was auf gestörte Immuneffektorfunktionen zurückgeführt wird. Polyomavirus BK (BK Virus) wird seit 1995 für den vorzeitigen Verlust von ca. 5% der Nierentransplantaten verantwortlich gemacht. Da keine wirksamen Virostatika verfügbar sind, besteht derzeit die einzige Intervention in der Reduktion der immmunsuppressiven Therapie mit dem Risiko der nachfolgenden Abstossung. In klinischen Untersuchungen konnten wir die quantitative Bestimmung der BK Viruslast im Plasma als einen wichtigen Surrogatmarker für Diagnose und Verlauf etablieren. Unsere virologischen Untersuchungen zeigen, dass bei Patienten mit Polyomavirus-Nephropathie zum Teil massive genetische Veränderungen in der nichtkodierenden Kontroll-Region (NCCR) vorhanden sind, die sich von den NCCR der Archetypen unterscheiden, die bei nicht-immunsupprimierten Patienten im Urin nachweisbar sind. Mit einem bi-direktionalen Reporter-Konstrukt, das frühe und späte Genexpression als Rot- bzw. Grün-Fluoreszierendes Protein sichtbar macht, konnten wir signifikante funktionelle Unterschiede der NCCR-Rearrangements nachweisen, die aber weiterhin durch das virale Regulatorprotein Large-T-Antigen moduliert werden. In immunologischen Studien bereiten wir die Quantifizierung von BK Virus-spezifischen CD4- und CD8-T-Zellen vor, die die BK Viruslast im Plasma bezüglich Risiko und Verlauf bei Transplantationspatienten ergänzen sollen. Cytomegalieviruslast und die spezifische T-Zell-Aktivität dienen als Kontrolle. Eine Idenifizierung der relevanten Epitope sollte auch die Möglichkeit der Entwicklung eines BK Virus Impfstoffs und des adoptiven T-Zelltransfers ermöglichen.

Selected Publications

- Hirsch, H.H. Knowles W., Dickenmann M., Passweg J., Klimkait T., Mihatsch M.J., Steiger J. (2002) Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 347: 488-96.
- Hirsch, H.H. (2003) BK virus replication and disease in solid organ transplant recipients: an update. Curr Opin Org Transplant 8: 262-268.
- Hirsch, H.H. and Steiger, J. (2003) Polyomavirus BK. Lancet Infect Dis 3: 611-623.
- Drachenberg CB, Papadimitriou JC, Wali R, Nogueira J, Mendley S, Hirsch HH, Cangro CB, Klassen DK, Weir MR, Bartlett ST, Ramos E. (2004) Improved outcome of polyoma virus allograft nephropathy with early biopsy. Transplant Proc 36: 758-9.
- Drachenberg C.D., Papadimitriou J.C., Hirsch H.H., Wali R., Crowder C., Nogueira J., Cangro C.B., Mendley S., Mian A., Ramos E. (2004). Histological patterns of polyomavirus nephropathy: Correlation with graft outcome and viral load. Am J Transplant 4: 2201-2211.

Malignant hyperthermia
Central core disease
Calcium homeostasis
Mutations
Proteomics

Perioperative Patient Safety

Dr. Susan Treves
Departement Anästhesie
Departement Forschung
Universitätsspital Basel

Group members
Prof. Dr. Albert Urwyler
Prof. Dr. Francesco Zorzato
Dr. Ayuk Agbor Anderson
Dr. Soledad Levano
Esther Schmid (technician)
Martine Singer (techncian)
Antonio Teixera (technician)
Evgueni Voronkov (technician)
Sylvie Ducreux (PhD student)

Anaesthetics and Disease: Ryanodine Receptor 1 Mutations and their Impact on Calcium Homeostasis.

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 ($[Ca^{2+}]$) 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 Ca^{2+} in cell physiology, eukaryotic cells have developed specialized organelles (or subregions of organelles) to finely control the cellular $[Ca^{2+}]$ and many proteins (from channels on the plasma membrane which allow Ca^{2+} ions to flux into the cytoplasm from the extracellular milieu, to intracellular calcium storing proteins, intracellular calcium channels and Ca^{2+} pumps or CaATPases), are devoted to calcium homeostasis. The most specialized organelle involved in Ca^{2+} 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 $[Ca^{2+}]$ is illustrated by two neuromuscular diseases, which in the majority of cases, are linked to mutations in the ryanodine receptor calcium channel: malignant hyperthermia (MH) and central core disease (CCD):

(i) Malignant hyperthermia (MH) is an autosomal dominant pharmacogenetic disease due to abnormal regulation of calcium homeostasis. In more than 50% of the cases MHS individuals carry mutations in the RYR1 gene; these render this calcium channel more sensitive to agonists, so that more calcium is released from the sarcoplasmic reticulum and available to bind to the contractile elements and lead to muscle contraction.

(ii) CCD is a rare autosomal dominant congenital myopathy. Individuals affected by this disease have hypotonic muscles and generalized muscle weakness; in children one of the classical findings is a delay in achieving motor milestones. The clinical diagnosis relies on the histological examination of a muscle biopsy which is characterized by the presence of large centrally located cores which run the length of the muscle fiber. These cores do not stain with oxidative and phosphorylase histochemical stains and contain amorphous looking material.

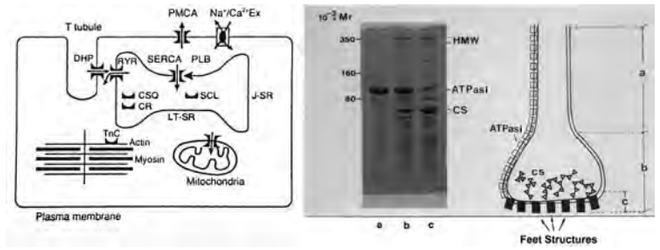


Fig. 1: Structural and biochemical subspecilaization of membrane compartments involved in skeletal muscle calcium homeostasis.

To date more than 60 missense mutations have been identified in the RYR1 gene and are associated with CCD and/or the MHS phenotype.
The aim of the research carried in our laboratory is:

(I) Determining the functional impact of RYR1 mutations linked to MH and CCD. Since ryanodine receptors are intracellular calcium channels, the functional effect of most mutations linked to these neuromuscular disorders lead to a dysregulation of intracellular calcium homeostasis.

(II) Studying if there is a genotype-phenotype correlation between RYR1 mutations and specific alterations of intracellular calcium homeostasis.

(III) Only approximately 50% of MHS individuals have mutations in the RYR1; we are also using a proteomic approach to identify novel proteins which are involved in calcium homeostasis and which, upon mutation, may cause neuromuscular diseases.

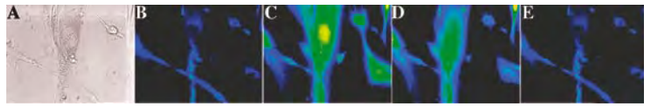


Fig. 2: Calcium release stimulated by KCl in human myotubes Single cell intracellular Ca^{2+} measurements of fura-2 loaded human myotubes. (A) Phase contrast; (B) resting $[Ca^{2+}]i$ before the application of 100 mM KCl; (C) 10, (D) 30 and (E) 40 seconds after the application of 100 mM KCl.

Clinics

The first reports of "Malignant Hyperthermia (MH)" or anaesthesia-related deaths associated with hyperthermia date to the beginning of the 20th century. MH is an autosomal dominant pharmacogenetic disorder, which develops in genetically predisposed individuals after exposure to trigger agents (halogenated inhalative anesthetics and depolarizing muscle relaxants). Such individuals are free of any symptoms in daily life but contact with the trigger agent can cause a dramatic life-threatening increase in metabolism. Clinical symptoms present as elevated muscular activity and hypermetabolism. Supportive measures and specific therapy with dantrolene are essential in case of a MH episode. With these therapeutic actions MH mortality has decreased dramatically from 70% to less than 10%.
As MH is a subclinical myopathy, specific testing must be used to diagnose MH susceptibility (MHS). Presymptomatic testing is important, because safe alternatives exist for anesthesia in MHS patients. The gold standard for MH diagnosis is an *in vitro* muscle contracture test: after an open muscle biopsy, a muscle bundle is challenged *in vitro* with caffeine and halothane. Contractile thresholds to both drugs are determined in several muscle strips.
MH research has focused on the establishment of noninvasive or less invasive testing. The European MH Group (EMHG) published guidelines for genetic MHS tests. The Swiss MH investigation unit of our laboratory is an active member of the EMHG. We perform MH diagnosis for all of Switzerland and Liechtenstein as well as southern parts of Germany and parts of France. Since 1986 the *in vitro contracture test* is performed in our laboratory and in recent years we introduced molecular genetic methods for MH diagnosis in selected MH families.

Dr. Thierry Girard
Departement Anästhesie
Departement Forschung
Universitätsspital Basel

Maligne Hyperthermie

Die Maligne Hyperthermie (MH) ist eine seltene aber gefürchtete Anästhesiekomplikation. Bestimmte Narkosemittel führen bei MH empfindlichen Personen zu einem dramatischen Anstieg des Stoffwechsels der Skelettmuskulatur, welcher unbehandelt rasch tödlich verlaufen kann. Symptome treten ausschliesslich bei Kontakt mit auslösenden Anästhetika auf, im Alltag sind die betroffenen Personen beschwerdefrei. Die Veranlagung zur MH wird dominant vererbt.
Unser Labor ist das nationale MH Referenzzentrum für die Schweiz und Liechtenstein, sowie für den süddeutschen Raum und das Elsass. Personen, welche eine MH Episode erlebt haben oder Angehörige MH positiver Personen werden auf MH getestet. Die Standardmethode zur Diagnose einer MH Emfpindlichkeit ist der in-vitro Kontrakturtest. Hierzu muss ein Stück Muskulatur aus dem Bein operativ entnommen und unmittelbar danach im Labor untersucht werden. Im Ryanodinrezeptor des Skelettmuskels sind verschiedene genetische Veränderungen bekannt, welche für MH verantwortlich sind. In bestimmten Familien erlauben uns diese Mutationen eine nicht-invasive MH Diagnostik. Bisher sind nur in 50% der MH Familien Mutationen bekannt, sodass sich unsere Forschung darauf konzentriert, die Hintergründe der MH besser zu verstehen und zusätzliche Ursachen zu identifizieren. Das Ziel ist es, eine nicht-invasive Testmöglichkeit für die MH zu entwickeln, um diese Veranlagung im Vorfeld einer Anästhesie zu erkennen und somit die perioperative Patientensicherheit zu erhöhen.

Selected Publications

– F. Zorzato, N. Yamaguchi, L. Xu, G. Meissner, C. R. Müller, P. Pouliquin, F. Muntoni, C. Sewry, T. Girard and S. Treves (2003). Clinical and functional effects of a deletion in a COOH-terminal lumenal loop of the skeletal muscle ryanodine receptor. Human Mol. Genetics 12:379-388
– Anderson, S. Treves, D. Biral, R. Betto, D. Sandonà, M. Ronjat and F Zorzato (2003). The novel skeletal muscle sarcoplasmic reticulum JP-45 protein: molecular cloning, tissue distribution, developmental expression and interaction with a.1 subunit of the voltage gated calcium channel. J. Biol.Chem. 278: 39987-39992
– T. Girard, S. Treves, E. Voronkov, M Siegemund and A. Urwyler (2004). Molecular genetic testing for Malignant Hyperthermia susceptibility. Aesthesiology 100:1076-1080
– S. Treves, C. Franzini-Armstrong, L. Moccagatta, C. Arnoult, C. Grasso, A. Schrum, S. Ducreux, M.X. Zhu, K. Mikoshiba, T. Girard, S. Smida-Rezgui, M. Ronjat and F. Zorzato (2004). Junctate is a key element in calcium entry induced by activation of InsP3 receptors and/or calcium store depletion J. Cell Biol. 166: 537-548
– S. Ducreux, F. Zorzato, C. R. Müller, C. Sewry, F, Muntoni, R. Quinlivan, G. Restagno, T. Girard and S. Treves (2004). Effect of ryanodine receptor mutations on IL-6 release and intracellular calcium homeostasis in human myotubes from malignant hyperthermia susceptible individuals and patients affected by central core disease. J. Biol.Chem. (in press)

aponetics

Founded in October 2000, Aponetics focuses on the discovery and development of novel anti-cancer therapeutics that modulate apoptosis, the body's physiological ability to destroy diseased or damaged cells. In cancer cells the apoptotic program is disrupted allowing tumors to grow in an uncontrolled fashion. Therefore, the concept of apoptosis represents a rational approach for the discovery of drugs able to induce or restore the natural apoptotic program in cancer cells.
The company's objective is to bring novel and safer anti-cancer drugs to patients.To support its drug discovery and development activities, Aponetics has built up capabilities in high throughput screening, medicinal chemistry and preclinical research. Aponetics has also generated a solid patent portfolio to protect its screening technology as well as the newly identified chemical entities and their therapeutic use in oncology.

Business Strategy

Aponetics' business strategy is to concentrate its research efforts in the discovery and development of novel anti-cancer small molecules with a better therapeutic window than conventional chemotherapeutic agents, i.e. more specific and with less side effects.
Aponetics has discovered new drug candidates, representing different chemical classes, that have proven to significantly inhibit tumor growth in mice xenografted with human tumors.
Aponetics will advance these projects through preclinical and clinical studies up to Phase II, before out-licensing them.

Aponetics Facts

Aponetics started operations in June 2001 and has 12 employees. As of August 2004 the company has raised CHF 10 million.

Contact
Dr. Alessandro Strebel
Head of Business Development
Tel: +41 (0)61 726 86 01
Aponetics Ltd., Benkenstrasse 254, CH-4108 Witterswil,
www.aponetics.com

Product Pipeline

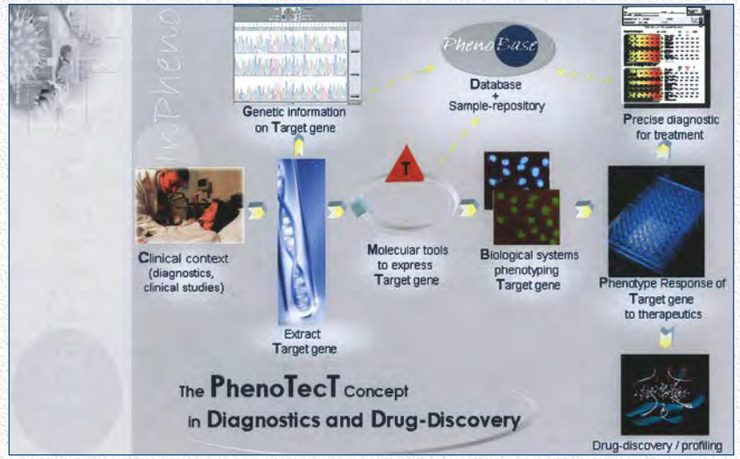
Project / Product	Preclinical Research (*in vitro* / *in vivo*)	Preclinical Development	Phase I / IIa
AP 17322	→	Candidate selection in 1Q 2005	Start in 1H 2006
AP 2313	→		
AP 21856	→		
AP 57060	→		
AP 1811	→		
AP 55802	→		

InPheno ...the real answer

InPheno is a spin-off from the University of Basel, Switzerland. It was founded by specialists in the fields of Microbiology & molecular Oncology and by scientists with experience in the development of modern therapeutics in pharmaceutical industry.

The mission for ***InPheno*** is: "To provide novel test platforms for a direct phenotypic evaluation (for diagnostics or drug-discovery) of resistances to therapeutic intervention as a consequence of genetic instability in human diseases"

A first successful development of ***InPheno*** is the "diagno-technological" platform **PhenoTecT**. This complex, yet robust tool is used for the diagnostics of HIV-resistance as the only phenotypic test accredited and reimbursed by federal authorities. The next development of **PhenoTecT** will adapt the platform to the field of Oncology.



The success of **PhenoTecT** combined with a flexible policy for collaborations allowed establishing a series of robust partnerships with the Pharma/Biotech Industry.

InPheno also develops a novel proprietary molecule inhibitor of HIV replication (TF53) foreseen to enter clinical evaluation in 2006.

Early 2005 will see the opening of ***InPheno***'s operations in the USA.

CEO
Dr. Thomas Klimkait

CSO
Dr. François Hamy

InPheno AG
Socinstrasse 55a
CH-4051 Basel

Phone +41 (0)61 284 81 50
info@inpheno.com

www.inpheno.com

ErfindungsVerwertung AG (EVA) Basel

www.eva-basel.ch info@eva-basel.ch

Jump start for innovative people
Formation and coaching of companies in Biotechnology, Medicine, Chemistry, Nanotechnology

EVA supports through
Project challenging (Innovation level, Competition and Market, Patent situation)
Business plan challenging (Plausibility, Design, Financial information)
Contacts to investors
Company formation and coaching

Companies with EVA participation:

Aponetics AG, Witterswil
Biomit AG, Basel
Bogar AG, Zürich
Chemspeed AG, Augst
Covalys AG, Witterswil
Herbonis AG, Augst
InPheno AG, Basel
Medgate AG, Basel
Synphabase AG, Muttenz
TheraSTrat AG, Allschwil

CEO
Dr. Jost Harr

Chairman
Dr. Peter Schütz

ErfindungsVerwertung AG (EVA)
Birsigstrasse 10
CH-4054 Basel

Phone +41 (0)61 283 84 85
Fax +41 (0)61 293 84 86

DKBW Publications 2000–2004

Only papers with peer review are listed

Adamina, M., Bolli, M., Albo, F., Cavazza, A., Zajac, P., Padovan, E., Schumacher, R., Reschner, A., Feder, C., Marti, W. R., Oertli, D., Heberer, M., and Spagnoli, G. C. (2004). Encapsulation into sterically stabilised liposomes enhances the immunogenicity of melanoma-associated Melan-A/MART-1 epitopes, Br J Cancer 90, 263-9.

Adcock, K. H., Metzger, F., and Kapfhammer, J. P. (2004). Purkinje cell dendritic tree development in the absence of excitatory neurotransmission and of brain-derived neurotrophic factor in organotypic slice cultures, Neuroscience 127, 137-45.

Aellig, M., and Battegay, E. (2004). [Combination therapy versus monotherapy: which strategy is better?], Schweiz Rundsch Med Prax 93, 865-9.

Affolter, N., Krahenbuhl, S., and Schlienger, R. G. (2003). Appropriateness of serum level determinations of antiepileptic drugs, Swiss Med Wkly 133, 591-7.

Akdis, C. A., Kussebi, F., Pulendran, B., Akdis, M., Lauener, R. P., Schmidt-Weber, C. B., Klunker, S., Isitmangil, G., Hansjee, N., Wynn, T. A., Dillon, S., Erb, P., Baschang, G., Blaser, K., and Alkan, S. S. (2003). Inhibition of T helper 2-type responses, IgE production and eosinophilia by synthetic lipopeptides, Eur J Immunol 33, 2717-26.

Albertsen, B. K., Schroder, H., Ingerslev, J., Jakobsen, P., Avramis, V. I., Muller, H. J., Carlsen, N. T., and Schmiegelow, K. (2001a). Comparison of intramuscular therapy with Erwinia asparaginase and asparaginase Medac: pharmacokinetics, pharmacodynamics, formation of antibodies and influence on the coagulation system, Br J Haematol 115, 983-90.

Albertsen, B. K., Schroder, H., Jakobsen, P., Avramis, V. I., Muller, H. J., Schmiegelow, K., and Carlsen, N. T. (2002). Antibody formation during intravenous and intramuscular therapy with Erwinia asparaginase, Med Pediatr Oncol 38, 310-6.

Albertsen, B. K., Schroder, H., Jakobsen, P., Muller, H. J., Carlsen, N. T., and Schmiegelow, K. (2001b). Monitoring of Erwinia asparaginase therapy in childhood ALL in the Nordic countries, Br J Clin Pharmacol 52, 433-7.

Albo, F., Cavazza, A., Giardina, B., Lippa, S., Marini, M., Roda, L. G., and Spagnoli, G. (2003). Degradation of the immunogenic peptide gp100(280-288) by the monocyte-like U937 cell line, Peptides 24, 371-8.

Albo, F., Cavazza, A., Giardina, B., Marini, M., Roda, L. G., Schumacher, R., and Spagnoli, G. C. (2004). Degradation of the tumor antigen epitope gp100(280-288) by fibroblast-associated enzymes abolishes specific immunorecognition, Biochim Biophys Acta 1671, 59-69.

Alessandri, B., Basciani, R., Langemann, H., Lyrer, P., Pluess, D., Landolt, H., and Gratz, O. (2000). Chronic effects of an aminosteroid on microdialytically measured parameters after experimental middle cerebral artery occlusion in the rat, J Clin Neurosci 7, 47-51.

Altman, G. H., Horan, R. L., Lu, H. H., Moreau, J., Martin, I., Richmond, J. C., and Kaplan, D. L. (2002a). Silk matrix for tissue engineered anterior cruciate ligaments, Biomaterials 23, 4131-41.

Altman, G. H., Horan, R. L., Martin, I., Farhadi, J., Stark, P. R., Volloch, V., Richmond, J. C., Vunjak-Novakovic, G., and Kaplan, D. L. (2002b). Cell differentiation by mechanical stress, Faseb J 16, 270-2. Epub 2001 Dec 28.

Altman, G. H., Lu, H. H., Horan, R. L., Calabro, T., Ryder, D., Kaplan, D. L., Stark, P., Martin, I., Richmond, J. C., and Vunjak-Novakovic, G. (2002c). Advanced bioreactor with controlled application of multi-dimensional strain for tissue engineering, J Biomech Eng 124, 742-9.

Ammann, P., Kiencke, S., Schaer, B., Cron, T. A., Sticherling, C., Huldi, C., Linka, A., Buser, P., Pfisterer, M., and Osswald, S. (2004). Cardiac resynchronization in severe heart failure and left bundle branch block: a single center experience, Swiss Med Wkly 134, 277-82.

Anderson, A. A., Treves, S., Biral, D., Betto, R., Sandona, D., Ronjat, M., and Zorzato, F. (2003). The novel skeletal muscle sarcoplasmic reticulum JP-45 protein. Molecular cloning, tissue distribution, developmental expression, and interaction with alpha 1.1 subunit of the voltage-gated calcium channel, J Biol Chem 278, 39987-92. Epub 2003 Jul 17.

Antonescu, C. R., Busam, K. J., Iversen, K., Kolb, D., Coplan, K., Spagnoli, G. C., Ladanyi, M., Old, L. J., and Jungbluth, A. A. (2002). MAGE antigen expression in monophasic and biphasic synovial sarcoma, Hum Pathol 33, 225-9.

Anwar, A., Gaspoz, J. M., Pampallona, S., Zahid, A. A., Sigaud, P., Pichard, C., Brink, M., and Delafontaine, P. (2002a). Effect of congestive heart failure on the insulin-like growth factor-1 system, Am J Cardiol 90, 1402-5.

Anwar, A., Zahid, A. A., Scheidegger, K. J., Brink, M., and Delafontaine, P. (2002b). Tumor necrosis factor-alpha regulates insulin-like growth factor-1 and insulin-like growth factor binding protein-3 expression in vascular smooth muscle, Circulation 105, 1220-5.

Arber, C., Passweg, J. R., Fluckiger, U., Pless, M., Gregor, M., Tichelli, A., Schifferli, J. A., and Gratwohl, A. (2000). C-reactive protein and fever in neutropenic patients, Scand J Infect Dis 32, 515-20.

Arcaro, A., Gregoire, C., Boucheron, N., Stotz, S., Palmer, E., Malissen, B., and Luescher, I. F. (2000). Essential role of CD8 palmitoylation in CD8 coreceptor function, J Immunol 165, 2068-76.

Arefieva, T. I., Provatorov, S. I., Samko, A. N., Krasnikova, T. L., Resink, T. J., Erne, P., Tkachuk, V. A., and Chazov, E. I. (2001). Monocyte integrin expression and monocyte-platelet complex formation in humans with coronary restenosis, Clin Exp Pharmacol Physiol 28, 804-8.

Arranto, C. A., Mueller, C., Hunziker, P. R., Marsch, S. C., and Eriksson, U. (2003). Adverse cardiac events in ICU patients with presumptive antidepressant overdose, Swiss Med Wkly 133, 479-83.

Asmar, R. G., London, G. M., O'Rourke, M. E., Mallion, J. M., Romero, R., Rahn, K. H., Trimarco, B., Fitzgerald, D., Hedner, T., Duprez, D., De Leeuw, P. W., Sever, P., Battegay, E., Hitzenberger, G., de Luca, N., Polonia, P., Benetos, A., Chastang, C., Ollivier, J. P., and Safar, M. E. (2001). Amelioration of arterial properties with a perindopril-indapamide very-low-dose combination, J Hypertens Suppl 19, S15-20.

Asosingh, K., Gunthert, U., Bakkus, M. H., De Raeve, H., Goes, E., Van Riet, I., Van Camp, B., and Vanderkerken, K. (2000). In vivo induction of insulin-like growth factor-I receptor and CD44v6 confers homing and adhesion to murine multiple myeloma cells, Cancer Res 60, 3096-104.

Asosingh, K., Gunthert, U., De Raeve, H., Van Riet, I., Van Camp, B., and Vanderkerken, K. (2001). A unique pathway in the homing of murine multiple myeloma cells: CD44v10 mediates binding to bone marrow endothelium, Cancer Res 61, 2862-5.

Aubry, F., Satie, A. P., Rioux-Leclercq, N., Rajpert-De Meyts, E., Spagnoli, G. C., Chomez, P., De Backer, O., Jegou, B., and Samson, M. (2001). MAGE-A4, a germ cell specific marker, is expressed differentially in testicular tumors, Cancer 92, 2778-85.

Auer, M., Pfister, L. A., Leppert, D., Tauber, M. G., and Leib, S. L. (2000). Effects of clinically used antioxidants in experimental pneumococcal meningitis, J Infect Dis 182, 347-50. Epub 2000 Jul 6.

Auf der Maur, C., Chatterjee, T., and Erne, P. (2004). Percutaneous transcatheter closure of coronary-pulmonary artery fistula using polytetrafluoroethylene-covered graft stents, J Invasive Cardiol 16, 386-8.

Aufderhaar, U., Holzgreve, W., Danzer, E., Tichelli, A., Troeger, C., and Surbek, D. V. (2003). The impact of intrapartum factors on umbilical cord blood stem cell banking, J Perinat Med 31, 317-22.

Azzola, A., Havryk, A., Chhajed, P., Hostettler, K., Black, J., Johnson, P., Roth, M., Glanville, A., and Tamm, M. (2004). Everolimus and mycophenolate mofetil are potent inhibitors of fibroblast proliferation after lung transplantation, Transplantation 77, 275-80.

Bachli, H., Avoledo, P., Gratzl, O., and Tolnay, M. (2003). Therapeutic strategies and management of desmoplastic infantile ganglioglioma: two case reports and literature overview, Childs Nerv Syst 19, 359-66. Epub 2003 May 29.

Bachli, H., Minet, J. C., and Gratzl, O. (2004). Cerebral toxocariasis: a possible cause of epileptic seizure in children, Childs Nerv Syst 12, 12.

Bachmann, A., Dickenmann, M., Gurke, L., Giannini, O., Langer, I., Gasser, T. C., Steiger, J., and Sulser, T. (2004). Retroperitoneoscopic living donor nephrectomy: a retrospective comparison to the open approach, Transplantation 78, 168-71.

Bachmann, F., Buechner, S. A., Wernli, M., Strebel, S., and Erb, P. (2001). Ultraviolet light downregulates CD95 ligand and TRAIL receptor expression facilitating actinic keratosis and squamous cell carcinoma formation, J Invest Dermatol 117, 59-66.

Baechli, H., Nordmann, A., Bucher, H. C., and Gratzl, O. (2004). Demographics and prevalent risk factors of chronic subdural haematoma: results of a large single-center cohort study, Neurosurg Rev 18, 18.

Balciunaite, G., Keller, M. P., Balciunaite, E., Piali, L., Zuklys, S., Mathieu, Y. D., Gill, J., Boyd, R., Sussman, D. J., and Hollander, G. A. (2002). Wnt glycoproteins regulate the expression of FoxN1, the gene defective in nude mice, Nat Immunol 3, 1102-8.

Balmelli, N., Domine, F., Pfisterer, M., Krahenbuhl, S., and Marsch, S. (2002). Fatal drug interaction between cholestyramine and phenprocoumon, Eur J Intern Med 13, 210-211.

Barbero, A., Grogan, S., Schafer, D., Heberer, M., Mainil-Varlet, P., and Martin, I. (2004). Age related changes in human articular chondrocyte yield, proliferation and post-expansion chondrogenic capacity, Osteoarthritis Cartilage 12, 476-84.

Barbero, A., Ploegert, S., Heberer, M., and Martin, I. (2003). Plasticity of clonal populations of dedifferentiated adult human articular chondrocytes, Arthritis Rheum 48, 1315-25.

Barkhof, F., van Waesberghe, J. H., Filippi, M., Yousry, T., Miller, D. H., Hahn, D., Thompson, A. J., Kappos, L., Brex, P., Pozzilli, C., and Polman, C. H. (2001). T(1) hypointense lesions in secondary progressive multiple sclerosis: effect of interferon beta-1b treatment, Brain 124, 1396-402.

Bassetti, S., and Battegay, M. (2004). Staphylococcus aureus infections in injection drug users: risk factors and prevention strategies, Infection 32, 163-9.

Bassetti, S., Battegay, M., and Sudre, P. (2000a). Access to antiretroviral therapy, Jama 283, 883-4; author reply 884.

Bassetti, S., Dunagan, D. P., D'Agostino, R. B., Jr., and Sherertz, R. J. (2001a). Nasal carriage of Staphylococcus aureus among patients receiving allergen-injection immunotherapy: associated factors and quantitative nasal cultures, Infect Control Hosp Epidemiol 22, 741-5.

Bassetti, S., Hoffmann, M., Bucher, H. C., Fluckiger, U., and Battegay, M. (2002). Infections requiring hospitalization of injection drug users who participated in an injection opiate maintenance program, Clin Infect Dis 34, 711-3. Epub 2002 Jan 22.

Bassetti, S., Hu, J., D'Agostino, R. B., Jr., and Sherertz, R. J. (2000b). In vitro zones of inhibition of coated vascular catheters predict efficacy in preventing catheter infection with Staphylococcus aureus in vivo, Eur J Clin Microbiol Infect Dis 19, 612-7.

Bassetti, S., Hu, J., D'Agostino, R. B., Jr., and Sherertz, R. J. (2001b). Prolonged antimicrobial activity of a catheter containing chlorhexidine-silver sulfadiazine extends protection against catheter infections in vivo, Antimicrob Agents Chemother 45, 1535-8.

Bassetti, S., Wolfisberg, L., Jaussi, B., Frei, R., Kuntze, M. F., Battegay, M., and Widmer, A. F. (2004). Carriage of Staphylococcus aureus among injection drug users: lower prevalence in an injection heroin maintenance program than in an oral methadone program, Infect Control Hosp Epidemiol 25, 133-7.

Batchu, R. B., Moreno, A. M., Szmania, S., Gupta, S. K., Zhan, F., Rosen, N., Kozlowski, M., Spencer, T., Spagnoli, G. C., Shaughnessy, J., Barlogie, B., Tricot, G., and van Rhee, F. (2003). High-level expression of cancer/testis antigen NY-ESO-1 and human granulocyte-macrophage colony-stimulating factor in dendritic cells with a bicistronic retroviral vector, Hum Gene Ther 14, 1333-45.

Battegay, E. (2003). [Modern therapy of hypertension], Schweiz Rundsch Med Prax 92, 2153-7.

Battegay, M. (2001). Critical issues of HIV treatment in the era of highly active antiretroviral therapy, Expert Opin Investig Drugs 10, 175-83.

Battegay, M., Berger, C., Rochlitz, C., Hurwitz, N., Hirsch, H. H., De Geyter, C., Haque, T., and Nadal, D. (2004a). Epstein-Barr virus load correlating with clinical manifestation and treatment response in a patient with angioimmunoblastic T-cell lymphoma, Antivir Ther 9, 453-9.

Battegay, M., Bucher, H. C., and Vernazza, P. (2004b). Sexual risk behavior in HIV-infected injection drug users, Clin Infect Dis 38, 1175-7. Epub 2004 Apr 5.

Battegay, M., and Fluckiger, U. (2003). [Therapy of severe fungal infections], Internist (Berl) 44, 1549-56.

Battegay, M., Holdener, M., Naef, M., and Wernli, M. (2000). Human immunodeficiency and hepatitis C virus coinfection influenced by interferon-gamma, Immunol Lett 71, 141-2.

Battegay, M., and Manns, M. P. (2004). [Travel in a smaller world], Internist (Berl) 45, 639-40.

Battegay, M., Seiler, P., Hunziker, L., Wolf, K., and Zinkernagel, R. M. (2001a). Neutralizing antiviral antibodies reduce hematogenic viral spread but not antiviral cytotoxic T cell induction and subsequent immunopathology, J Infect Dis 183, 1425-7.

Battegay, M., Vernazza, P. L., Bernasconi, E., Flepp, M., Sendi, P., Erb, P., Malinverni, R., Jaccard, C., Morgenthaler, S., Bedoucha, V., and Hirschel, B. (2001b). Combined therapy with saquinavir, ritonavir and stavudine in moderately to severely immunosuppressed HIV-infected protease inhibitor-naive patients, HIV Med 2, 35-42.

Baumann, T. P., Hurwitz, N., Karamitopolou-Diamantis, E., Probst, A., Herrmann, R., and Steck, A. J. (2000). Diagnosis and treatment of intravascular lymphomatosis, Arch Neurol 57, 374-7.

Baykut, D., Bernet, F., Wehrle, J., Weichelt, K., Schwartz, P., and Zerkowski, H. R. (2001a). New surface biopolymers for oxygenators: an in vitro hemocompatibility test of poly(2-methoxyethylacrylate), Eur J Med Res 6, 297-305.

Baykut, D., Guller, U., Gebhard, M. M., Kadipasaoglu, K., Zerkowski, H. R., and Frazier, O. H. (2001b). [Intravascular detection of myocardial ischemia by spectrometry in the near infrared spectrum in experimental animals], Arch Mal Coeur Vaiss 94, 995-1000.

Baykut, D., Weichelt, K., Wehrle, J., Zerkowski, H. R., and Bernet, F. (2003). The value of heparin concentration monitoring in off-pump coronary bypass surgery, Eur J Med Res 8, 161-4.

Baykut, D., and Zerkowski, H. R. (2004). [Biocompatibility of the extracorporeal circulation. The present and the future], Schweiz Rundsch Med Prax 93, 366-8.

Becker, K. L., Nylen, E. S., Snider, R. H., Muller, B., and White, J. C. (2003). Immunoneutralization of procalcitonin as therapy of sepsis, J Endotoxin Res 9, 367-74.

Becker, K. L., Nylen, E. S., White, J. C., Muller, B., and Snider, R. H., Jr. (2004). Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors, J Clin Endocrinol Metab 89, 1512-25.

Becker, K. L., White, J.C., Nylen, E.S., Wagner, K.E., Muller, B., Preas, H.L., Suffradini, A.F., Snider, R.H. (2001). Toxicity of Procalcitonin: Beneficial Effects of its Immunoneutralization., J Anästes Intensivbeh 2001 2: 64-6.

Beglinger, C. (2002). Overview. Cholecystokinin and eating, Curr Opin Investig Drugs 3, 587-8.

Beglinger, C. (2004). Comments from the Editors, Digestion 69, 1.

Beglinger, C., Degen, L., Matzinger, D., D'Amato, M., and Drewe, J. (2001). Loxiglumide, a CCK-A receptor antagonist, stimulates calorie intake and hunger feelings in humans, Am J Physiol Regul Integr Comp Physiol 280, R1149-54.

Beglinger, C., Rosch, T., Renner, E. L., Schofl, R., Bauerfeind, P., Schwizer, W., Wirth, H. P., and Fried, M. (2004). [Highlights in gastroenterology 2003], Schweiz Rundsch Med Prax 93, 655-65.

Benacquista, B. L., Sharma, M. R., Samso, M., Zorzato, F., Treves, S., and Wagenknecht, T. (2000). Amino acid residues 4425-4621 localized on the three-dimensional structure of the skeletal muscle ryanodine receptor, Biophys J 78, 1349-58.

Bender, R., Hoffmann, M. C., Frotscher, M., and Nitsch, C. (2000). Species-specific expression of parvalbumin in the entorhinal cortex of the Mongolian gerbil: dependence on local activity but not extrinsic afferents, Neuroscience 99, 423-31.

Benjamin, D., Colombi, M., and Moroni, C. (2004). A GFP-based assay for rapid screening of compounds affecting ARE-dependent mRNA turnover, Nucleic Acids Res 32, e89. Print 2004 Jun.

Benz, C. C., Thor, A. D., Eppenberger-Castori, S., Eppenberger, U., and Moore, D., 3rd (2003). Understanding the age dependency of breast cancer biomarkers, Adv Gerontol 11, 117-20.

Berneis, K., Battegay, M., Bassetti, S., Nuesch, R., Leisibach, A., Bilz, S., and Keller, U. (2000). Nutritional supplements combined with dietary counselling diminish whole body protein catabolism in HIV-infected patients, Eur J Clin Invest 30, 87-94.

Berneis, K., Buitrago-Tellez, C., Muller, B., Keller, U., and Tsakiris, D. A. (2003). Antiphospholipid syndrome and endocrine damage: why bilateral adrenal thrombosis?, Eur J Haematol 71, 299-302.

Berneis, K., and Keller, U. (2000). Bioelectrical impedance analysis during acute changes of extracellular osmolality in man, Clin Nutr 19, 361-6.

Berneis, K., Staub, J. J., Gessler, A., Meier, C., Girard, J., and Muller, B. (2002). Combined stimulation of adrenocorticotropin and compound-S by single dose metyrapone test as an outpatient procedure to assess hypothalamic-pituitary-adrenal function, J Clin Endocrinol Metab 87, 5470-5.

Bernheim, A., and Buser, P. (2004). [In Process Citation], Schweiz Rundsch Med Prax 93, 527-30.

Berns, H., Humar, R., Hengerer, B., Kiefer, F. N., and Battegay, E. J. (2000). RACK1 is up-regulated in angiogenesis and human carcinomas, Faseb J 14, 2549-58.

Bertolotto, A., Gilli, F., Sala, A., Capobianco, M., Malucchi, S., Milano, E., Melis, F., Marnetto, F., Lindberg, R. L., Bottero, R., Di Sapio, A., and Giordana, M. T. (2003). Persistent neutralizing antibodies abolish the interferon beta bioavailability in MS patients, Neurology 60, 634-9.

Betticher, D. C., Hsu Schmitz, S. F., Totsch, M., Hansen, E., Joss, C., von Briel, C., Schmid, R. A., Pless, M., Habicht, J., Roth, A. D., Spiliopoulos, A., Stahel, R., Weder, W., Stupp, R., Egli, F., Furrer, M., Honegger, H., Wernli, M., Cerny, T., and Ris, H. B. (2003). Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial, J Clin Oncol 21, 1752-9.

Bettler, B., Kaupmann, K., Mosbacher, J., and Gassmann, M. (2004). Molecular structure and physiological functions of GABA(B) receptors, Physiol Rev 84, 835-67.

Bhatnagar, A., Gulland, S., Bascand, M., Palmer, E., Gardner, T. G., Kearse, K. P., and Backstrom, B. T. (2003). Mutational analysis of conserved amino acids in the T cell receptor alpha-chain transmembrane region: a critical role of leucine 112 and phenylalanine 127 for assembly and surface expression, Mol Immunol 39, 953-63.

Bianchi, M., Rey-Roldan, E., Bettler, B., Ristig, D., Malitschek, B., Libertun, C., and Lux-Lantos, V. (2001). Ontogenic expression of anterior pituitary GABA(B) receptor subunits, Neuropharmacology 40, 185-92.

Biedermann, B., Bringmann, A., Franze, K., Faude, F., Wiedemann, P., and Reichenbach, A. (2004). GABA(A) receptors in Muller glial cells of the human retina, Glia 46, 302-10.

Biedermann, B., Landmann, C., Kann, R., Passweg, J., Soler, M., Lohri, A., Rochlitz, C., Herrmann, R., and Pless, M. (2000). Combined chemoradiotherapy with daily low-dose cisplatin in locally advanced inoperable non-small cell lung cancer, Radiother Oncol 56, 169-73.

Biedermann, B. C. (2001). Vascular endothelium: checkpoint for inflammation and immunity, News Physiol Sci 16, 84-8.

Biedermann, B. C., Sahner, S., Gregor, M., Tsakiris, D. A., Jeanneret, C., Pober, J. S., and Gratwohl, A. (2002). Endothelial injury mediated by cytotoxic T lymphocytes and loss of microvessels in chronic graft versus host disease, Lancet 359, 2078-83.

Biedermann, B. C., Tsakiris, D. A., Gregor, M., Pober, J. S., and Gratwohl, A. (2003). Combining altered levels of effector transcripts in circulating T cells with a marker of endothelial injury is specific for active graft-versus-host disease, Bone Marrow Transplant 32, 1077-84.

Bigliardi, P. L., Buchner, S., Rufli, T., and Bigliardi-Qi, M. (2002). Specific stimulation of migration of human keratinocytes by mu-opiate receptor agonists, J Recept Signal Transduct Res 22, 191-9.

Bigliardi, P. L., Sumanovski, L. T., Buchner, S., Rufli, T., and Bigliardi-Qi, M. (2003). Different expression of mu-opiate receptor in chronic and acute wounds and the effect of beta-endorphin on transforming growth factor beta type II receptor and cytokeratin 16 expression, J Invest Dermatol 120, 145-52.

Bigliardi-Qi, M., Bigliardi, P. L., Eberle, A. N., Buchner, S., and Rufli, T. (2000). beta-endorphin stimulates cytokeratin 16 expression and downregulates mu-opiate receptor expression in human epidermis, J Invest Dermatol 114, 527-32.

Bigliardi-Qi, M., Sumanovski, L.T., Buchner, S., Rufli, T., Bigliardi, P.L., (2004). Mu-opiate receptor and beta-endorphin expression in nerve endings and keratinocytes in humanin skin., Dermatology.

Bihl, M. P., Heinimann, K., Rudiger, J. J., Eickelberg, O., Perruchoud, A. P., Tamm, M., and Roth, M. (2002). Identification of a novel IL-6 isoform binding to the endogenous IL-6 receptor, Am J Respir Cell Mol Biol 27, 48-56.

Bilz, S., Wagner, S., Schmitz, M., Bedynek, A., Keller, U., and Demant, T. (2004). Effects of atorvastatin versus fenofibrate on apoB-100 and apoA-I kinetics in mixed hyperlipidemia, J Lipid Res 45, 174-85. Epub 2003 Oct 1.

Bischoff, F. Z., Hahn, S., Johnson, K. L., Simpson, J. L., Bianchi, D. W., Lewis, D. E., Weber, W. D., Klinger, K., Elias, S., Jackson, L. G., Evans, M. I., Holzgreve, W., and de la Cruz, F. (2003). Intact fetal cells in maternal plasma: are they really there?, Lancet 361, 139-40.

Bisset, L. R., Cone, R. W., Fischer, M., Battegay, M., Vernazza, P. L., Dubs, R. W., Weber, R., Grob, P. J., and Opravil, M. (2001). Long-term evaluation of T-cell subset changes after effective combination antiretroviral therapy during asymptomatic HIV-infection, J Acquir Immune Defic Syndr 27, 266-71.

Black, J. L., Roth, M., Lee, J., Carlin, S., and Johnson, P. R. (2001). Mechanisms of airway remodeling. Airway smooth muscle, Am J Respir Crit Care Med 164, S63-6.

Blanchard, C., Durual, S., Estienne, M., Bouzakri, K., Heim, M. H., Blin, N., and Cuber, J. C. (2004). IL-4 and IL-13 up-regulate intestinal trefoil factor expression: requirement for STAT6 and de novo protein synthesis, J Immunol 172, 3775-83.

Blindenbacher, A., Duong, F. H., Hunziker, L., Stutvoet, S. T., Wang, X., Terracciano, L., Moradpour, D., Blum, H. E., Alonzi, T., Tripodi, M., La Monica, N., and Heim, M. H. (2003a). Expression of hepatitis c virus proteins inhibits interferon alpha signaling in the liver of transgenic mice, Gastroenterology 124, 1465-75.

Blindenbacher, A., Wang, X., Langer, I., Savino, R., Terracciano, L., and Heim, M. H. (2003b). Interleukin 6 is important for survival after partial hepatectomy in mice, Hepatology 38, 674-82.

Block, L. H., and Roth, M. (1996). [Cell proliferation factors and vascular damage], Cardiologia 41, 13-7.

Bogman, K., Erne-Brand, F., Alsenz, J., and Drewe, J. (2003). The role of surfactants in the reversal of active transport mediated by multidrug resistance proteins, J Pharm Sci 92, 1250-61.

Bogman, K., Peyer, A. K., Torok, M., Kusters, E., and Drewe, J. (2001). HMG-CoA reductase inhibitors and P-glycoprotein modulation, Br J Pharmacol 132, 1183-92.

Bogman, K., Zysset, Y., Degen, L., Hopfgartner, G., Gutmann, H., Alsenz, J., Drewe, J. (2004). P-glycoprotein and surfactants: effect on intestinal talinolol absorption., Clin Pharmacol Ther 2004 (in press).

Bolli, M., Kocher, T., Adamina, M., Guller, U., Dalquen, P., Haas, P., Mirlacher, M., Gambazzi, F., Harder, F., Heberer, M., Sauter, G., and Spagnoli, G. C. (2002). Tissue microarray evaluation of Melanoma antigen E (MAGE) tumor-associated antigen expression: potential indications for specific immunotherapy and prognostic relevance in squamous cell lung carcinoma, Ann Surg 236, 785-93; discussion 793.

Bolliger, C. T., Guckel, C., Engel, H., Stohr, S., Wyser, C. P., Schoetzau, A., Habicht, J., Soler, M., Tamm, M., and Perruchoud, A. P. (2002). Prediction of functional reserves after lung resection: comparison between quantitative computed tomography, scintigraphy, and anatomy, Respiration 69, 482-9.

Bolton, A. E., Peng, B., Hubert, M., Krebs-Brown, A., Capdeville, R., Keller, U., and Seiberling, M. (2004). Effect of rifampicin on the pharmacokinetics of imatinib mesylate (Gleevec, STI571) in healthy subjects, Cancer Chemother Pharmacol 53, 102-6. Epub 2003 Nov 7.

Boni, J., Bisset, L. R., Burckhardt, J. J., Joller-Jemelka, H. I., Burgisser, P., Perrin, L., Gorgievski, M., Erb, P., Fierz, W., Piffaretti, J. C., and Schupbach, J. (2004). Prevalence of human T-cell leukemia virus types I and II in Switzerland, J Med Virol 72, 328-37.

Borger, P., Black, J. L., and Roth, M. (2002). Asthma and the CCAAT-enhancer binding proteins: a holistic view on airway inflammation and remodeling, J Allergy Clin Immunol 110, 841-6.

Boulay, J. L., Mild, G., Lowy, A., Reuter, J., Lagrange, M., Terracciano, L., Laffer, U., Herrmann, R., and Rochlitz, C. (2002). SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer, Br J Cancer 87, 630-4.

Boulay, J. L., Mild, G., Lowy, A., Reuter, J., Lagrange, M., Terracciano, L., Laffer, U., Herrmann, R., and Rochlitz, C. (2003). SMAD7 is a prognostic marker in patients with colorectal cancer, Int J Cancer 104, 446-9.

Boulay, J. L., Mild, G., Reuter, J., Lagrange, M., Terracciano, L., Lowy, A., Laffer, U., Orth, B., Metzger, U., Stamm, B., Martinoli, S., Herrmann, R., and Rochlitz, C. (2001). Combined copy status of 18q21 genes in colorectal cancer shows frequent retention of SMAD7, Genes Chromosomes Cancer 31, 240-7.

Boulay, J. L., Perruchoud, A. P., Reuter, J., Bolliger, C., Herrmann, R., and Rochlitz, C. (2000). P21 gene expression as an indicator for the activity of adenovirus-p53 gene therapy in non-small cell lung cancer patients, Cancer Gene Ther 7, 1215-9.

Boureau, F., Kappos, L., Schoenen, J., Esperanca, P., and Ashford, E. (2000). A clinical comparison of sumatriptan nasal spray and dihydroergotamine nasal spray in the acute treatment of migraine, Int J Clin Pract 54, 281-6.

Boussard, C., Klimkait, T., Mahmood, N., Pritchard, M., and Gilbert, I. H. (2004). Design, synthesis and evaluation of potential inhibitors of HIV gp120-CD4 interactions, Bioorg Med Chem Lett 14, 2673-6.

Bowery, N. G., Bettler, B., Froestl, W., Gallagher, J. P., Marshall, F., Raiteri, M., Bonner, T. I., and Enna, S. J. (2002). International Union of Pharmacology. XXXIII. Mammalian gamma-aminobutyric acid(B) receptors: structure and function, Pharmacol Rev 54, 247-64.

Bravo, A. E., Egger, S. S., Crespo, S., Probst, W. L., and Krahenbuhl, S. (2004). Lithium intoxication as a result of an interaction with rofecoxib, Ann Pharmacother 38, 1189-93. Epub 2004 Jun 8.

Breitenbach, U., Tuckermann, J. P., Gebhardt, C., Richter, K. H., Furstenberger, G., Christofori, G., and Angel, P. (2001). Keratinocyte-specific onset of serine protease BSSP expression in experimental carcinogenesis, J Invest Dermatol 117, 634-40.

Brem, R., Certa, U., Neeb, M., Nair, A. P., and Moroni, C. (2001). Global analysis of differential gene expression after transformation with the v-H-ras oncogene in a murine tumor model, Oncogene 20, 2854-8.

Brennan, L. E., Sune, C., and Klimkait, T. (2002). A neutravidin-based assay for reverse transcriptase suitable for high throughput screening of retroviral activity, J Biochem Mol Biol 35, 262-6.

Brett, W., Mandinova, A., Remppis, A., Sauder, U., Ruter, F., Heizmann, C. W., Aebi, U., and Zerkowski, H. R. (2001). Translocation of S100A1(1) calcium binding protein during heart surgery, Biochem Biophys Res Commun 284, 698-703.

Brettenthaler, N., De Geyter, C., Huber, P. R., and Keller, U. (2004). Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome, J Clin Endocrinol Metab 89, 3835-40.

Brex, P. A., Molyneux, P. D., Smiddy, P., Barkhof, F., Filippi, M., Yousry, T. A., Hahn, D., Rolland, Y., Salonen, O., Pozzilli, C., Polman, C. H., Thompson, A. J., Kappos, L., and Miller, D. H. (2001). The effect of IFNbeta-1b on the evolution of enhancing lesions in secondary progressive MS, Neurology 57, 2185-90.

Brezesinski, G., Muller, H. J., Toca-Herrera, J. L., and Krustev, R. (2001). X-ray diffraction and foam film investigations of PC head group interaction in water/ethanol mixtures, Chem Phys Lipids 110, 183-94.

Briata, P., Ilengo, C., Corte, G., Moroni, C., Rosenfeld, M. G., Chen, C. Y., and Gherzi, R. (2003). The Wnt/beta-catenin-- Pitx2 pathway controls the turnover of Pitx2 and other unstable mRNAs, Mol Cell 12, 1201-11.

Brink, M., Anwar, A., and Delafontaine, P. (2002). Neurohormonal factors in the development of catabolic/anabolic imbalance and cachexia, Int J Cardiol 85, 111-21, discussion 121-4.

Brink, M., Du, J., Peng, T., Mottironi, B., and Delafontaine, P. (2001a). Thrombin regulates insulin-like growth factor-1 receptor transcription in vascular smooth muscle: characterization of the signaling pathway, Circ Res 88, 1044-52.

Brink, M., Price, S. R., Chrast, J., Bailey, J. L., Anwar, A., Mitch, W. E., and Delafontaine, P. (2001b). Angiotensin II induces skeletal muscle wasting through enhanced protein degradation and down-regulates autocrine insulin-like growth factor I, Endocrinology 142, 1489-96.

Brodmann, S., Passweg, J. R., Gratwohl, A., Tichelli, A., and Skoda, R. C. (2000). Myeloproliferative disorders: complications, survival and causes of death, Ann Hematol 79, 312-8.

Brody, S., Keller, U., Degen, L., Cox, D. J., and Schachinger, H. (2004). Selective processing of food words during insulin-induced hypoglycemia in healthy humans, Psychopharmacology (Berl) 173, 217-20. Epub 2004 Jan 15.

Brondani, V., Klimkait, T., Egly, J. M., and Hamy, F. (2002). Promoter of FGF8 reveals a unique regulation by unliganded RARalpha, J Mol Biol 319, 715-28.

Brooks, H., and Krahenbuhl, S. (2001). Identification and tissue distribution of two differentially spliced variants of the rat carnitine transporter OCTN2, FEBS Lett 508, 175-80.

Bruder, E., Ersch, J., Hebisch, G., Ehrbar, T., Klimkait, T., and Stallmach, T. (2000). Fetal varicella syndrome: disruption of neural development and persistent inflammation of non-neural tissues, Virchows Arch 437, 440-4.

Brune, T., Beier, K., Exeler, R., Harms, E., and Louwen, F. (2003). Neonatal Lymphocytes Dominate against Lymphocytes of Their Own Mother but Not against Allogenic Maternal or Adult Lymphocytes in Bidirectional Mixed Lymphocyte Cultures, Fetal Diagn Ther 18, 154-9.

Bruno, L., Schaniel, C., and Rolink, A. (2002). Plasticity of Pax-5(-/-) pre-B I cells, Cells Tissues Organs 171, 38-43.

Brutsche, M. H., Joos, L., Carlen Brutsche, I. E., Bissinger, R., Tamm, M., Custovic, A., and Woodcock, A. (2002). Array-based diagnostic gene-expression score for atopy and asthma, J Allergy Clin Immunol 109, 271-3.

Bucher, H. C., Bichsel, M., Taffe, P., Furrer, H., Telenti, A., Hirschel, B., Weber, R., Bernasconi, E., Vernazza, P., Minder, C., and Battegay, M. (2002). Ritonavir plus saquinavir versus single protease inhibitor therapy in protease inhibitor-naive HIV-infected patients: the Swiss HIV Cohort Study, HIV Med 3, 247-53.

Bucher, H. C., Kofler, A., Nuesch, R., Young, J., Battegay, M., and Opravil, M. (2003). Meta-analysis of randomized controlled trials of simplified versus continued protease inhibitor-based antiretroviral therapy in HIV-1-infected patients, Aids 17, 2451-9.

Buechner, S., Wernli, M., Bachmann, F., Harr, T., and Erb, P. (2002). Intralesional interferon in basal cell carcinoma: how does it work?, Recent Results Cancer Res 160, 246-50.

Buess, M., Terracciano, L., Reuter, J., Ballabeni, P., Boulay, J. L., Laffer, U., Metzger, U., Herrmann, R., and Rochlitz, C. (2004). Amplification of SKI is a prognostic marker in early colorectal cancer, Neoplasia 6, 207-12.

Burgess, J. K., Johnson, P. R., Ge, Q., Au, W. W., Poniris, M. H., McParland, B. E., King, G., Roth, M., and Black, J. L. (2003). Expression of connective tissue growth factor in asthmatic airway smooth muscle cells, Am J Respir Crit Care Med 167, 71-7.

Busam, K. J., Iversen, K., Berwick, M., Spagnoli, G. C., Old, L. J., and Jungbluth, A. A. (2000). Immunoreactivity with the anti-MAGE antibody 57B in malignant melanoma: frequency of expression and correlation with prognostic parameters, Mod Pathol 13, 459-65.

Busslinger, M., Nutt, S. L., and Rolink, A. G. (2000). Lineage commitment in lymphopoiesis, Curr Opin Immunol 12, 151-8.

Butz, S., Driamov, S., Remondino, A., Bellahcene, M., Beier, K., Ziegler, A., Buser, P. T., and Zaugg, C. E. (2004). Losartan but not enalaprilat acutely reduces reperfusion ventricular tachyarrhythmias in hypertrophied rat hearts after low-flow ischaemia, J Pharm Pharmacol 56, 521-8.

Cabrita, M. A., and Christofori, G. (2003). Sprouty proteins: antagonists of endothelial cell signaling and more, Thromb Haemost 90, 586-90.

Caduff, J., Sansano, S., Bonnet, A., Suter, U., and Schaeren-Wiemers, N. (2001). Characterization of GFP-MAL expression and incorporation in rafts, Microsc Res Tech 52, 645-55.

Camillo, F., Marmorini, P., Romagnoli, S., Cela, M., Duchamp, G., and Palmer, E. (2000). Clinical studies on daily low dose oxytocin in mares at term, Equine Vet J 32, 307-10.

Capone, M., Lees, R. K., Finke, D., Ernst, B., Meerwijk, J. P., and MacDonald, H. R. (2003). Selective absence of CD8 TCRalpha beta intestinal epithelial cells in transgenic mice expressing beta2-microglobulin-associated ligands exclusively on thymic cortical epithelium, Eur J Immunol 33, 1471-7.

Capone, M., Troesch, M., Eberl, G., Hausmann, B., Palmer, E., and MacDonald, H. R. (2001). A critical role for the T cell receptor alpha-chain connecting peptide domain in positive selection of CD1-independent NKT cells, Eur J Immunol 31, 1867-75.

Carlin, S., Resink, T.J., Tamm, M., Roth, M. (2004). Urokinase signal transduction and its role in cell migration., FASEB-J 2004 (in press).

Carlin, S. M., Roth, M., and Black, J. L. (2003). Urokinase potentiates PDGF-induced chemotaxis of human airway smooth muscle cells, Am J Physiol Lung Cell Mol Physiol 284, L1020-6. Epub 2003 Feb 7.

Carrier, L., Knoll, R., Vignier, N., Keller, D. I., Bausero, P., Prudhon, B., Isnard, R., Ambroisine, M. L., Fiszman, M., Ross, J., Jr., Schwartz, K., and Chien, K. R. (2004). Asymmetric septal hypertrophy in heterozygous cMyBP-C null mice, Cardiovasc Res 63, 293-304.

Casella, R., Moch, H., Rochlitz, C., Meier, V., Seifert, B., Mihatsch, M. J., and Gasser, T. C. (2001). Metastatic primitive neuroectodermal tumor of the kidney in adults, Eur Urol 39, 613-7.

Cathomas, G., Erne, P., Schwenkglenks, M., and Szucs, T. D. (2002). The economic efficiency of amlodipine in the treatment of coronary atherosclerosis--an analysis based on the PREVENT study, Cardiovasc Drugs Ther 16, 61-6.

Cavagna, D., Zorzato, F., Babini, E., Prestipino, G., and Treves, S. (2000). Methyl p-hydroxybenzoate (E-218) a preservative for drugs and food is an activator of the ryanodine receptor Ca(2) release channel, Br J Pharmacol 131, 335-41.

Cavallaro, U., and Christofori, G. (2000). Molecular mechanisms of tumor angiogenesis and tumor progression, J Neurooncol 50, 63-70.

Cavallaro, U., and Christofori, G. (2001). Cell adhesion in tumor invasion and metastasis: loss of the glue is not enough, Biochim Biophys Acta 1552, 39-45.

Cavallaro, U., and Christofori, G. (2004a). Cell adhesion and signalling by cadherins and Ig-CAMs in cancer, Nat Rev Cancer 4, 118-32.

Cavallaro, U., and Christofori, G. (2004b). Multitasking in tumor progression: signaling functions of cell adhesion molecules, Ann N Y Acad Sci 1014, 58-66.

Cavallaro, U., Niedermeyer, J., Fuxa, M., and Christofori, G. (2001). N-CAM modulates tumour-cell adhesion to matrix by inducing FGF-receptor signalling, Nat Cell Biol 3, 650-7.

Cavallaro, U., Schaffhauser, B., and Christofori, G. (2002). Cadherins and the tumour progression: is it all in a switch?, Cancer Lett 176, 123-8.

Cavazza, A., Adamina, M., Ausiello, C. M., Giardina, B., Marini, M., Palazzo, R., Roda, L. G., and Spagnoli, G. C. (2004). Hydrolysis of the tumor-associated antigen epitope gp100(280-288) by membrane-associated and soluble enzymes expressed by immature and mature dendritic cells, Clin Immunol 111, 252-61.

Caversaccio, M., Frenz, M., Schar, P., and Hausler, R. (2001). Endonasal and transcanalicular Er:YAG laser dacryocystorhinostomy, Rhinology 39, 28-32.

Cazzola, M., and Skoda, R. C. (2000). Translational pathophysiology: a novel molecular mechanism of human disease, Blood 95, 3280-8.

Cejka, P., Stojic, L., Mojas, N., Russell, A. M., Heinimann, K., Cannavo, E., di Pietro, M., Marra, G., and Jiricny, J. (2003). Methylation-induced G(2)/M arrest requires a full complement of the mismatch repair protein hMLH1, Embo J 22, 2245-54.

Ceredig, R., Bosco, N., Maye, P. N., Andersson, J., and Rolink, A. (2003). In interleukin-7-transgenic mice, increasing B lymphopoiesis increases follicular but not marginal zone B cell numbers, Eur J Immunol 33, 2567-76.

Ceredig, R., Rolink, A. G., Melchers, F., and Andersson, J. (2000). The B cell receptor, but not the pre-B cell receptor, mediates arrest of B cell differentiation, Eur J Immunol 30, 759-67.

Cerletti, A., Drewe, J., Fricker, G., Eberle, A. N., and Huwyler, J. (2000). Endocytosis and transcytosis of an immunoliposome-based brain drug delivery system, J Drug Target 8, 435-46.

Certa, U., Seiler, M., Padovan, E., and Spagnoli, G. C. (2001). High density oligonucleotide array analysis of interferon- alpha2a sensitivity and transcriptional response in melanoma cells, Br J Cancer 85, 107-14.

Certa, U., Seiler, M., Padovan, E., and Spagnoli, G. C. (2002). Interferon-a sensitivity in melanoma cells: detection of potential response marker genes, Recent Results Cancer Res 160, 85-91.

Chambost, H., Van Baren, N., Brasseur, F., Godelaine, D., Xerri, L., Landi, S. J., Theate, I., Plumas, J., Spagnoli, G. C., Michel, G., Coulie, P. G., and Olive, D. (2000). Expression of gene MAGE-A4 in Reed-Sternberg cells, Blood 95, 3530-3.

Chatterjee, T., and Erne, P. (2003). Anomalous right coronary artery originating from the mid left main coronary artery, Heart 89, 132.

Chatterjee, T., Juelke, P. D., Thum, P., and Erne, P. (2003). Successful brachytherapy of coronary vasospasm, Heart 89, e25.

Chen, C. Y., Gherzi, R., Ong, S. E., Chan, E. L., Raijmakers, R., Pruijn, G. J., Stoecklin, G., Moroni, C., Mann, M., and Karin, M. (2001). AU binding proteins recruit the exosome to degrade ARE-containing mRNAs, Cell 107, 451-64.

Chen, D., Lucey, M. J., Phoenix, F., Lopez-Garcia, J., Hart, S. M., Losson, R., Buluwela, L., Coombes, R. C., Chambon, P., Schar, P., and Ali, S. (2003). T: G mismatch-specific thymine-DNA glycosylase potentiates transcription of estrogen-regulated genes through direct interaction with estrogen receptor alpha, J Biol Chem 278, 38586-92. Epub 2003 Jul 21.

Chhajed, P. N., and Tamm, M. (2003). Radiofrequency heat ablation for lung tumors: potential applications, Med Sci Monit 9, ED5-7.

Chitale, D. A., Jungbluth, A. A., Marshall, D. S., Leitao, M. M., Hedvat, C. V., Kolb, D., Spagnoli, G. C., Iversen, K., and Soslow, R. A. (2004). Expression of cancer-testis antigens in endometrial carcinomas using a tissue microarray, Mod Pathol 23, 23.

Chklovskaia, E., Nissen, C., Landmann, L., Rahner, C., Pfister, O., and Wodnar-Filipowicz, A. (2001). Cell-surface trafficking and release of flt3 ligand from T lymphocytes is induced by common cytokine receptor gamma-chain signaling and inhibited by cyclosporin A, Blood 97, 1027-34.

Chklovskaia, E., Nowbakht, P., Nissen, C., Gratwohl, A., Bargetzi, M., and Wodnar-Filipowicz, A. (2004). Reconstitution of dendritic and natural killer-cell subsets after allogeneic stem cell transplantation: effects of endogenous flt3 ligand, Blood 103, 3860-8. Epub 2004 Feb 5.

Christ, O., Gunthert, U., Haas, R., and Zoller, M. (2001). Importance of CD44v7 isoforms for homing and seeding of hematopoietic progenitor cells, J Leukoc Biol 69, 343-52.

Christ, O., Gunthert, U., Schmidt, D. S., and Zoller, M. (2002). Allogeneic reconstitution after nonmyeloablative conditioning: mitigation of graft-versus-host and host-versus-graft reactivity by anti-CD44v6, J Leukoc Biol 71, 33-46.

Christ-Crain, M., Jaccard-Stolz, D., Bingisser, R., Gencay, M. M., Huber, P. R., Tamm, M., and Muller, B. (2004a). Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial, Lancet 363, 600-7.

Christ-Crain, M., Meier, C., Guglielmetti, M., Huber, P. R., Riesen, W., Staub, J. J., and Muller, B. (2003). Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial, Atherosclerosis 166, 379-86.

Christ-Crain, M., Meier, C., Huber, P., Zimmerli, L., Trummler, M., and Muller, B. (2004b). Comparison of different methods for the measurement of serum testosterone in the aging male, Swiss Med Wkly 134, 193-7.

Christ-Crain, M., Meier, C., Roth, C. B., Huber, P., Staub, J. J., and Muller, B. (2002). Basal TSH levels compared with TRH-stimulated TSH levels to diagnose different degrees of TSH suppression: diagnostic and therapeutic impact of assay performance, Eur J Clin Invest 32, 931-7.

Christ-Crain, M., Meier, C., Huber, P.R., Keller, U., Staub, J.J., Muller, B. (2004a). Effect of L-Thyroxine Replacement Therapy on Skeletal and Cardiac Function in Subclinical Hypothyroidism., The Endocrinologist 2004 14: 161-6.

Christ-Crain, M., Meier, C., Puder, J.J., Staub, J.J., Huber, P.R., Keller, U., Muller, B. (2004b). Changes of Liver Function Test correlate with the Improvement of Lipid Profile after Restoration of Euthyroidism in Patients with Subclinical Hypothyroidism., EXCLI Journal 2004 3: 1-9.

Christ-Crain, M., Meier, C., Zulewski, H., Huber, P.R., Keller, U., Staub, J.J., Muller, B. (2003). Effect of Restoration of Euthyroidism on Peripheral Blood Cells in Women with Subclinical Hypothyroidism., Hormones 2003 2: 209-14.

Christ-Crain, M., Mueller, B., Gasser, T. C., Kraenzlin, M., Trummler, M., Huber, P., and Meier, C. (2004c). Is there a clinical relevance of partial androgen deficiency of the aging male?, J Urol 172, 624-7.

Christofori, G. (2003a). Changing neighbours, changing behaviour: cell adhesion molecule-mediated signalling during tumour progression, Embo J 22, 2318-23.

Christofori, G. (2003b). Split personalities: the agonistic antagonist Sprouty, Nat Cell Biol 5, 377-9.

Cipolat, C., Bader, U., Rufli, T., and Burg, G. (2003). Teledermatology in Switzerland, Curr Probl Dermatol 32, 257-60.

Clanet, M., Kappos, L., Hartung, H. P., and Hohlfeld, R. (2004). Interferon beta-1a in relapsing multiple sclerosis: four-year extension of the European IFNbeta-1a Dose-Comparison Study, Mult Scler 10, 139-44.

Clanet, M., Radue, E. W., Kappos, L., Hartung, H. P., Hohlfeld, R., Sandberg-Wollheim, M., Kooijmans-Coutinho, M. F., Tsao, E. C., and Sandrock, A. W. (2002). A randomized, double-blind, dose-comparison study of weekly interferon beta-1a in relapsing MS, Neurology 59, 1507-17.

Clarke, S., Bellmann, A., Meuli, R. A., Assal, G., and Steck, A. J. (2000). Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways, Neuropsychologia 38, 797-807.

Clement-Jones, M., Schiller, S., Rao, E., Blaschke, R. J., Zuniga, A., Zeller, R., Robson, S. C., Binder, G., Glass, I., Strachan, T., Lindsay, S., and Rappold, G. A. (2000). The short stature homeobox gene SHOX is involved in skeletal abnormalities in Turner syndrome, Hum Mol Genet 9, 695-702.

Coers, J., Ranft, C., and Skoda, R. C. (2004). A truncated isoform of c-mpl with an essential C-terminal peptide targets the full-length receptor for degradation, J Biol Chem 21, 21.

Comi, G., Kappos, L., Clanet, M., Ebers, G., Fassas, A., Fazekas, F., Filippi, M., Hartung, H. P., Hertenstein, B., Karussis, D., Martino, G., Tyndall, A., and van der Meche, F. G. (2000). Guidelines for autologous blood and marrow stem cell transplantation in multiple sclerosis: a consensus report written on behalf of the European Group for Blood and Marrow Transplantation and the European Charcot Foundation. BMT-MS Study Group, J Neurol 247, 376-82.

Compagni, A., and Christofori, G. (2000). Recent advances in research on multistage tumorigenesis, Br J Cancer 83, 1-5.

Compagni, A., Wilgenbus, P., Impagnatiello, M. A., Cotten, M., and Christofori, G. (2000). Fibroblast growth factors are required for efficient tumor angiogenesis, Cancer Res 60, 7163-9.

Confavreux, C., Suissa, S., Saddier, P., Bourdes, V., and Vukusic, S. (2001). Vaccinations and the risk of relapse in multiple sclerosis. Vaccines in Multiple Sclerosis Study Group, N Engl J Med 344, 319-26.

Constantinescu, C. S., Freitag, P., and Kappos, L. (2000). Increase in serum levels of uric acid, an endogenous antioxidant, under treatment with glatiramer acetate for multiple sclerosis, Mult Scler 6, 378-81.

Constantinescu, C. S., Grygar, C., Kappos, L., and Leppert, D. (2001). Interleukin 15 stimulates production of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by human peripheral blood mononuclear cells, Cytokine 13, 244-7.

Crabtree, M., Sieber, O. M., Lipton, L., Hodgson, S. V., Lamlum, H., Thomas, H. J., Neale, K., Phillips, R. K., Heinimann, K., and Tomlinson, I. P. (2003). Refining the relation between 'first hits' and 'second hits' at the APC locus: the 'loose fit' model and evidence for differences in somatic mutation spectra among patients, Oncogene 22, 4257-65.

Crnic, I., and Christofori, G. (2004). Novel technologies and recent advances in metastasis research, Int J Dev Biol 48, 573-581.

Cron, T. A., Zellweger, M. J., Buser, P. T., Pfisterer, M. E., and Osswald, S. (2002). Late potential analysis: is a mathematically-derived X,Y,Z lead system comparable to a true orthogonal X,Y,Z lead system?, Ann Noninvasive Electrocardiol 7, 302-6.

Cryan, J. F., Kelly, P. H., Chaperon, F., Gentsch, C., Mombereau, C., Lingenhoehl, K., Froestl, W., Bettler, B., Kaupmann, K., and Spooren, W. P. (2004). Behavioural Characterization of the Novel Gamma-Aminobuytric Acid (B) (Gabab) Receptor Positive Modulator Gs39783 (N, N - Dicyclopentyl-2-Methylsulfanyl-5-Nitro-Pyrimidine-4,6-Diamine): Anxiolytic-Like Activity without Side-Effects Associated with Baclofen or Benzodiazepines, J Pharmacol Exp Ther 27, 27.

Czaplinski, A., Radziwill, A. J., and Steck, A. J. (2003a). [Actual aspects of myasthenia gravis treatment], Pol Merkuriusz Lek 14, 256-60.

Czaplinski, A., and Steck, A. J. (2004). Immune mediated neuropathies--an update on therapeutic strategies, J Neurol 251, 127-37.

Czaplinski, A., Steck, A. J., Andersen, P. M., and Weber, M. (2004). Flail arm syndrome: a clinical variant of amyotrophic lateral sclerosis, Eur J Neurol 11, 567-8.

Czaplinski, A., Steck, A. J., and Fuhr, P. (2003b). Ice pack test for myasthenia gravis. A simple, noninvasive and safe diagnostic method, J Neurol 250, 883-4.

Czaplinski, A., Strobel, W., Gobbi, C., Steck, A. J., Fuhr, P., and Leppert, D. (2003c). Respiratory failure due to bilateral diaphragm palsy as an early manifestation of ALS, Med Sci Monit 9, CS34-6.

D'Orazio, D., Muller, P. Y., Heinimann, K., Albrecht, C., Bendik, I., Herzog, U., Tondelli, P., Bauerfeind, P., Muller, H., and Dobbie, Z. (2002). Overexpression of Wnt target genes in adenomas of familial adenomatous polyposis patients, Anticancer Res 22, 3409-14.

Daelemans, D., Schols, D., Witvrouw, M., Pannecouque, C., Hatse, S., van Dooren, S., Hamy, F., Klimkait, T., de Clercq, E., and VanDamme, A. M. (2000). A second target for the peptoid Tat/transactivation response element inhibitor CGP64222: inhibition of human immunodeficiency virus replication by blocking CXC-chemokine receptor 4-mediated virus entry, Mol Pharmacol 57, 116-24.

Danzer, E., Holzgreve, W., Batukan, C., Miny, P., Tercanli, S., and Hoesli, I. (2001). Myomectomy during the first trimester associated with fetal limb anomalies and hydrocephalus in a twin pregnancy, Prenat Diagn 21, 848-51.

Danzer, E., Holzgreve, W., Troeger, C., Kostka, U., Steimann, S., Bitzer, J., Gratwohl, A., Tichelli, A., Seelmann, K., and Surbek, D. V. (2003). Attitudes of Swiss mothers toward unrelated umbilical cord blood banking 6 months after donation, Transfusion 43, 604-8.

Davidson, G., Dono, R., and Zeller, R. (2001). FGF signalling is required for differentiation-induced cytoskeletal reorganisation and formation of actin-based processes by podocytes, J Cell Sci 114, 3359-66.

De Geyter, C., De Geyter, M., Huber, P. R., Nieschlag, E., and Holzgreve, W. (2002). Progesterone serum levels during the follicular phase of the menstrual cycle originate from the crosstalk between the ovaries and the adrenal cortex, Hum Reprod 17, 933-9.

De Geyter, C., Schmitter, M., De Geyter, M., Nieschlag, E., Holzgreve, W., and Schneider, H. P. (2000). Prospective evaluation of the ultrasound appearance of the endometrium in a cohort of 1,186 infertile women, Fertil Steril 73, 106-13.

De Libero, G. (2000). Tissue distribution, antigen specificity and effector functions of gamma delta T cells in human diseases, Springer Semin Immunopathol 22, 219-38.

De Libero, G. (2004). Immunology. The Robin Hood of antigen presentation, Science 303, 485-7.

De Libero, G., Donda, A., Gober, H. J., Manolova, V., Mazorra, Z., Shamshiev, A., and Mori, L. (2002). A new aspect in glycolipid biology: glycosphingolipids as antigens recognized by T lymphocytes, Neurochem Res 27, 675-85.

De Libero, G., Donda, A., Mori, L., Manolova, V., and Shamshiev, A. (2001). Immunity to glycolipid antigens in microbial infections, J Biol Regul Homeost Agents 15, 249-56.

De Libero, G., and Mori, L. (2003). Self glycosphingolipids: new antigens recognized by autoreactive T lymphocytes, News Physiol Sci 18, 71-6.

Degen, L., Matzinger, D., Drewe, J., and Beglinger, C. (2001). The effect of cholecystokinin in controlling appetite and food intake in humans, Peptides 22, 1265-9.

Delafontaine, P., and Brink, M. (2000). The growth hormone and insulin-like growth factor 1 axis in heart failure, Ann Endocrinol (Paris) 61, 22-6.

Delco, F., Tchambaz, L., Schlienger, R., Drewe, J., Krahenbuhl, S. (2004). Dosing in patients with liver disease., Drug Safety 2004 (in press).

Deller, T., Korte, M., Chabanis, S., Drakew, A., Schwegler, H., Stefani, G. G., Zuniga, A., Schwarz, K., Bonhoeffer, T., Zeller, R., Frotscher, M., and Mundel, P. (2003). Synaptopodin-deficient mice lack a spine apparatus and show deficits in synaptic plasticity, Proc Natl Acad Sci U S A 100, 10494-9. Epub 2003 Aug 19.

Delles, C., Schmidt, B. M., Muller, H. J., Oehmer, S., Klingbeil, A. U., and Schmieder, R. E. (2003). Functional relevance of aldosterone for the determination of left ventricular mass, Am J Cardiol 91, 297-301.

Demarteau, O., Jakob, M., Schafer, D., Heberer, M., and Martin, I. (2003a). Development and validation of a bioreactor for physical stimulation of engineered cartilage, Biorheology 40, 331-6.

Demarteau, O., Wendt, D., Braccini, A., Jakob, M., Schafer, D., Heberer, M., and Martin, I. (2003b). Dynamic compression of cartilage constructs engineered from expanded human articular chondrocytes, Biochem Biophys Res Commun 310, 580-8.

Demartines, N., Battegay, E., Liebermann, J., Oberholzer, M., Rufli, T., and Harder, F. (2000). [Telemedicine: perspectives and multidisciplinary approach], Schweiz Med Wochenschr 130, 314-23.

Devitt, P., Smith, J. R., and Palmer, E. (2001). Improved student learning in ophthalmology with computer-aided instruction, Eye 15, 635-9.

Dhein, S., Giessler, C., Wangemann, T., Silber, R. E., Zerkowski, H. R., and Brodde, O. E. (2000). Differential pattern of endothelin-1-induced inotropic effects in right atria and left ventricles of the human heart, J Cardiovasc Pharmacol 36, 564-9.

Diacon, A. H., Wyser, C., Bolliger, C. T., Tamm, M., Pless, M., Perruchoud, A. P., and Soler, M. (2000). Prospective randomized comparison of thoracoscopic talc poudrage under local anesthesia versus bleomycin instillation for pleurodesis in malignant pleural effusions, Am J Respir Crit Care Med 162, 1445-9.

Dickenmann, M., Schaub, S., Nickeleit, V., Mihatsch, M., Steiger, J., and Brunner, F. (2002). Fibrillary glomerulonephritis: early diagnosis associated with steroid responsiveness, Am J Kidney Dis 40, E9.

Dickenmann, M. J., Cathomas, G., Steiger, J., Mihatsch, M. J., Thiel, G., and Tamm, M. (2001). Cytomegalovirus infection and graft rejection in renal transplantation, Transplantation 71, 764-7.

Dickenmann, M. J., Kabulbayev, K., Steiger, J., Cathomas, G., Reusser, P., and Tamm, M. (2004). Ganciclovir prophylaxis to prevent CMV disease in kidney recipients undergoing anti-lymphocyte globulin treatment for acute rejection, Clin Microbiol Infect 10, 337-9.

Dobbie, Z., Muller, P. Y., Heinimann, K., Albrecht, C., D'Orazio, D., Bendik, I., Muller, H., and Bauerfeind, P. (2002). Expression of COX-2 and Wnt pathway genes in adenomas of familial adenomatous polyposis patients treated with meloxicam, Anticancer Res 22, 2215-20.

Domenech, V. S., Nylen, E. S., White, J. C., Snider, R. H., Becker, K. L., Landmann, R., and Muller, B. (2001). Calcitonin gene-related peptide expression in sepsis: postulation of microbial infection-specific response elements within the calcitonin I gene promoter, J Investig Med 49, 514-21.

Donda, A., Mori, L., Shamshiev, A., Carena, I., Mottet, C., Heim, M. H., Beglinger, C., Grunert, F., Rochlitz, C., Terracciano, L., Jantscheff, P., and De Libero, G. (2000). Locally inducible CD66a (CEACAM1) as an amplifier of the human intestinal T cell response, Eur J Immunol 30, 2593-603.

Dono, R., Faulhaber, J., Galli, A., Zuniga, A., Volk, T., Texido, G., Zeller, R., and Ehmke, H. (2002). FGF2 signaling is required for the development of neuronal circuits regulating blood pressure, Circ Res 90, E5-E10.

Dory, D., Echchannaoui, H., Letiembre, M., Ferracin, F., Pieters, J., Adachi, Y., Akashi, S., Zimmerli, W., and Landmann, R. (2003). Generation and functional characterization of a clonal murine periportal Kupffer cell line from H-2Kb -tsA58 mice, J Leukoc Biol 74, 49-59.

Doucey, M. A., Goffin, L., Naeher, D., Michielin, O., Baumgartner, P., Guillaume, P., Palmer, E., and Luescher, I. F. (2003a). CD3 delta establishes a functional link between the T cell receptor and CD8, J Biol Chem 278, 3257-64. Epub 2002 Sep 4.

Doucey, M. A., Legler, D. F., Faroudi, M., Boucheron, N., Baumgaertner, P., Naeher, D., Cebecauer, M., Hudrisier, D., Ruegg, C., Palmer, E., Valitutti, S., Bron, C., and Luescher, I. F. (2003b). The beta1 and beta3 integrins promote T cell receptor-mediated cytotoxic T lymphocyte activation, J Biol Chem 278, 26983-91. Epub 2003 Apr 10.

Doyl, V. E., Klimkait, T., Mahmood, N., Slater, M., Hazen, R. J., and Gilbert, I. H. (2002). Synthesis of potential anti-HIV GP120 inhibitors using a lysine template, J Enzyme Inhib Med Chem 17, 175-82.

Drachenberg, C. B., Papadimitriou, J. C., Wali, R., Nogueira, J., Mendley, S., Hirsch, H. H., Cangro, C. B., Klassen, D. K., Weir, M. R., Bartlett, S. T., and Ramos, E. (2004). Improved outcome of polyoma virus allograft nephropathy with early biopsy, Transplant Proc 36, 758-9.

Drewe, J. (2003). [Desired effects and adverse effects of cannabis use], Ther Umsch 60, 313-6.

Drewe, J., Ball, H. A., Beglinger, C., Peng, B., Kemmler, A., Schachinger, H., and Haefeli, W. E. (2000a). Effect of P-glycoprotein modulation on the clinical pharmacokinetics and adverse effects of morphine, Br J Clin Pharmacol 50, 237-46.

Drewe, J., Beglinger, C., and Fricker, G. (2001). Effect of ischemia on intestinal permeability of lipopolysaccharides, Eur J Clin Invest 31, 138-44.

Drewe, J., Delco, F., Kissel, T., and Beglinger, C. (2003). Effect of intravenous infusions of thiamine on the disposition kinetics of thiamine and its pyrophosphate, J Clin Pharm Ther 28, 47-51.

Drewe, J., and Krahenbuhl, S. (2000). [Clinical pharmacology: proteins for the transport of drugs], Schweiz Med Wochenschr 130, 727-31.

Drewe, J., Narjes, H., Heinzel, G., Brickl, R. S., Rohr, A., and Beglinger, C. (2000b). Absorption of lefradafiban from different sites of the gastrointestinal tract, Br J Clin Pharmacol 50, 69-72.

Driamov, S., Bellahcene, M., Ziegler, A., Barbosa, V., Traub, D., Butz, S., Buser, P. T., and Zaugg, C. E. (2004). Antiarrhythmic effect of ischemic preconditioning during low-flow ischemia. The role of bradykinin and sarcolemmal versus mitochondrial ATP-sensitive K( ) channels, Basic Res Cardiol 99, 299-308. Epub 2004 Mar 2.

Dubbers, A., Wurthwein, G., Muller, H. J., Schulze-Westhoff, P., Winkelhorst, M., Kurzknabe, E., Lanvers, C., Pieters, R., Kaspers, G. J., Creutzig, U., Ritter, J., and Boos, J. (2000). Asparagine synthetase activity in paediatric acute leukaemias: AML-M5 subtype shows lowest activity, Br J Haematol 109, 427-9.

Duber, S., Engel, H., Rolink, A., Kretschmer, K., and Weiss, S. (2003). Germline transcripts of immunoglobulin light chain variable regions are structurally diverse and differentially expressed, Mol Immunol 40, 509-16.

Ducreux, S., Zorzato, F., Muller, C. R., Sewry, C., Muntoni, F., Quinlivan, R., Restagno, G., Girard, T., and Treves, S. (2004). Effect of ryanodine receptor mutations on IL-6 release and intracellular calcium homeostasis in human myotubes from malignant hyperthermia susceptible individuals and patients affected by central core disease, J Biol Chem 8, 8.

Dukes, K. A., Sullivan, L. M., Lewis, D., Johnson, K. L., Bianchi, D. W., Simpson, J. L., Holzgreve, W., Hahn, S., Bischoff, F. Z., and Jackson, L. G. (2004). The effect of the elapsed time between blood draw and processing on the recovery of fetal cells from maternal blood, J Soc Gynecol Investig 11, 154-65.

Duong, F. H., Filipowicz, M., Tripodi, M., La Monica, N., and Heim, M. H. (2004). Hepatitis C virus inhibits interferon signaling through up-regulation of protein phosphatase 2A, Gastroenterology 126, 263-77.

Duthey, B., Caudron, S., Perroy, J., Bettler, B., Fagni, L., Pin, J. P., and Prezeau, L. (2002). A single subunit (GB2) is required for G-protein activation by the heterodimeric GABA(B) receptor, J Biol Chem 277, 3236-41. Epub 2001 Nov 15.

Eberle, A. N., Bodi, J., Orosz, G., Suli-Vargha, H., Jaggin, V., and Zumsteg, U. (2001). Antagonist and agonist activities of the mouse agouti protein fragment (91-131) at the melanocortin-1 receptor, J Recept Signal Transduct Res 21, 25-45.

Eberle, A. N., and Froidevaux, S. (2003). Radiolabeled alpha-melanocyte-stimulating hormone analogs for receptor-mediated targeting of melanoma: from tritium to indium, J Mol Recognit 16, 248-54.

Echchannaoui, H., Frei, K., Schnell, C., Leib, S. L., Zimmerli, W., and Landmann, R. (2002). Toll-like receptor 2-deficient mice are highly susceptible to Streptococcus pneumoniae meningitis because of reduced bacterial clearing and enhanced inflammation, J Infect Dis 186, 798-806. Epub 2002 Aug 16.

Egan, R. A., Pless, M., and Shults, W. T. (2001). Monocular blindness as a complication of trigeminal radiofrequency rhizotomy, Am J Ophthalmol 131, 237-40.

Eggenberger, E. R., Desai, N. P., Kaufman, D. I., and Pless, M. (2000). Internuclear ophthalmoplegia after coronary artery catheterization and percutaneous transluminal coronary balloon angioplasty, J Neuroophthalmol 20, 123-6.

Egger, D., and Bienz, K. (2002). Recombination of poliovirus RNA proceeds in mixed replication complexes originating from distinct replication start sites, J Virol 76, 10960-71.

Egger, D., Teterina, N., Ehrenfeld, E., and Bienz, K. (2000). Formation of the poliovirus replication complex requires coupled viral translation, vesicle production, and viral RNA synthesis, J Virol 74, 6570-80.

Egger, D., Wolk, B., Gosert, R., Bianchi, L., Blum, H. E., Moradpour, D., and Bienz, K. (2002). Expression of hepatitis C virus proteins induces distinct membrane alterations including a candidate viral replication complex, J Virol 76, 5974-84.

Egger, S. S., Drewe, J., and Schlienger, R. G. (2003). Potential drug-drug interactions in the medication of medical patients at hospital discharge, Eur J Clin Pharmacol 58, 773-8.

Eickelberg, O., Pansky, A., Koehler, E., Bihl, M., Tamm, M., Hildebrand, P., Perruchoud, A. P., Kashgarian, M., and Roth, M. (2001). Molecular mechanisms of TGF-(beta) antagonism by interferon (gamma) and cyclosporine A in lung fibroblasts, Faseb J 15, 797-806.

Eickelberg, O., Roth, M., and Block, L. H. (1997). Effects of amlodipine on gene expression and extracellular matrix formation in human vascular smooth muscle cells and fibroblasts: implications for vascular protection, Int J Cardiol 62, S31-7.

Eickelberg, O., Roth, M., and Perruchoud, A. P. (1998). [Matrix metalloproteases and their inhibitors in the pleura], Pneumologie 52, 526-30.

Eisterer, W., Bechter, O., Hilbe, W., van Driel, M., Lokhorst, H. M., Thaler, J., Bloem, A. C., Gunthert, U., and Stauder, R. (2001). CD44 isoforms are differentially regulated in plasma cell dyscrasias and CD44v9 represents a new independent prognostic parameter in multiple myeloma, Leuk Res 25, 1051-7.

Eisterer, W., Bechter, O., Soderberg, O., Nilsson, K., Terol, M., Greil, R., Thaler, J., Herold, M., Finke, L., Gunthert, U., Montserrat, E., and Stauder, R. (2004). Elevated levels of soluble CD44 are associated with advanced disease and in vitro proliferation of neoplastic lymphocytes in B-cell chronic lymphocytic leukaemia, Leuk Res 28, 1043-51.

Elliott, M. A., Becker, C., Boucart, M., and Muller, H. J. (2000a). Enhanced GABA(A) inhibition enhances synchrony coding in human perception, Neuroreport 11, 3403-7.

Elliott, M. A., Herrmann, C. S., Mecklinger, A., and Muller, H. J. (2000b). The loci of oscillatory visual-object priming: a combined electroencephalographic and reaction-time study, Int J Psychophysiol 38, 225-41.

Elliott, M. A., and Muller, H. J. (2000). Evidence for 40-Hz oscillatory short-term visual memory revealed by human reaction-time measurements, J Exp Psychol Learn Mem Cogn 26, 703-18.

Elzi, L., Decker, M., Battegay, M., Rutishauser, J., and Blum, J. (2004). Chest pain after travel to the tropics, Lancet 363, 1198.

Empl, M., Renaud, S., Erne, B., Fuhr, P., Straube, A., Schaeren-Wiemers, N., and Steck, A. J. (2001). TNF-alpha expression in painful and nonpainful neuropathies, Neurology 56, 1371-7.

Engelter, S. T., Lyrer, P. A., Kirsch, E. C., and Steck, A. J. (2000). Long-term follow-up after extracranial internal carotid artery dissection, Eur Neurol 44, 199-204.

Engelter, S. T., Rueegg, S., Kirsch, E. C., Fluri, F., Probst, A., Steck, A. J., and Lyrer, P. A. (2002). CADASIL mimicking primary angiitis of the central nervous system, Arch Neurol 59, 1480-3.

Engelter, S. T., Wetzel, S. G., Radue, E. W., Rausch, M., Steck, A. J., and Lyrer, P. A. (2004). The clinical significance of diffusion-weighted MR imaging in infratentorial strokes, Neurology 62, 574-80.

Eppenberger-Castori, S., Kueng, W., Benz, C., Caduff, R., Varga, Z., Bannwart, F., Fink, D., Dieterich, H., Hohl, M., Muller, H., Paris, K., Schoumacher, F., and Eppenberger, U. (2001). Prognostic and predictive significance of ErbB-2 breast tumor levels measured by enzyme immunoassay, J Clin Oncol 19, 645-56.

Eppenberger-Castori, S., Moore, D. H., Jr., Thor, A. D., Edgerton, S. M., Kueng, W., Eppenberger, U., and Benz, C. C. (2002). Age-associated biomarker profiles of human breast cancer, Int J Biochem Cell Biol 34, 1318-30.

Erb, M., Steck, A. J., Nave, K. A., and Schaeren-Wiemers, N. (2003). Differential expression of L- and S-MAG upon cAMP stimulated differentiation in oligodendroglial cells, J Neurosci Res 71, 326-37.

Erb, P., Battegay, M., Zimmerli, W., Rickenbach, M., and Egger, M. (2000a). Effect of antiretroviral therapy on viral load, CD4 cell count, and progression to acquired immunodeficiency syndrome in a community human immunodeficiency virus-infected cohort. Swiss HIV Cohort Study, Arch Intern Med 160, 1134-40.

Erb, S., Ferracin, F., Fuhr, P., Rosler, K. M., Hess, C. W., Kuntzer, T., Bogousslavsky, J., Sztajzel, R., and Steck, A. J. (2000b). Polyneuropathy attributes: a comparison between patients with anti-MAG and anti-sulfatide antibodies, J Neurol 247, 767-72.

Eriksson, U., Duc, G., Froesch, E. R., and Zapf, J. (1993). Insulin-like growth factors (IGF) I and II and IGF binding proteins (IGFBPs) in human colostrum/transitory milk during the first week postpartum: comparison with neonatal and maternal serum, Biochem Biophys Res Commun 196, 267-73.

Eriksson, U., Kurrer, M. O., Bingisser, R., Eugster, H. P., Saremaslani, P., Follath, F., Marsch, S., and Widmer, U. (2001a). Lethal autoimmune myocarditis in interferon-gamma receptor-deficient mice: enhanced disease severity by impaired inducible nitric oxide synthase induction, Circulation 103, 18-21.

Eriksson, U., Kurrer, M. O., Schmitz, N., Marsch, S. C., Fontana, A., Eugster, H. P., and Kopf, M. (2003a). Interleukin-6-deficient mice resist development of autoimmune myocarditis associated with impaired upregulation of complement C3, Circulation 107, 320-5.

Eriksson, U., Kurrer, M. O., Sebald, W., Brombacher, F., and Kopf, M. (2001b). Dual role of the IL-12/IFN-gamma axis in the development of autoimmune myocarditis: induction by IL-12 and protection by IFN-gamma, J Immunol 167, 5464-9.

Eriksson, U., Kurrer, M. O., Sonderegger, I., Iezzi, G., Tafuri, A., Hunziker, L., Suzuki, S., Bachmaier, K., Bingisser, R. M., Penninger, J. M., and Kopf, M. (2003b). Activation of dendritic cells through the interleukin 1 receptor 1 is critical for the induction of autoimmune myocarditis, J Exp Med 197, 323-31.

Eriksson, U., Seifert, B., and Schaffner, A. (2001c). Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial, Bmj 322, 579-82.

Erne, B., Sansano, S., Frank, M., and Schaeren-Wiemers, N. (2002). Rafts in adult peripheral nerve myelin contain major structural myelin proteins and myelin and lymphocyte protein (MAL) and CD59 as specific markers, J Neurochem 82, 550-62.

Erne, P., Jamshidi, P., Hafner, H.-P., Thum, P., Resink, T. (2004). Brachytherapy: Potential therapy for refractory coronary Spasm., J Amer Col Cardiol (in press).

Esser, C., Temchura, V., Majora, M., Hundeiker, C., Schwarzler, C., and Gunthert, U. (2004). Signaling via the AHR leads to enhanced usage of CD44v10 by murine fetal thymic emigrants: possible role for CD44 in emigration, Int Immunopharmacol 4, 805-18.

Esslinger, C., Chapatte, L., Finke, D., Miconnet, I., Guillaume, P., Levy, F., and MacDonald, H. R. (2003). In vivo administration of a lentiviral vaccine targets DCs and induces efficient CD8( ) T cell responses, J Clin Invest 111, 1673-81.

Estevez, M., Chu, C., and Pless, M. (2002). Small B-cell lymphoma presenting as diffuse dural thickening with cranial neuropathies, J Neurooncol 59, 243-7.

Exer, P., Staub, J. J., Zulewski, H., Muller, B., Kunz, M., and Huber, P. (1992). [Evaluation of TSH suppression using a 3d-generation TSH assay: diagnostic and therapeutic consequences], Schweiz Med Wochenschr 122, 1964-7.

Fagard, C., Le Braz, M., Gunthard, H., Hirsch, H. H., Egger, M., Vernazza, P., Bernasconi, E., Telenti, A., Ebnother, C., Oxenius, A., Perneger, T., Perrin, L., and Hirschel, B. (2003a). A controlled trial of granulocyte macrophage-colony stimulating factor during interruption of HAART, Aids 17, 1487-92.

Fagard, C., Oxenius, A., Gunthard, H., Garcia, F., Le Braz, M., Mestre, G., Battegay, M., Furrer, H., Vernazza, P., Bernasconi, E., Telenti, A., Weber, R., Leduc, D., Yerly, S., Price, D., Dawson, S. J., Klimkait, T., Perneger, T. V., McLean, A., Clotet, B., Gatell, J. M., Perrin, L., Plana, M., Phillips, R., and Hirschel, B. (2003b). A prospective trial of structured treatment interruptions in human immunodeficiency virus infection, Arch Intern Med 163, 1220-6.

Fassas, A., Passweg, J. R., Anagnostopoulos, A., Kazis, A., Kozak, T., Havrdova, E., Carreras, E., Graus, F., Kashyap, A., Openshaw, H., Schipperus, M., Deconinck, E., Mancardi, G., Marmont, A., Hansz, J., Rabusin, M., Zuazu Nagore, F. J., Besalduch, J., Dentamaro, T., Fouillard, L., Hertenstein, B., La Nasa, G., Musso, M., Papineschi, F., Rowe, J. M., Saccardi, R., Steck, A., Kappos, L., Gratwohl, A., Tyndall, A., Samijn, J., and Samign, J. (2002). Hematopoietic stem cell transplantation for multiple sclerosis. A retrospective multicenter study, J Neurol 249, 1088-97.

Fassbender, K., Walter, S., Kuhl, S., Landmann, R., Ishii, K., Bertsch, T., Stalder, A. K., Muehlhauser, F., Liu, Y., Ulmer, A. J., Rivest, S., Lentschat, A., Gulbins, E., Jucker, M., Staufenbiel, M., Brechtel, K., Walter, J., Multhaup, G., Penke, B., Adachi, Y., Hartmann, T., and Beyreuther, K. (2004). The LPS receptor (CD14) links innate immunity with Alzheimer s disease, Faseb J 18, 203-5. Epub 2003 Nov 3.

Feinle-Bisset, C., Meier, B., Fried, M., and Beglinger, C. (2003). Role of cognitive factors in symptom induction following high and low fat meals in patients with functional dyspepsia, Gut 52, 1414-8.

Felger, I., Steiger, S., Hatz, C., Smith, T., and Beck, H. P. (2003). Antigenic cross-reactivity between different alleles of the Plasmodium falciparum merozoite surface protein 2, Parasite Immunol 25, 531-43.

Felix, K., Rolink, A., Melchers, F., and Janz, S. (2003). Bcl-2 reduces mutant rates in a transgenic lacZ reporter gene in mouse pre-B lymphocytes, Mutat Res 522, 135-44.

Fellay, J., Boubaker, K., Ledergerber, B., Bernasconi, E., Furrer, H., Battegay, M., Hirschel, B., Vernazza, P., Francioli, P., Greub, G., Flepp, M., and Telenti, A. (2001). Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study, Lancet 358, 1322-7.

Felley, C., Morris, M. A., Wonkam, A., Hirschel, B., Flepp, M., Wolf, K., Furrer, H., Battegay, M., Bernasconi, E., Telenti, A., and Frossard, J. L. (2004). The role of CFTR and SPINK-1 mutations in pancreatic disorders in HIV-positive patients: a case-control study, Aids 18, 1521-1527.

Feng, J., Tamaskovic, R., Yang, Z., Brazil, D. P., Merlo, A., Hess, D., and Hemmings, B. A. (2004). Stabilization of Mdm2 via decreased ubiquitination is mediated by protein kinase B/Akt-dependent phosphorylation, J Biol Chem 28, 28.

Feuerstein, T. H., Langemann, H., Gratzl, O., and Mendelowitsch, A. (2000). A four lumen screwing device for multiparametric brain monitoring, Acta Neurochir (Wien) 142, 909-12.

Filipovic, M., Jeger, R., Probst, C., Girard, T., Pfisterer, M., Gurke, L., Skarvan, K., and Seeberger, M. D. (2003). Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease, J Am Coll Cardiol 42, 1767-76.

Filipovic, M., Seeberger, M. D., Rohlfs, R., Dergeloo, O., Studer, W., Atar, D., Buser, P., and Skarvan, K. (2002). Doppler indices of diastolic transmitral flow velocity are invalid indicators of myocardial ischaemia during high-dose dobutamine infusion in anaesthetized patients, Eur J Anaesthesiol 19, 789-95.

Finke, D., and Acha-Orbea, H. (2001). Differential migration of in vivo primed B and T lymphocytes to lymphoid and non-lymphoid organs, Eur J Immunol 31, 2603-11.

Finke, D., Acha-Orbea, H., Mattis, A., Lipp, M., and Kraehenbuhl, J. (2002). CD4 CD3- cells induce Peyer's patch development: role of alpha4beta1 integrin activation by CXCR5, Immunity 17, 363-73.

Finke, D., Baribaud, F., Diggelmann, H., and Acha-Orbea, H. (2001). Extrafollicular plasmablast B cells play a key role in carrying retroviral infection to peripheral organs, J Immunol 166, 6266-75.

Finke, D., and Kraehenbuhl, J. P. (2001). Formation of Peyer s patches, Curr Opin Genet Dev 11, 561-7.

Finke, D., Luther, S. A., and Acha-Orbea, H. (2003). The role of neutralizing antibodies for mouse mammary tumor virus transmission and mammary cancer development, Proc Natl Acad Sci U S A 100, 199-204. Epub 2002 Dec 26.

Finke, D. a. A.-O., H. (2001). Immune response to murine and feline retroviruses, Retroviral Immunology, Eds G Pantaleo & B D Walker, Humana Press, New York, NY, 125-157.

Fisher, R. S., Thistle, J., Lembo, A., Novick, J., O'Kane, P., Chey, W. D., Beglinger, C., Rueegg, P., Shi, V., Dogra, A., Luo, D., and Earnest, D. L. (2004). Tegaserod Does not Alter Fasting or Meal-Induced Biliary Tract Motility, Am J Gastroenterol 99, 1342-9.

Flammer, J., Pache, M., and Resink, T. (2001). Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye, Prog Retin Eye Res 20, 319-49.

Fleck, O., and Schar, P. (2004). Translesion DNA synthesis: little fingers teach tolerance, Curr Biol 14, R389-91.

Fluckiger, U. (2001). [What is the optimal treatment duration of group A streptococcal pharyngitis?], Hno 49, 253-5.

Fluckiger, U., Zimmerli, W., Sax, H., Frei, R., and Widmer, A. F. (2000). Clinical impact of an infectious disease service on the management of bloodstream infection, Eur J Clin Microbiol Infect Dis 19, 493-500.

Flugel, A., Matsumuro, K., Neumann, H., Klinkert, W. E., Birnbacher, R., Lassmann, H., Otten, U., and Wekerle, H. (2001). Anti-inflammatory activity of nerve growth factor in experimental autoimmune encephalomyelitis: inhibition of monocyte transendothelial migration, Eur J Immunol 31, 11-22.

Fluri, F., Ferracin, F., Erne, B., and Steck, A. J. (2003). Microheterogeneity of anti-myelin-associated glycoprotein antibodies, J Neurol Sci 207, 43-9.

Folster-Holst, R., Rufli, T., and Christophers, E. (2000). [Treatment of scabies with special consideration of the approach in infancy, pregnancy and while nursing], Hautarzt 51, 7-13.

Found, A., and Muller, H. J. (2001). Efficient search for size targets on a background texture gradient: is detection guided by discontinuities in the retinal-size gradient of items?, Perception 30, 21-48.

Frank, O., Heim, M., Jakob, M., Barbero, A., Schafer, D., Bendik, I., Dick, W., Heberer, M., and Martin, I. (2002). Real-time quantitative RT-PCR analysis of human bone marrow stromal cells during osteogenic differentiation in vitro, J Cell Biochem 85, 737-46.

Franz, S. E., Buylaert, M. A., Moll, S., and Schifferli, J. A. (2003). A well-meant present from a friend, Nephrol Dial Transplant 18, 613-4.

Freeman, J. A., Thompson, A. J., Fitzpatrick, R., Hutchinson, M., Miltenburger, C., Beckmann, K., Dahlke, F., Kappos, L., Polman, C., and Pozzilli, C. (2001). Interferon-beta1b in the treatment of secondary progressive MS: impact on quality of life, Neurology 57, 1870-5.

Freiermuth, O., Todorov, A., Bolli, M., and Heberer, M. (2003). [Swiss surgery: quo vadis? Reader and market analysis for strategic positioning of a specialty journal], Swiss Surg 9, 43-53.

Freitag, P., Kappos, L., Radue, E.W. (2000). [Value of MRI in diagnosis and monitoring of disease in multiple sclerosis]. Schw Arch Neurol Psychiat 151/2: 47-56.

Fremeaux-Bacchi, V., Noel, L. H., and Schifferli, J. A. (2002). No lupus nephritis in the absence of antiC1q autoantibodies?, Nephrol Dial Transplant 17, 2041-3.

Freudenthaler, S. M., Lucht, I., Schenk, T., Brink, M., and Gleiter, C. H. (2000). Dose-dependent effect of angiotensin II on human erythropoietin production, Pflugers Arch 439, 838-44.

Frigerio, S., Hollander, G. A., and Zumsteg, U. (2002a). Functional IL-18 Is produced by primary pancreatic mouse islets and NIT-1 beta cells and participates in the progression towards destructive insulitis, Horm Res 57, 94-104.

Frigerio, S., Junt, T., Lu, B., Gerard, C., Zumsteg, U., Hollander, G. A., and Piali, L. (2002b). Beta cells are responsible for CXCR3-mediated T-cell infiltration in insulitis, Nat Med 8, 1414-20.

Fritsche, G., Nitsch, C., Pietrowsky, R., and Diener, H. C. (2000). [Psychological descriptors of excessive use of analgesic medication], Schmerz 14, 217-25.

Fritschy, J. M., Sidler, C., Parpan, F., Gassmann, M., Kaupmann, K., Bettler, B., and Benke, D. (2004). Independent maturation of the GABA(B) receptor subunits GABA(B1) and GABA(B2) during postnatal development in rodent brain, J Comp Neurol 477, 235-52.

Froestl, W., Bettler, B., Bittiger, H., Heid, J., Kaupmann, K., Mickel, S. J., and Strub, D. (2001). Ligands for expression cloning and isolation of GABA(B) receptors, Farmaco 56, 101-5.

Froestl, W., Bettler, B., Bittiger, H., Heid, J., Kaupmann, K., Mickel, S. J., and Strub, D. (2003). Ligands for expression cloning and isolation of GABA(B) receptors, Farmaco 58, 173-83.

Froidevaux, S., Calame-Christe, M., Schuhmacher, J., Tanner, H., Saffrich, R., Henze, M., and Eberle, A. N. (2004). A gallium-labeled DOTA-alpha-melanocyte- stimulating hormone analog for PET imaging of melanoma metastases, J Nucl Med 45, 116-23.

Froidevaux, S., Calame-Christe, M., Sumanovski, L., Tanner, H., and Eberle, A. N. (2003). DOTA alpha-melanocyte-stimulating hormone analogues for imaging metastatic melanoma lesions, Ann N Y Acad Sci 994, 378-83.

Froidevaux, S., Calame-Christe, M., Tanner, H., Sumanovski, L., and Eberle, A. N. (2002a). A novel DOTA-alpha-melanocyte-stimulating hormone analog for metastatic melanoma diagnosis, J Nucl Med 43, 1699-706.

Froidevaux, S., and Eberle, A. N. (2002a). Homologous regulation of melanocortin-1 receptor (MC1R) expression in melanoma tumor cells in vivo, J Recept Signal Transduct Res 22, 111-21.

Froidevaux, S., and Eberle, A. N. (2002b). Somatostatin analogs and radiopeptides in cancer therapy, Biopolymers 66, 161-83.

Froidevaux, S., Eberle, A. N., Christe, M., Sumanovski, L., Heppeler, A., Schmitt, J. S., Eisenwiener, K., Beglinger, C., and Macke, H. R. (2002b). Neuroendocrine tumor targeting: study of novel gallium-labeled somatostatin radiopeptides in a rat pancreatic tumor model, Int J Cancer 98, 930-7.

Froidevaux, S., Heppeler, A., Eberle, A. N., Meier, A. M., Hausler, M., Beglinger, C., Behe, M., Powell, P., and Macke, H. R. (2000). Preclinical comparison in AR4-2J tumor-bearing mice of four radiolabeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-somatostatin analogs for tumor diagnosis and internal radiotherapy, Endocrinology 141, 3304-12.

Fuhr, P., Borggrefe-Chappuis, A., Schindler, C., and Kappos, L. (2001). Visual and motor evoked potentials in the course of multiple sclerosis, Brain 124, 2162-8.

Fuhr, P., and Kappos, L. (2001). Evoked potentials for evaluation of multiple sclerosis, Clin Neurophysiol 112, 2185-9.

Fuhr, P., and Leppert, D. (2000). Neuroimages. Cardiac arrest during partial seizure, Neurology 54, 2026.

Furrer, H., Battegay, M., Spirig, R., and Flepp, M. (2003). [Challenges in HIV long-term care], Dtsch Med Wochenschr 128, 1064-9.

Furtinger, S., Bettler, B., and Sperk, G. (2003). Altered expression of GABAB receptors in the hippocampus after kainic-acid-induced seizures in rats, Brain Res Mol Brain Res 113, 107-15.

Gajendran, N., Frey, J. R., Lefkovits, I., Kuhn, L., Fountoulakis, M., Krapfenbauer, K., and Brenner, H. R. (2002). Proteomic analysis of secreted muscle components: Search for factors involved in neuromuscular synapse formation, Proteomics 2, 1601-15.

Galbiati, F., Polastri, L., Gregori, S., Freschi, M., Casorati, M., Cavallaro, U., Fiorina, P., Bertuzzi, F., Zerbi, A., Pozza, G., Adorini, L., Folli, F., Christofori, G., and Davalli, A. M. (2002). Antitumorigenic and antiinsulinogenic effects of calcitriol on insulinoma cells and solid beta-cell tumors, Endocrinology 143, 4018-30.

Galbiati, F., Polastri, L., Thorens, B., Dupraz, P., Fiorina, P., Cavallaro, U., Christofori, G., and Davalli, A. M. (2003). Molecular pathways involved in the antineoplastic effects of calcitriol on insulinoma cells, Endocrinology 144, 1832-41.

Galli, A., Roure, A., Zeller, R., and Dono, R. (2003). Glypican 4 modulates FGF signalling and regulates dorsoventral forebrain patterning in Xenopus embryos, Development 130, 4919-29. Epub 2003 Aug 20.

Galvez, T., Duthey, B., Kniazeff, J., Blahos, J., Rovelli, G., Bettler, B., Prezeau, L., and Pin, J. P. (2001). Allosteric interactions between GB1 and GB2 subunits are required for optimal GABA(B) receptor function, Embo J 20, 2152-9.

Galvez, T., Prezeau, L., Milioti, G., Franek, M., Joly, C., Froestl, W., Bettler, B., Bertrand, H. O., Blahos, J., and Pin, J. P. (2000a). Mapping the agonist-binding site of GABAB type 1 subunit sheds light on the activation process of GABAB receptors, J Biol Chem 275, 41166-74.

Galvez, T., Urwyler, S., Prezeau, L., Mosbacher, J., Joly, C., Malitschek, B., Heid, J., Brabet, I., Froestl, W., Bettler, B., Kaupmann, K., and Pin, J. P. (2000b). Ca(2) requirement for high-affinity gamma-aminobutyric acid (GABA) binding at GABA(B) receptors: involvement of serine 269 of the GABA(B)R1 subunit, Mol Pharmacol 57, 419-26.

Gannon, G., Mandriota, S. J., Cui, L., Baetens, D., Pepper, M. S., and Christofori, G. (2002). Overexpression of vascular endothelial growth factor-A165 enhances tumor angiogenesis but not metastasis during beta-cell carcinogenesis, Cancer Res 62, 603-8.

Gasser, O., Hess, C., Miot, S., Deon, C., Sanchez, J. C., and Schifferli, J. A. (2003). Characterisation and properties of ectosomes released by human polymorphonuclear neutrophils, Exp Cell Res 285, 243-57.

Gasser, O. S., and Schifferli, J. A. (2004). Activated Polymorphonuclear Neutrophils disseminate Anti-inflammatory Microparticles by Ectocytosis, Blood 22, 22.

Gassmann, M., Shaban, H., Vigot, R., Sansig, G., Haller, C., Barbieri, S., Humeau, Y., Schuler, V., Muller, M., Kinzel, B., Klebs, K., Schmutz, M., Froestl, W., Heid, J., Kelly, P. H., Gentry, C., Jaton, A. L., Van der Putten, H., Mombereau, C., Lecourtier, L., Mosbacher, J., Cryan, J. F., Fritschy, J. M., Luthi, A., Kaupmann, K., and Bettler, B. (2004). Redistribution of GABAB(1) protein and atypical GABAB responses in GABAB(2)-deficient mice, J Neurosci 24, 6086-97.

Gatti, E., Velleca, M. A., Biedermann, B. C., Ma, W., Unternaehrer, J., Ebersold, M. W., Medzhitov, R., Pober, J. S., and Mellman, I. (2000). Large-scale culture and selective maturation of human Langerhans cells from granulocyte colony-stimulating factor-mobilized CD34 progenitors, J Immunol 164, 3600-7.

Gencay, M., and Roth, M. (2003). Chlamydia pneumoniae infections in asthma: clinical implications, Am J Respir Med 2, 31-8.

Gencay, M., Rudiger, J. J., Tamm, M., Soler, M., Perruchoud, A. P., and Roth, M. (2001). Increased frequency of Chlamydia pneumoniae antibodies in patients with asthma, Am J Respir Crit Care Med 163, 1097-100.

Gencay, M. M., Tamm, M., Glanville, A., Perruchoud, A. P., and Roth, M. (2003). Chlamydia pneumoniae activates epithelial cell proliferation via NF-kappaB and the glucocorticoid receptor, Infect Immun 71, 5814-22.

Georgiadis, D., Berger, A., Kowatschev, E., Lautenschlager, C., Borner, A., Lindner, A., Schulte-Mattler, W., Zerkowski, H. R., Zierz, S., and Deufel, T. (2000). Predictive value of S-100beta and neuron-specific enolase serum levels for adverse neurologic outcome after cardiac surgery, J Thorac Cardiovasc Surg 119, 138-47.

Georgiadis, D., Braun, S., Uhlmann, F., Bernacca, G. M., Schulte-Mattler, W. J., Zierz, S., and Zerkowski, H. R. (2001). Doppler microembolic signals in patients with two different types of bileaflet valves, J Thorac Cardiovasc Surg 121, 1101-6.

Georgiadis, D., Hempel, A., Baumgartner, R. W., and Zerkowski, H. R. (2003). Doppler microembolic signals during cardiac surgery: comparison between arterial line and middle cerebral artery, J Thorac Cardiovasc Surg 126, 1638-9.

Georgiadis, D., Stets, R., Schorch, A., Baumgartner, R. W., Bernet, F., and Zerkowski, H. R. (2004). Doppler microembolic signals during cardiopulmonary bypass: comparison of two membrane oxygenators, Neurol Res 26, 99-102.

Gherzi, R., Lee, K. Y., Briata, P., Wegmuller, D., Moroni, C., Karin, M., and Chen, C. Y. (2004). A KH domain RNA binding protein, KSRP, promotes ARE-directed mRNA turnover by recruiting the degradation machinery, Mol Cell 14, 571-83.

Ghia, P., Melchers, F., and Rolink, A. G. (2000). Age-dependent changes in B lymphocyte development in man and mouse, Exp Gerontol 35, 159-65.

Ghia, P., Transidico, P., Veiga, J. P., Schaniel, C., Sallusto, F., Matsushima, K., Sallan, S. E., Rolink, A. G., Mantovani, A., Nadler, L. M., and Cardoso, A. A. (2001). Chemoattractants MDC and TARC are secreted by malignant B-cell precursors following CD40 ligation and support the migration of leukemia-specific T cells, Blood 98, 533-40.

Gierens, H., Nauck, M., Roth, M., Schinker, R., Schurmann, C., Scharnagl, H., Neuhaus, G., Wieland, H., and Marz, W. (2000). Interleukin-6 stimulates LDL receptor gene expression via activation of sterol-responsive and Sp1 binding elements, Arterioscler Thromb Vasc Biol 20, 1777-83.

Gieselmann, V., Franken, S., Klein, D., Mansson, J. E., Sandhoff, R., Lullmann Rauch, R., Hartmann, D., Saravanan, V. P., De Deyn, P. P., D'Hooge, R., Van Der Linden, A. M., and Schaeren-Wiemers, N. (2003). Metachromatic leukodystrophy: consequences of sulphatide accumulation, Acta Paediatr Suppl 92, 74-9; discussion 45.

Gijsens, A., Derycke, A., Missiaen, L., De Vos, D., Huwyler, J., Eberle, A., and de Witte, P. (2002). Targeting of the photocytotoxic compound AlPcS4 to Hela cells by transferrin conjugated PEG-liposomes, Int J Cancer 101, 78-85.

Gill, J., Malin, M., Hollander, G. A., and Boyd, R. (2002). Generation of a complete thymic microenvironment by MTS24( ) thymic epithelial cells, Nat Immunol 3, 635-42.

Gilleron, M., Stenger, S., Mazorra, Z., Wittke, F., Mariotti, S., Bohmer, G., Prandi, J., Mori, L., Puzo, G., and De Libero, G. (2004). Diacylated Sulfoglycolipids Are Novel Mycobacterial Antigens Stimulating CD1-restricted T Cells during Infection with Mycobacterium tuberculosis, J Exp Med 199, 649-659. Epub 2004 Feb 23.

Gilli, F., Bertolotto, A., Sala, A., Hoffmann, F., Capobianco, M., Malucchi, S., Glass, T., Kappos, L., Lindberg, R. L., and Leppert, D. (2004). Neutralizing antibodies against IFN-beta in multiple sclerosis: antagonization of IFN-beta mediated suppression of MMPs, Brain 127, 259-68. Epub 2003 Nov 7.

Ginz, H. F., Girard, T., Censier, K., and Urwyler, A. (2004). Similar susceptibility to halothane, caffeine and ryanodine in vitro reflects pharmacogenetic variability of malignant hyperthermia, Eur J Anaesthesiol 21, 151-7.

Ginz, H. F., Ummenhofer, W. C., Erb, T., and Urwyler, A. (2001). [The hereditary motor-sensory neuropathy Charcot-Marie-Tooth disease: anesthesiologic management--case report with literature review], Anaesthesist 50, 767-71.

Girard, T., Bally, S., Langer, I., and Schurch, M. (2003). Diagnosis of malignant hyperthermia susceptibility during CABG surgery, Acta Anaesthesiol Scand 47, 233-5.

Girard, T., Cavagna, D., Padovan, E., Spagnoli, G., Urwyler, A., Zorzato, F., and Treves, S. (2001a). B-lymphocytes from malignant hyperthermia-susceptible patients have an increased sensitivity to skeletal muscle ryanodine receptor activators, J Biol Chem 276, 48077-82.

Girard, T., and Filipovic, M. (2004). From the echocardiography machine to the lecture room: a simple method for transferring echocardiographic frames and loops to a personal computer, Anesth Analg 98, 703-5, table of contents.

Girard, T., Treves, S., Censier, K., Mueller, C. R., Zorzato, F., and Urwyler, A. (2002). Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells, Br J Anaesth 89, 571-9.

Girard, T., Treves, S., Voronkov, E., Siegemund, M., and Urwyler, A. (2004). Molecular genetic testing for malignant hyperthermia susceptibility, Anesthesiology 100, 1076-80.

Girard, T., Urwyler, A., Censier, K., Mueller, C. R., Zorzato, F., and Treves, S. (2001b). Genotype-phenotype comparison of the Swiss malignant hyperthermia population, Hum Mutat 18, 357-8.

Giraud, S., Greco, A., Brink, M., Diaz, J. J., and Delafontaine, P. (2001). Translation initiation of the insulin-like growth factor I receptor mRNA is mediated by an internal ribosome entry site, J Biol Chem 276, 5668-75.

Glanville, A. R., Gencay, M., Tamm, M., Chhajed, P., Hopkins, P., Aboyoun, C., Adams, S., Rainer, S., Roth, M., Malouf, M. (2004). Chlamydia pneumoniae infection after lung transplantation., J Heart Lung Transplant 2004 (in press).

Gobbi, C., Buess, M., Probst, A., Ruegg, S., Schraml, P., Herrmann, R., Steck, A. J., and Dirnhofer, S. (2003). Enteropathy-associated T-cell lymphoma with initial manifestation in the CNS, Neurology 60, 1718-9.

Gober, H. J., Kistowska, M., Angman, L., Jeno, P., Mori, L., and De Libero, G. (2003). Human T cell receptor gammadelta cells recognize endogenous mevalonate metabolites in tumor cells, J Exp Med 197, 163-8.

Goedecke, J. H., Barsdorf, M., Beglinger, C., Levitt, N. S., and Lambert, E. V. (2003). Effects of a lipase inhibitor (Orlistat) on cholecystokinin and appetite in response to a high-fat meal, Int J Obes Relat Metab Disord 27, 1479-85.

Goerke, C., Fluckiger, U., Steinhuber, A., Zimmerli, W., and Wolz, C. (2001). Impact of the regulatory loci agr, sarA and sae of Staphylococcus aureus on the induction of alpha-toxin during device-related infection resolved by direct quantitative transcript analysis, Mol Microbiol 40, 1439-47.

Golubnitschaja, O., Yeghiazaryan, K., Liu, R., Monkemann, H., Leppert, D., Schild, H., Haefliger, I. O., and Flammer, J. (2004). Increased expression of matrix metalloproteinases in mononuclear blood cells of normal-tension glaucoma patients, J Glaucoma 13, 66-72.

Gonchar, Y., Pang, L., Malitschek, B., Bettler, B., and Burkhalter, A. (2001). Subcellular localization of GABA(B) receptor subunits in rat visual cortex, J Comp Neurol 431, 182-97.

Gosert, R., Kanjanahaluethai, A., Egger, D., Bienz, K., and Baker, S. C. (2001). Comparison of replicase localization in different types of mouse hepatitis virus (MHV)-infected cells, Adv Exp Med Biol 494, 275-81.

Gosert, R., Kanjanahaluethai, A., Egger, D., Bienz, K., and Baker, S. C. (2002). RNA replication of mouse hepatitis virus takes place at double-membrane vesicles, J Virol 76, 3697-708.

Grapow, M. T., Kern, T., Reineke, D. C., Brett, W., Bernet, F., Rueter, F., Muller-Schweinitzer, E., and Zerkowski, H. R. (2003a). Improved endothelial function after a modified harvesting technique of the internal thoracic artery, Eur J Cardiothorac Surg 23, 956-60; discussion 960-1.

Grapow, M. T., Matt, P., Zerkowski, H. R., and Bernet, F. (2004). Pseudoaneurysm in a marfan patient 16 years after Bentall operation, Asian Cardiovasc Thorac Ann 12, 182-3.

Grapow, M. T., Todorov, A., Bernet, F., and Zerkowski, H. R. (2003b). [Ambulatory long-term management of a left ventricular assist device. Current modality in terminal heart failure], Swiss Surg 9, 27-30.

Graumann, U., Reynolds, R., Steck, A. J., and Schaeren-Wiemers, N. (2003). Molecular changes in normal appearing white matter in multiple sclerosis are characteristic of neuroprotective mechanisms against hypoxic insult, Brain Pathol 13, 554-73.

Greiner, E. F., Kirfel, J., Greschik, H., Huang, D., Becker, P., Kapfhammer, J. P., and Schule, R. (2000). Differential ligand-dependent protein-protein interactions between nuclear receptors and a neuronal-specific cofactor, Proc Natl Acad Sci U S A 97, 7160-5.

Greub, G., Cozzi-Lepri, A., Ledergerber, B., Staszewski, S., Perrin, L., Miller, V., Francioli, P., Furrer, H., Battegay, M., Vernazza, P., Bernasconi, E., Gunthard, H. F., Hirschel, B., Phillips, A. N., and Telenti, A. (2002). Intermittent and sustained low-level HIV viral rebound in patients receiving potent antiretroviral therapy, Aids 16, 1967-9.

Greub, G., Ledergerber, B., Battegay, M., Grob, P., Perrin, L., Furrer, H., Burgisser, P., Erb, P., Boggian, K., Piffaretti, J. C., Hirschel, B., Janin, P., Francioli, P., Flepp, M., and Telenti, A. (2000). Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study, Lancet 356, 1800-5.

Grobholz, R., Verbeke, C. S., Schleger, C., Kohrmann, K. U., Hein, B., Wolf, G., Bleyl, U., Spagnoli, G. C., Coplan, K., Kolb, D., Iversen, K., and Jungbluth, A. A. (2000). Expression of MAGE antigens and analysis of the inflammatory T-cell infiltrate in human seminoma, Urol Res 28, 398-403.

Groscurth, P., Eggli, P., Kapfhammer, J., Rager, G., Hornung, J. P., and Fasel, J. D. (2001). Gross anatomy in the surgical curriculum in Switzerland: improved cadaver preservation, anatomical models, and course development, Anat Rec 265, 254-6.

Gross, T., Martinoli, S., Spagnoli, G., Badia, F., and Malacrida, R. (2001). Attitudes and behavior of young European adults towards the donation of organs--a call for better information, Am J Transplant 1, 74-81.

Grossman, R. I., Kappos, L., and Wolinsky, J. S. (2000). The contribution of magnetic resonance imaging in the differential diagnosis of the damage of the cerebral hemispheres, J Neurol Sci 172, S57-62.

Gschwandtner, U., Aston, J., Borgwardt, S., Drewe, M., Feinendegen, C., Lacher, D., Lanzarone, A., Stieglitz, R. D., and Riecher-Rossler, A. (2003). Neuropsychological and neurophysiological findings in individuals suspected to be at risk for schizophrenia: preliminary results from the Basel early detection of psychosis study – Fruherkennung von Psychosen (FEPSY), Acta Psychiatr Scand 108, 152-5.

Guex, A. C., Bucher, H. C., Demartines, N., Fluckiger, U., and Battegay, M. (2002). Inflammatory bowel perforation during immune restoration after one year of antiretroviral and antituberculous therapy in an HIV-1-infected patient: report of a case, Dis Colon Rectum 45, 977-8.

Guller, U., Zajac, P., Schnider, A., Bosch, B., Vorburger, S., Zuber, M., Spagnoli, G. C., Oertli, D., Maurer, R., Metzger, U., Harder, F., Heberer, M., and Marti, W. R. (2002). Disseminated single tumor cells as detected by real-time quantitative polymerase chain reaction represent a prognostic factor in patients undergoing surgery for colorectal cancer, Ann Surg 236, 768-75; discussion 775-6.

Gundlfinger, A., Kapfhammer, J. P., Kruse, F., Leitges, M., and Metzger, F. (2003). Different regulation of Purkinje cell dendritic development in cerebellar slice cultures by protein kinase Calpha and -beta, J Neurobiol 57, 95-109.

Guth, U., Moch, H., Herberich, L., and Holzgreve, W. (2004a). Noninflammatory breast carcinoma with skin involvement, Cancer 100, 470-8.

Guth, U., Wight, E., Moch, H., and Holzgreve, W. (2004b). Detection of minute breast cancers: a therapeutic challenge with a potential danger of overtreatment, Breast J 10, 373-4.

Gutmann, H., Bruggisser, R., Schaffner, W., Bogman, K., Botomino, A., and Drewe, J. (2002). Transport of amentoflavone across the blood-brain barrier in vitro, Planta Med 68, 804-7.

Gutmann, H., Miller, D. S., Droulle, A., Drewe, J., Fahr, A., and Fricker, G. (2000). P-glycoprotein- and mrp2-mediated octreotide transport in renal proximal tubule, Br J Pharmacol 129, 251-6.

Gutzwiller, J. P., Degen, L., Heuss, L., and Beglinger, C. (2004a). Glucagon-like peptide 1 (GLP-1) and eating, Physiol Behav 82, 17-9.

Gutzwiller, J. P., Degen, L., Matzinger, D., Prestin, S., and Beglinger, C. (2004b). Interaction between GLP-1 and CCK33 in inhibiting food intake and appetite in men, Am J Physiol Regul Integr Comp Physiol 22, 22.

Gutzwiller, J. P., Drewe, J., Ketterer, S., Hildebrand, P., Krautheim, A., and Beglinger, C. (2000). Interaction between CCK and a preload on reduction of food intake is mediated by CCK-A receptors in humans, Am J Physiol Regul Integr Comp Physiol 279, R189-95.

Gutzwiller, J. P., Tschopp, S., Bock, A., Zehnder, C. E., Huber, A. R., Kreyenbuehl, M., Gutmann, H., Drewe, J., Henzen, C., Goeke, B., and Beglinger, C. (2004c). Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men, J Clin Endocrinol Metab 89, 3055-61.

Gybels, Y., Grapow, M. T., Todorov, A., Wagner, G., and Zerkowski, H. R. (2000). Aberrant right pulmonary artery and double outlet ventricle: one-stage repair, Ann Thorac Surg 69, 630-2.

Gyr, N., Zeller, A., and Battegay, M. (2001). [The Basel Medical University Polyclinic on the brink of the 21st century: retrospective and prospective view], Schweiz Rundsch Med Prax 90, 1387-97.

Haberle, B., Hero, B., Berthold, F., and von Schweinitz, D. (2002). Characteristics and outcome of thoracic neuroblastoma, Eur J Pediatr Surg 12, 145-50.

Habicht, J. M., Matt, P., Passweg, J. R., Reichenberger, F., Gratwohl, A., Zerkowski, H. R., and Tamm, M. (2001). Invasive pulmonary fungal infection in hematologic patients: is resection effective?, Hematol J 2, 250-6.

Habicht, J. M., Passweg, J., Kuhne, T., Leibundgut, K., and Zerkowski, H. R. (2000a). Successful local excision and long-term survival for invasive pulmonary aspergillosis during neutropenia after bone marrow transplantation, J Thorac Cardiovasc Surg 119, 1286-7.

Habicht, J. M., Preiss, M., Passweg, J., Dalquen, P., Matt, P., Adler, H., Frei, R., and Zerkowski, H. R. (2002). Invasive pulmonary aspergillosis: effects of early resection in a neutropenic rat model, Eur J Cardiothorac Surg 22, 728-32.

Habicht, J. M., Scherr, P., Zerkowski, H. R., and Hoffmann, A. (2000b). Late conduction defects following aortic valve replacement, J Heart Valve Dis 9, 629-32.

Hadziselimovic, F., Fliegel, C. H., and Miny, P. (2001). A novel syndrome involving primary skeletal growth and retardation in siblings, Clin Dysmorphol 10, 33-6.

Haecker, F. M., Oertli, D., Gissler, S., Zumsteg, U., Avoledo, P., and Von Schweinitz, D. (2003). Multiple endocrine neoplasias type 2A and thyroid medullary carcinoma: an interdisciplinary challenge, Pediatr Surg Int 19, 62-4.

Haecker, F. M., Wehrmann, M., Hacker, H. W., Stuhldreier, G., and von Schweinitz, D. (2002). Renal dysplasia in children with posterior urethral valves: a primary or secondary malformation?, Pediatr Surg Int 18, 119-22.

Hahn, S., and Holzgreve, W. (2002a). Fetal cells and cell-free fetal DNA in maternal blood: new insights into pre-eclampsia, Hum Reprod Update 8, 501-8.

Hahn, S., and Holzgreve, W. (2002b). Prenatal diagnosis using fetal cells and cell-free fetal DNA in maternal blood: what is currently feasible?, Clin Obstet Gynecol 45, 649-56; discussion 730-2.

Hahn, S., Zhong, X. Y., Burk, M. R., Troeger, C., Kang, A., and Holzgreve, W. (2001). Both maternal and fetal cell-free DNA in plasma fluctuate, Ann N Y Acad Sci 945, 141-4.

Hahn, S., Zhong, X. Y., and Holzgreve, W. (2002). Single cell PCR in laser capture microscopy, Methods Enzymol 356, 295-301.

Haller, C., Casanova, E., Mueller, M., Vacher, C.-M., Vigot, R., Doll, T., Barbieri, S., Gassmann, M., Bettler, B. (2004). A floxed allele for conditional inactivation of the GABA B(1)-gene., Genesis.

Hamy, F., Brondani, V., Spoerri, R., Rigo, S., Stamm, C., and Klimkait, T. (2003). Specific block of androgen receptor activity by antisense oligonucleotides, Prostate Cancer Prostatic Dis 6, 27-33.

Hamy, F., Felder, E., Lipson, K., and Klimkait, T. (2001). Merged screening for human immunodeficiency virus Tat and Rev inhibitors, J Biomol Screen 6, 179-87.

Hamy, F., Gelus, N., Zeller, M., Lazdins, J. L., Bailly, C., and Klimkait, T. (2000). Blocking HIV replication by targeting Tat protein, Chem Biol 7, 669-76.

Hanna, N., Shepherd, F. A., Fossella, F. V., Pereira, J. R., De Marinis, F., von Pawel, J., Gatzemeier, U., Tsao, T. C., Pless, M., Muller, T., Lim, H. L., Desch, C., Szondy, K., Gervais, R., Shaharyar, Manegold, C., Paul, S., Paoletti, P., Einhorn, L., and Bunn, P. A., Jr. (2004). Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy, J Clin Oncol 22, 1589-97.

Hansel, A., Bucher, H. C., Nuesch, R., and Battegay, M. (2001). Reasons for discontinuation of first highly active antiretroviral therapy in a cohort of proteinase inhibitor-naive HIV-infected patients, J Acquir Immune Defic Syndr 26, 191-3.

Hansjee, N., Kaufmann, G., Strub, C., Weber, R., Battegay, M., Erb, P. (2004). Persistent apoptosis in HIV-1-infected individuals receiving potent antiretroviral therapy is associated with poor recovery of CD4 T lymphocytes., J Acq Immune Defic Syndr 36: 671-677.

Hardeland, U., Bentele, M., Jiricny, J., and Schar, P. (2000). Separating substrate recognition from base hydrolysis in human thymine DNA glycosylase by mutational analysis, J Biol Chem 275, 33449-56.

Hardeland, U., Bentele, M., Jiricny, J., and Schar, P. (2003). The versatile thymine DNA-glycosylase: a comparative characterization of the human, Drosophila and fission yeast orthologs, Nucleic Acids Res 31, 2261-71.

Hardeland, U., Bentele, M., Lettieri, T., Steinacher, R., Jiricny, J., and Schar, P. (2001). Thymine DNA glycosylase, Prog Nucleic Acid Res Mol Biol 68, 235-53.

Hardeland, U., Steinacher, R., Jiricny, J., and Schar, P. (2002). Modification of the human thymine-DNA glycosylase by ubiquitin-like proteins facilitates enzymatic turnover, Embo J 21, 1456-64.

Hardmeier, M., Wagenpfeil, S., Freitag, P., Fisher, E., Rudick, R. A., Kooijmans-Coutinho, M., Clanet, M., Radue, E. W., and Kappos, L. (2003). Atrophy is detectable within a 3-month period in untreated patients with active relapsing remitting multiple sclerosis, Arch Neurol 60, 1736-9.

Hasan, S., El-Andaloussi, N., Hardeland, U., Hassa, P. O., Burki, C., Imhof, R., Schar, P., and Hottiger, M. O. (2002). Acetylation regulates the DNA end-trimming activity of DNA polymerase beta, Mol Cell 10, 1213-22.

Haselhorst, R., Kappos, L., Bilecen, D., Scheffler, K., Mori, D., Radu, E. W., and Seelig, J. (2000). Dynamic susceptibility contrast MR imaging of plaque development in multiple sclerosis: application of an extended blood-brain barrier leakage correction, J Magn Reson Imaging 11, 495-505.

Hashemolhosseini, S., Moore, C., Landmann, L., Sander, A., Schwarz, H., Witzemann, V., Sakmann, B., and Brenner, H. R. (2000). Electrical activity and postsynapse formation in adult muscle: gamma-AChRs are not required, Mol Cell Neurosci 16, 697-707.

Hausermann, P., Gutersohn, T., Beltraminelli, H., Schiller, P., Buchner, S. A., and Rufli, T. (2002). [Oral pemphigus vulgaris. Successful treatment with minocycline and nicotinamide], Hautarzt 53, 813-5.

Hausermann, P., Khanna, N., Buess, M., Itin, P. H., Battegay, M., Dirnhofer, S., and Buechner, S. A. (2004). Cutaneous plasmablastic lymphoma in an HIV-positive male: an unrecognized cutaneous manifestation, Dermatology 208, 287-90.

Hausermann, P., Lutter, S., Meigel, W., Rufli, T. (2002a). Das Lewandowsky-Lutz-Syndrom: Die Erstbeschreibung und drei weitere Basler Fälle der Epidermodysplasia verruciformis., Z Hautkrh 77: 176-80.

Hausermann, P., Lutter, S., Meigel, W., Rufli, T. (2002b). Zur Person Felix Lewandowsky., Z Hautkrh 77 77: 182-3.

Hausmann, Kirsch, E., Radu, E., Mindermann, T. H., and Gratzl, O. (2001a). Coagulopathy induced spinal intradural extramedullary haematoma: report of three cases and review of the literature, Acta Neurochir (Wien) 143, 135-40.

Hausmann, O. N., Kirsch, E. C., Tolnay, M., and Gratzl, O. (2001b). Intramedullary spinal cord tumours: a clinical outcome and radiological follow-up study, Swiss Med Wkly 131, 582-7.

Havlickova, M., Prezeau, L., Duthey, B., Bettler, B., Pin, J. P., and Blahos, J. (2002). The intracellular loops of the GB2 subunit are crucial for G-protein coupling of the heteromeric gamma-aminobutyrate B receptor, Mol Pharmacol 62, 343-50.

Heese, K., Beck, K. F., Behrens, M. H., Pluss, K., Fierlbeck, W., Huwiler, A., Muhl, H., Geiger, H., Otten, U., and Pfeilschifter, J. (2003). Effects of high glucose on cytokine-induced nerve growth factor (NGF) expression in rat renal mesangial cells, Biochem Pharmacol 65, 293-301.

Heider, H., and Wintergerst, E. S. (2001). Mimicking phosphorylation at Ser-48 strongly reduces surface expression of human macrophage scavenger receptor class A: implications on cell motility, FEBS Lett 505, 185-90.

Heim, M., Frank, O., Kampmann, G., Sochocky, N., Pennimpede, T., Fuchs, P., Hunziker, W., Weber, P., Martin, I., and Bendik, I. (2004). The phytoestrogen genistein enhances osteogenesis and represses adipogenic differentiation of human primary bone marrow stromal cells, Endocrinology 145, 848-59. Epub 2003 Nov 6.

Heim, M. H. (2000). Intracellular signalling and antiviral effects of interferons, Dig Liver Dis 32, 257-63.

Heim, M. H. (2003). A new survival trick of hepatitis C virus: blocking the activation of interferon regulatory factor-3, Hepatology 38, 1582-4.

Heinimann, K., Muller, H., and Dobbie, Z. (2000). Microsatellite instability in colorectal cancer, N Engl J Med 342, 1607-8.

Heinimann, K., Thompson, A., Locher, A., Furlanetto, T., Bader, E., Wolf, A., Meier, R., Walter, K., Bauerfeind, P., Marra, G., Muller, H., Foernzler, D., and Dobbie, Z. (2001). Nontruncating APC germ-line mutations and mismatch repair deficiency play a minor role in APC mutation-negative polyposis, Cancer Res 61, 7616-22.

Henger, A., Tutt, P., Riesen, W. F., Hulter, H. N., and Krapf, R. (2000). Acid-base and endocrine effects of aldosterone and angiotensin II inhibition in metabolic acidosis in human patients, J Lab Clin Med 136, 379-89.

Hengstler, P., Battegay, E., Cornuz, J., Bucher, H., and Battegay, M. (2002). Evidence for prevention and screening: recommendations in adults, Swiss Med Wkly 132, 363-73.

Hengstler, P., and Battegay, M. (2001). [Vaccinations in adults], Schweiz Rundsch Med Prax 90, 2001-4.

Heppeler, A., Froidevaux, S., Eberle, A. N., and Maecke, H. R. (2000). Receptor targeting for tumor localisation and therapy with radiopeptides, Curr Med Chem 7, 971-94.

Hermosilla, E., Lagueny, A., Vital, C., Vital, A., Ferrer, X., Steck, A., and Julien, J. (1996). Peripheral neuropathy associated with monoclonal IgG of undetermined significance: clinical, electrophysiologic, pathologic and therapeutic study of 14 cases, J Peripher Nerv Syst 1, 139-48.

Herrmann, M., Stern, M., Vollenweider, F., and Nitsch, C. (2004). Effect of inherent epileptic seizures on brain injury after transient cerebral ischemia in Mongolian gerbils, Exp Brain Res 154, 176-82. Epub 2003 Oct 14.

Herzig, M., and Christofori, G. (2002). Recent advances in cancer research: mouse models of tumorigenesis, Biochim Biophys Acta 1602, 97-113.

Hess, C., Altfeld, M., Thomas, S. Y., Addo, M. M., Rosenberg, E. S., Allen, T. M., Draenert, R., Eldrige, R. L., van Lunzen, J., Stellbrink, H. J., Walker, B. D., and Luster, A. D. (2004a). HIV-1 specific CD8 T cells with an effector phenotype and control of viral replication, Lancet 363, 863-6.

Hess, C., Klimkait, T., Schlapbach, L., Del Zenero, V., Sadallah, S., Horakova, E., Balestra, G., Werder, V., Schaefer, C., Battegay, M., and Schifferli, J. A. (2002). Association of a pool of HIV-1 with erythrocytes in vivo: a cohort study, Lancet 359, 2230-4.

Hess, C., Means, T. K., Autissier, P., Woodberry, T., Altfeld, M., Addo, M. M., Frahm, N., Brander, C., Walker, B. D., and Luster, A. D. (2004b). IL-8 responsiveness defines a subset of CD8 T cells poised to kill, Blood 3, 3.

Hess, C., Sadallah, S., and Schifferli, J. A. (2000). Induction of neutrophil responsiveness to myeloperoxidase antibodies by their exposure to supernatant of degranulated autologous neutrophils, Blood 96, 2822-7.

Hess, C., and Schifferli, J. A. (2003). Immune adherence revisited: novel players in an old game, News Physiol Sci 18, 104-8.

Heuss, L. T., and Beglinger, C. (2004). Quality assurance in endoscopy should include data on sedation, Endoscopy 36, 569.

Heuss, L. T., Drewe, J., Schnieper, P., Tapparelli, C. B., Pflimlin, E., and Beglinger, C. (2004). Patient-controlled versus nurse-administered sedation with propofol during colonoscopy. A prospective randomized trial, Am J Gastroenterol 99, 511-8.

Heuss, L. T., Schnieper, P., Drewe, J., Pflimlin, E., and Beglinger, C. (2003a). Conscious sedation with propofol in elderly patients: a prospective evaluation, Aliment Pharmacol Ther 17, 1493-501.

Heuss, L. T., Schnieper, P., Drewe, J., Pflimlin, E., and Beglinger, C. (2003b). Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologist: a prospective observational study of more than 2000 cases, Gastrointest Endosc 57, 664-71.

Heuss, L. T., Schnieper, P., Drewe, J., Pflimlin, E., and Beglinger, C. (2003c). Safety of propofol for conscious sedation during endoscopic procedures in high-risk patients-a prospective, controlled study, Am J Gastroenterol 98, 1751-7.

Hildebrandt, B., Heide, I., Thiede, C., Nagel, S., Dieing, A., Jonas, S., Neuhaus, P., Rochlitz, C. F., Riess, H., and Neubauer, A. (2000). Lack of point mutations in exons 11-23 of the retinoblastoma susceptibility gene RB-1 in liver metastases of colorectal carcinoma, Oncology 59, 344-6.

Hintermann, E., Erb, C., Talke-Messerer, C., Liu, R., Tanner, H., Flammer, J., and Eberle, A. N. (2001a). Expression of the melanin-concentrating hormone receptor in porcine and human ciliary epithelial cells, Invest Ophthalmol Vis Sci 42, 206-9.

Hintermann, E., Tanner, H., Talke-Messerer, C., Schlumberger, S., Zumsteg, U., and Eberle, A. N. (2001b). Interaction of melanin-concentrating hormone (MCH), neuropeptide E-I (NEI), neuropeptide G-E (NGE), and alpha-MSH with melanocortin and MCH receptors on mouse B16 melanoma cells, J Recept Signal Transduct Res 21, 93-116.

Hirsch, H. H. (2002). Polyomavirus BK nephropathy: a (re-)emerging complication in renal transplantation, Am J Transplant 2, 25-30.

Hirsch, H. H. (2003a). BK virus replication and desease in solid organ transplantat recipients: an update., Curr Opin Organ Transpl 8: 262-8.

Hirsch, H. H. (2003b). [Polyomavirus associated nephropathy. A new opportunistic complication after kidney transplantation], Internist (Berl) 44, 653-5.

Hirsch, H. H. (2003c). [Viral infections after transplantation], Ther Umsch 60, 641-9.

Hirsch, H. H. (2003d). VP1 messenger RNA levels in urine for diagnosing BK virus nephropathy?, Transplantation 75, 2160.

Hirsch, H. H., and Battegay, M. (2002). Lipodystrophy syndrome by HAART in HIV-infected patients: manifestation, mechanisms and management, Infection 30, 293-8.

Hirsch, H. H., and Battegay, M. (2003). [HIV-infection, HAART (highly-active antiretroviral therapy) and hyperlipidemia], Dtsch Med Wochenschr 128, 1051-4.

Hirsch, H. H., Kaufmann, G., Sendi, P., and Battegay, M. (2004). Immune reconstitution in HIV-infected patients, Clin Infect Dis 38, 1159-66. Epub 2004 Apr 5.

Hirsch, H. H., Knowles, W., Dickenmann, M., Passweg, J., Klimkait, T., Mihatsch, M. J., and Steiger, J. (2002). Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients, N Engl J Med 347, 488-96.

Hirsch, H. H., Mohaupt, M., and Klimkait, T. (2001). Prospective monitoring of BK virus load after discontinuing sirolimus treatment in a renal transplant patient with BK virus nephropathy, J Infect Dis 184, 1494-5; author reply 1495-6.

Hirsch, H. H., and Nuesch, R. (2001). [Edema and lymphadenopathy. 55-year-old patient with edema and lymphadenopathy: significance of fine needle biopsy. Metastatic large cell undifferentiated carcinoma of unknown primary tumor (pancreas, stomach, bronchial differential diagnosis)], Schweiz Rundsch Med Prax 90, 1597-9.

Hirsch, H. H., and Steiger, J. (2003). Polyomavirus BK, Lancet Infect Dis 3, 611-23.

Hock, C., Heese, K., Muller-Spahn, F., Huber, P., Riesen, W., Nitsch, R. M., and Otten, U. (2000a). Increased cerebrospinal fluid levels of neurotrophin 3 (NT-3) in elderly patients with major depression, Mol Psychiatry 5, 510-3.

Hock, C., Heese, K., Muller-Spahn, F., Huber, P., Riesen, W., Nitsch, R. M., and Otten, U. (2000b). Increased CSF levels of nerve growth factor in patients with Alzheimer s disease, Neurology 54, 2009-11.

Hoesli, I., Danek, M., Lin, D., Li, Y., Hahn, S., and Holzgreve, W. (2002). Circulating erythroblasts in maternal blood are not elevated before onset of preterm labor, Obstet Gynecol 100, 992-6.

Hoesli, I. M., Strutas, D., Tercanli, S., and Holzgreve, W. (2003). Charts for cervical length in singleton pregnancy, Int J Gynaecol Obstet 82, 161-5.

Hofer, S., Eichhorn, K., Freitag, P., Reubi, J. C., Muller-Brand, J., Maecke, H., and Merlo, A. (2001). Successful diffusible brachytherapy (dBT) of a progressive low-grade astrocytoma using the locally injected peptidic vector and somatostatin analogue [90Y]-DOTA0-D-Phe1-Tyr3-octreotide (DOTATOC), Swiss Med Wkly 131, 640-4.

Hoffmann, M., Haller, P., Bucher, H. C., Gyr, N., and Battegay, M. (2001). [Hospitalizations in a cohort of 175 severely drug-addicted patients of a medically managed opiate withdrawal project], Schweiz Rundsch Med Prax 90, 2094-101.

Hoffmann, R., Bruno, L., Seidl, T., Rolink, A., and Melchers, F. (2003). Rules for gene usage inferred from a comparison of large-scale gene expression profiles of T and B lymphocyte development, J Immunol 170, 1339-53.

Hoffmann, R., Seidl, T., Neeb, M., Rolink, A., and Melchers, F. (2002). Changes in gene expression profiles in developing B cells of murine bone marrow, Genome Res 12, 98-111.

Hoffmann, T., De Libero, G., Colonna, M., Wodnar-Filipowicz, A., Passweg, J., Favre, G., Gratwohl, A., and Tichelli, A. (2000). Natural killer-type receptors for HLA class I antigens are clonally expressed in lymphoproliferative disorders of natural killer and T-cell type, Br J Haematol 110, 525-36.

Hofsaess, U., and Kapfhammer, J. P. (2003). Identification of numerous genes differentially expressed in rat brain during postnatal development by suppression subtractive hybridization and expression analysis of the novel rat gene rMMS2, Brain Res Mol Brain Res 113, 13-27.

Hohlfeld, R., and Kappos, L. (2004). Workshop Report: Neuroprotection in Multiple Sclerosis Report from the MS Forum 16th Modern Management Workshop, March 2004, Cernobbio, Italy*, Int MS J 11, 61-3.

Holzgreve, W., and Hahn, S. (2002). [Non-invasive prenatal diagnosis--already a reality?], Gynakol Geburtshilfliche Rundsch 42, 84-6.

Holzgreve, W., Surbek, D. (2004). Aktuelle Entwicklungen der Stammzellforschung: Implikationen für das Banking von Nabelschnurblut-Stammzellen., Geburtsh Frauenheilk 2004 64: 357-8.

Holzgreve, W., Zhong, X. Y., Burk, M. R., and Hahn, S. (2001). Enrichment of fetal cells and free fetal DNA from maternal blood: An insight into the Basel experience, Early Pregnancy 5, 43-4.

Hoppe, C., Klitz, W., Cheng, S., Apple, R., Steiner, L., Robles, L., Girard, T., Vichinsky, E., and Styles, L. (2004). Gene interactions and stroke risk in children with sickle cell anemia, Blood 103, 2391-6. Epub 2003 Nov 13.

Horakova, E., Gasser, O., Sadallah, S., Inal, J., Bourgeois, G., Ziekau, I., Klimkait, T., Schifferli, J.A. (2004). Complement mediates the binding of HIV to erythrocytes., J Immunol 2004 (in press).

Hornstein, P. S., Zaugg, C. E., Zhu, P., Allegrini, P. R., and Buser, P. T. (2001). Combined blockade of endothelin-1 and thromboxane A(2) receptors against postischaemic contractile dysfunction in rat hearts, Br J Pharmacol 132, 234-40.

Hosch, M., Muser, J., Hulter, H. N., and Krapf, R. (2004). Ureagenesis: evidence for a lack of hepatic regulation of acid-base equilibrium in humans, Am J Physiol Renal Physiol 286, F94-9.

Hostettler, K. E., Roth, M., Burgess, J. K., Johnson, P. R., Glanville, A. R., Tamm, M., Black, J. L., and Borger, P. (2004). Cyclosporine A mediates fibroproliferation through epithelial cells, Transplantation 77, 1886-93.

Hristoskova, S., Holzgreve, W., and Hahn, S. (2003). Fetal nucleated erythrocytes in maternal circulation do not display a classic membrane-associated apoptotic characteristic (phosphatidylserine exposure) despite being positive by terminal dUTP nuclear end labeling, Clin Chem 49, 1934-7.

Hruz, P., Mayr, M., Low, R., Drewe, J., and Huber, G. (2002). Fanconi's syndrome, acute renal failure, and tonsil ulcerations after colloidal bismuth subcitrate intoxication, Am J Kidney Dis 39, E18.

Humar, B., D'Orazio, D., Albrecht, C., Bauerfeind, P., Muller, H., Dobbie, Z., and Bendik, I. (2001a). Expression of putative anticancer targets in familial adenomatous polyposis and its association with the APC mutation status, Int J Oncol 19, 1179-86.

Humar, B., Giovanoli, O., Wolf, A., Attenhofer, M., Bendik, I., Meier, R., Muller, H., and Dobbie, Z. (2000). Germline alterations in the cyclooxygenase-2 gene are not associated with the development of extracolonic manifestations in a large swiss familial adenomatous polyposis kindred, Int J Cancer 87, 812-7.

Humar, B., Muller, H., and Scott, R. J. (2001b). Cell cycle dependent DNA break increase in ataxia telangiectasia lymphoblasts after radiation exposure, Mol Pathol 54, 347-50.

Humar, B., Toro, T., Graziano, F., Muller, H., Dobbie, Z., Kwang-Yang, H., Eng, C., Hampel, H., Gilbert, D., Winship, I., Parry, S., Ward, R., Findlay, M., Christian, A., Tucker, M., Tucker, K., Merriman, T., and Guilford, P. (2002a). Novel germline CDH1 mutations in hereditary diffuse gastric cancer families, Hum Mutat 19, 518-25.

Humar, R., Kiefer, F. N., Berns, H., Resink, T. J., and Battegay, E. J. (2002b). Hypoxia enhances vascular cell proliferation and angiogenesis in vitro via rapamycin (mTOR)-dependent signaling, Faseb J 16, 771-80.

Hunziker, P. R., Imsand, C., Keller, D., Hess, N., Barbosa, V., Nietlispach, F., Liel-Cohen, N., Weyman, A. E., Pfisterer, M., and Buser, P. (2002). Bedside quantification of atherosclerosis severity for cardiovascular risk stratification: a prospective cohort study, J Am Coll Cardiol 39, 702-9.

Hutter, P., Wijnen, J., Rey-Berthod, C., Thiffault, I., Verkuijlen, P., Farber, D., Hamel, N., Bapat, B., Thibodeau, S. N., Burn, J., Wu, J., MacNamara, E., Heinimann, K., Chong, G., and Foulkes, W. D. (2002). An MLH1 haplotype is over-represented on chromosomes carrying an HNPCC predisposing mutation in MLH1, J Med Genet 39, 323-7.

Huwyler, J., Cerletti, A., Fricker, G., Eberle, A. N., and Drewe, J. (2002). By-passing of P-glycoprotein using immunoliposomes, J Drug Target 10, 73-9.

Ikeda, N., Krustev, R., and Muller, H. J. (2004). Thermodynamic consideration on single oil in water emulsion film stabilized by cationic surfactant, Adv Colloid Interface Sci 108-109, 273-86.

Impagnatiello, M. A., Weitzer, S., Gannon, G., Compagni, A., Cotten, M., and Christofori, G. (2001). Mammalian sprouty-1 and -2 are membrane-anchored phosphoprotein inhibitors of growth factor signaling in endothelial cells, J Cell Biol 152, 1087-98.

Inal, J. M., Pascual, M., Lesavre, P., and Schifferli, J. A. (2003a). Complement inhibition in renal diseases, Nephrol Dial Transplant 18, 237-40.

Inal, J. M., and Schifferli, J. A. (2002). Complement C2 receptor inhibitor trispanning and the beta-chain of C4 share a binding site for complement C2, J Immunol 168, 5213-21.

Inal, J. M., Schneider, B., Armanini, M., and Schifferli, J. A. (2003b). A peptide derived from the parasite receptor, complement C2 receptor inhibitor trispanning, suppresses immune complex-mediated inflammation in mice, J Immunol 170, 4310-7.

Inglese, M., van Waesberghe, J. H., Rovaris, M., Beckmann, K., Barkhof, F., Hahn, D., Kappos, L., Miller, D. H., Polman, C., Pozzilli, C., Thompson, A. J., Yousry, T. A., Wagner, K., Comi, G., and Filippi, M. (2003). The effect of interferon beta-1b on quantities derived from MT MRI in secondary progressive MS, Neurology 60, 853-60.

Ivanov, D., Philippova, M., Antropova, J., Gubaeva, F., Iljinskaya, O., Tararak, E., Bochkov, V., Erne, P., Resink, T., and Tkachuk, V. (2001). Expression of cell adhesion molecule T-cadherin in the human vasculature, Histochem Cell Biol 115, 231-42.

Ivanov, D., Philippova, M., Tkachuk, V., Erne, P., and Resink, T. (2004). Cell adhesion molecule T-cadherin regulates vascular cell adhesion, phenotype and motility, Exp Cell Res 293, 207-18.

Iwanaga, Y., Gu, Y., Dieterle, T., Presotto, C., Del Soldato, P., Peterson, K. L., Ongini, E., Condorelli, G., and Ross, J., Jr. (2004a). A nitric oxide-releasing derivative of enalapril, NCX 899, prevents progressive cardiac dysfunction and remodeling in hamsters with heart failure, Faseb J 18, 587-8. Epub 2004 Jan 20.

Iwanaga, Y., Hoshijima, M., Gu, Y., Iwatate, M., Dieterle, T., Ikeda, Y., Date, M. O., Chrast, J., Matsuzaki, M., Peterson, K. L., Chien, K. R., and Ross, J., Jr. (2004b). Chronic phospholamban inhibition prevents progressive cardiac dysfunction and pathological remodeling after infarction in rats, J Clin Invest 113, 727-36.

Iwatate, M., Gu, Y., Dieterle, T., Iwanaga, Y., Peterson, K. L., Hoshijima, M., Chien, K. R., and Ross, J. (2003). In vivo high-efficiency transcoronary gene delivery and Cre-LoxP gene switching in the adult mouse heart, Gene Ther 10, 1814-20.

Izbicki, G., Trachsel, D., Rutishauser, M., Perruchoud, A. P., and Tamm, M. (2000). [Early detection of exacerbation of lung infections in patients with cystic fibrosis by means of daily spirometry], Schweiz Med Wochenschr 130, 1361-5.

Jacobson, M., Bornstein, S., Palmer, E., and Wallgren, P. (2000). Elimination of Sarcoptes scabiei in pig herds by single or double administrations of an avermectin, Acta Vet Scand 41, 227-35.

Jaeger, E. E., Woodford-Richens, K. L., Lockett, M., Rowan, A. J., Sawyer, E. J., Heinimann, K., Rozen, P., Murday, V. A., Whitelaw, S. C., Ginsberg, A., Atkin, W. S., Lynch, H. T., Southey, M. C., Debinski, H., Eng, C., Bodmer, W. F., Talbot, I. C., Hodgson, S. V., Thomas, H. J., and Tomlinson, I. P. (2003). An ancestral Ashkenazi haplotype at the HMPS/CRAC1 locus on 15q13-q14 is associated with hereditary mixed polyposis syndrome, Am J Hum Genet 72, 1261-7. Epub 2003 Apr 14.

Jaggy, C., von Overbeck, J., Ledergerber, B., Schwarz, C., Egger, M., Rickenbach, M., Furrer, H. J., Telenti, A., Battegay, M., Flepp, M., Vernazza, P., Bernasconi, E., and Hirschel, B. (2003). Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population, Lancet 362, 877-8.

Jakob, M., Demarteau, O., Schafer, D., Hintermann, B., Dick, W., Heberer, M., and Martin, I. (2001). Specific growth factors during the expansion and redifferentiation of adult human articular chondrocytes enhance chondrogenesis and cartilaginous tissue formation in vitro, J Cell Biochem 81, 368-77.

Jakob, M., Demarteau, O., Schafer, D., Stumm, M., Heberer, M., and Martin, I. (2003). Enzymatic digestion of adult human articular cartilage yields a small fraction of the total available cells, Connect Tissue Res 44, 173-80.

Jakob, M., Demarteau, O., Suetterlin, R., Heberer, M., and Martin, I. (2004). Chondrogenesis of expanded adult human articular chondrocytes is enhanced by specific prostaglandins, Rheumatology (Oxford) 43, 852-7. Epub 2004 Apr 27.

Jantscheff, P., Spagnoli, G., Zajac, P., and Rochlitz, C. F. (2002). Cell fusion: an approach to generating constitutively proliferating human tumor antigen-presenting cells, Cancer Immunol Immunother 51, 367-75. Epub 2002 Jun 25.

Jantscheff, P., Terracciano, L., Lowy, A., Glatz-Krieger, K., Grunert, F., Micheel, B., Brummer, J., Laffer, U., Metzger, U., Herrmann, R., and Rochlitz, C. (2003). Expression of CEACAM6 in resectable colorectal cancer: a factor of independent prognostic significance, J Clin Oncol 21, 3638-46.

Jehle, A. W., Khanna, N., Sigle, J. P., Glatz-Krieger, K., Battegay, M., Steiger, J., Dickenmann, M., and Hirsch, H. H. (2004). Acute renal failure on immune reconstitution in an HIV-positive patient with miliary tuberculosis, Clin Infect Dis 38, e32-5. Epub 2004 Jan 30.

Jehle, S., Hulter, H. N., and Krapf, R. (2000). On the mechanism of growth hormone-induced stimulation of renal acidification in humans: effect of dietary NaCl, Clin Sci (Lond) 99, 47-56.

Jelezarova, E., Schlumberger, M., Sadallah, S., Spath, P. J., Schifferli, J. A., and Lutz, H. U. (2001). A C3 convertase assay for nephritic factor functional activity, J Immunol Methods 251, 45-52.

Jensen, A. A., Mosbacher, J., Elg, S., Lingenhoehl, K., Lohmann, T., Johansen, T. N., Abrahamsen, B., Mattsson, J. P., Lehmann, A., Bettler, B., and Brauner-Osborne, H. (2002). The anticonvulsant gabapentin (neurontin) does not act through gamma-aminobutyric acid-B receptors, Mol Pharmacol 61, 1377-84.

Ji, J., Wernli, M., Buechner, S., and Erb, P. (2003a). Fas ligand downregulation with antisense oligonucleotides in cells and in cultured tissues of normal skin epidermis and basal cell carcinoma, J Invest Dermatol 120, 1094-9.

Ji, J., Wernli, M., Klimkait, T., and Erb, P. (2003b). Enhanced gene silencing by the application of multiple specific small interfering RNAs, FEBS Lett 552, 247-52.

Jimenez Bueno, G., Klimkait, T., Gilbert, I. H., and Simons, C. (2003). Solid-phase synthesis of diamine and polyamine amino acid derivatives as HIV-1 tat-TAR binding inhibitors, Bioorg Med Chem 11, 87-94.

Johnson, D. R., Biedermann, B. C., and Mook-Kanamori, B. (2000). Rapid cloning of HLA class I cDNAs by locus specific PCR, J Immunol Methods 233, 119-29.

Johnson, K. L., Dukes, K. A., Vidaver, J., LeShane, E. S., Ramirez, I., Weber, W. D., Bischoff, F. Z., Hahn, S., Sharma, A., Dang, D. X., Hire, L. M., Bianchi, D. W., Simpson, J. L., Holzgreve, W., Elias, S., and Klinger, K. W. (2004a). Interlaboratory comparison of fetal male DNA detection from common maternal plasma samples by real-time PCR, Clin Chem 50, 516-21. Epub 2004 Jan 12.

Johnson, P. R., Burgess, J. K., Underwood, P. A., Au, W., Poniris, M. H., Tamm, M., Ge, Q., Roth, M., and Black, J. L. (2004b). Extracellular matrix proteins modulate asthmatic airway smooth muscle cell proliferation via an autocrine mechanism, J Allergy Clin Immunol 113, 690-6.

Johnson, P. R., Roth, M., Tamm, M., Hughes, M., Ge, Q., King, G., Burgess, J. K., and Black, J. L. (2001). Airway smooth muscle cell proliferation is increased in asthma, Am J Respir Crit Care Med 164, 474-7.

Jones, G., Machado, J., Jr., and Merlo, A. (2001a). Loss of focal adhesion kinase (FAK) inhibits epidermal growth factor receptor-dependent migration and induces aggregation of nh(2)-terminal FAK in the nuclei of apoptotic glioblastoma cells, Cancer Res 61, 4978-81.

Jones, G., Machado, J., Jr., Tolnay, M., and Merlo, A. (2001b). PTEN-independent induction of caspase-mediated cell death and reduced invasion by the focal adhesion targeting domain (FAT) in human astrocytic brain tumors which highly express focal adhesion kinase (FAK), Cancer Res 61, 5688-91.

Joos, L., Carlen Brutsche, I. E., Laule-Kilian, K., Crawen, M., Tamm, M., and Brutsche, M. H. (2004). Systemic Th1- and Th2-gene signals in atopy and asthma, Swiss Med Wkly 134, 159-64.

Jover, R., Hoffmann, F., Scheffler-Koch, V., and Lindberg, R. L. (2000). Limited heme synthesis in porphobilinogen deaminase-deficient mice impairs transcriptional activation of specific cytochrome P450 genes by phenobarbital, Eur J Biochem 267, 7128-37.

Jungbluth, A. A., Busam, K. J., Kolb, D., Iversen, K., Coplan, K., Chen, Y. T., Spagnoli, G. C., and Old, L. J. (2000). Expression of MAGE-antigens in normal tissues and cancer, Int J Cancer 85, 460-5.

Juretic, A., Spagnoli, G. C., Schultz-Thater, E., and Sarcevic, B. (2003). Cancer/testis tumour-associated antigens: immunohistochemical detection with monoclonal antibodies, Lancet Oncol 4, 104-9.

Kafienah, W., Jakob, M., Demarteau, O., Frazer, A., Barker, M. D., Martin, I., and Hollander, A. P. (2002). Three-dimensional tissue engineering of hyaline cartilage: comparison of adult nasal and articular chondrocytes, Tissue Eng 8, 817-26.

Kaiser, C., Kuster, G. M., Erne, P., Amann, W., Naegeli, B., Osswald, S., Buser, P., Schlapfer, H., Brett, W., Zerkowski, H. R., Schindler, C., and Pfisterer, M. (2004). Risks and benefits of optimised medical and revascularisation therapy in elderly patients with angina – on-treatment analysis of the TIME trial, Eur Heart J 25, 1036-42.

Kalberer, C. P., Siegler, U., and Wodnar-Filipowicz, A. (2003). Human NK cell development in NOD/SCID mice receiving grafts of cord blood CD34 cells, Blood 102, 127-35.

Kappos, L. (2002). Interferon beta-1a and beta-1b for treatment of multiple sclerosis, Lancet 360, 1428; author reply 1428-9.

Kappos, L. (2004). Effect of drugs in secondary disease progression in patients with multiple sclerosis, Mult Scler 10, S46-54; discussion S54-5.

Kappos, L., Comi, G., Panitch, H., Oger, J., Antel, J., Conlon, P., and Steinman, L. (2000). Induction of a non-encephalitogenic type 2 T helper-cell autoimmune response in multiple sclerosis after administration of an altered peptide ligand in a placebo-controlled, randomized phase II trial. The Altered Peptide Ligand in Relapsing MS Study Group, Nat Med 6, 1176-82.

Kappos, L., and Duda, P. (2002). The Janus face of CNS-directed autoimmune response: a therapeutic challenge, Brain 125, 2379-80.

Kappos, L., and Kesselring, J. (2003). Interferons in relapsing remitting multiple sclerosis, Lancet 361, 1821-2; author reply 1823-4.

Kappos, L., Polman, C., Pozzilli, C., Thompson, A., Beckmann, K., and Dahlke, F. (2001). Final analysis of the European multicenter trial on IFN-beta-1b in secondary-progressive MS, Neurology 57, 1969-75.

Kappos, L., Polman, C., Thompson, A. J., Duda, P., Clanet, M., Comi, G., Hartung, H. P., and Montalban, X. (2003). Towards a european network for multiple sclerosis trials (ENMST), Mult Scler 9, 627-9.

Kaufmann, G. R., Khanna, N., Weber, R., Perrin, L., Furrer, H., Cavassini, M., Ledergerber, B., Vernazza, P., Bernasconi, E., Rickenbach, M., Hirschel, B., and Battegay, M. (2004). Long-term virological response to multiple sequential regimens of highly active antiretroviral therapy for HIV infection, Antivir Ther 9, 263-74.

Kaufmann, G. R., Perrin, L., Pantaleo, G., Opravil, M., Furrer, H., Telenti, A., Hirschel, B., Ledergerber, B., Vernazza, P., Bernasconi, E., Rickenbach, M., Egger, M., and Battegay, M. (2003). CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study, Arch Intern Med 163, 2187-95.

Kaufmann, G. R., Smith, D., Bucher, H. C., Phanuphak, P., Sendi, P. P., Mbidde, E. K., Cooper, D. A., and Battegay, M. (2002). Potential benefit and limitations of a broad access to potent antiretroviral therapy in developing countries, Expert Opin Investig Drugs 11, 1303-13.

Kaupmann, K., Cryan, J. F., Wellendorph, P., Mombereau, C., Sansig, G., Klebs, K., Schmutz, M., Froestl, W., van der Putten, H., Mosbacher, J., Brauner-Osborne, H., Waldmeier, P., and Bettler, B. (2003). Specific gamma-hydroxybutyrate-binding sites but loss of pharmacological effects of gamma-hydroxybutyrate in GABA(B)(1)-deficient mice, Eur J Neurosci 18, 2722-30.

Kavalar, R., Sarcevic, B., Spagnoli, G. C., Separovic, V., Samija, M., Terracciano, L., Heberer, M., and Juretic, A. (2001). Expression of MAGE tumour-associated antigens is inversely correlated with tumour differentiation in invasive ductal breast cancers: an immunohistochemical study, Virchows Arch 439, 127-31.

Keller, D., Osswald, S., Carrier, L. (Genetik der Familiären Hypertrophen Kardiomyopathie.). Kardiovaskuläre Medizin 2002, 5: 400-406.

Keller, D. I., Acharfi, S., Delacretaz, E., Benammar, N., Rotter, M., Pfammatter, J. P., Fressart, V., Guicheney, P., and Chahine, M. (2003a). A novel mutation in SCN5A, delQKP 1507-1509, causing long QT syndrome: role of Q1507 residue in sodium channel inactivation, J Mol Cell Cardiol 35, 1513-21.

Keller, D. I., Carrier, L., and Schwartz, K. (2002). Genetics of familial cardiomyopathies and arrhythmias, Swiss Med Wkly 132, 401-7.

Keller, D. I., Coirault, C., Rau, T., Cheav, T., Weyand, M., Amann, K., Lecarpentier, Y., Richard, P., Eschenhagen, T., and Carrier, L. (2004). Human homozygous R403W mutant cardiac myosin presents disproportionate enhancement of mechanical and enzymatic properties, J Mol Cell Cardiol 36, 355-62.

Keller, D. I., Osswald, S., Bremerich, J., Bongartz, G., Cron, T. A., Hilti, P., Pfisterer, M. E., and Buser, P. T. (2003b). Arrhythmogenic right ventricular cardiomyopathy: diagnostic and prognostic value of the cardiac MRI in relation to arrhythmia-free survival, Int J Cardiovasc Imaging 19, 537-43; discussion 545-7.

Keller, U., Szinnai, G., Bilz, S., and Berneis, K. (2003c). Effects of changes in hydration on protein, glucose and lipid metabolism in man: impact on health, Eur J Clin Nutr 57, S69-74.

Khanna, N., Goldenberger, D., Graber, P., Battegay, M., and Widmer, A. F. (2003). Gastroenteritis outbreak with norovirus in a Swiss university hospital with a newly identified virus strain, J Hosp Infect 55, 131-6.

Khanna, N., Klimkait, T., Schiffer, V., Irigoyen, J., Telenti, A., Hirschel, B., and Battegay, M. (2000). Salvage therapy with abacavir plus a non-nucleoside reverse transcriptase inhibitor and a protease inhibitor in heavily pre-treated HIV-1 infected patients. Swiss HIV Cohort Study, Aids 14, 791-9.

Kiefer, F. N., Misteli, H., Kalak, N., Tschudin, K., Fingerle, J., Van der Kooij, M., Stumm, M., Sumanovski, L. T., Sieber, C. C., and Battegay, E. J. (2002a). Inhibition of NO biosynthesis, but not elevated blood pressure, reduces angiogenesis in rat models of secondary hypertension, Blood Press 11, 116-24.

Kiefer, F. N., Neysari, S., Humar, R., Li, W., Munk, V. C., and Battegay, E. J. (2003). Hypertension and angiogenesis, Curr Pharm Des 9, 1733-44.

Kiefer, G., Battegay, M., Gyr, N., and Hatz, C. (2002b). [Mansonella perstans filariasis after stay in Cameroon. A 19-year-old patient born in Cameroon, in Switzerland for the last 10 years], Schweiz Rundsch Med Prax 91, 61-6.

Kiewitz, R., Acklin, C., Schafer, B. W., Maco, B., Uhrik, B., Wuytack, F., Erne, P., and Heizmann, C. W. (2003). Ca2 -dependent interaction of S100A1 with the sarcoplasmic reticulum Ca2 -ATPase2a and phospholamban in the human heart, Biochem Biophys Res Commun 306, 550-7.

Kindler, C. H., Girard, T., Gong, D., and Urwyler, A. (2002). The differential effect of halothane and 1,2-dichlorohexafluorocyclobutane on in vitro muscle contractures of patients susceptible to malignant hyperthermia, Anesth Analg 94, 1028-33, table of contents.

Klimkait, T. (2000). Restriction PCR – superior to restriction endonucleases in DNA-cloning applications., Journ of Biochem and Mol Biol 22(2): 162-5.

Klimkait, T. (2002). A sensitive replicative system to assess HIV-1 drug resistance, Am Clin Lab 21, 20-4.

Klingbeil, A. U., Muller, H. J., Delles, C., Fleischmann, E., and Schmieder, R. E. (2000). Regression of left ventricular hypertrophy by AT1 receptor blockade in renal transplant recipients, Am J Hypertens 13, 1295-300.

Kloeter, U. C., Jander, N. G., Buser, P. T., Osswald, S., Mueller-Brand, J., and Pfisterer, M. E. (2001). Long-term outcome of angioplasty for multivessel coronary disease: importance and price of complete revascularization, Int J Cardiol 79, 197-205.

Knecht, H., Baumberger, M., Tobon, A., and Steck, A. (2004). Sustained remission of CIDP associated with Evans syndrome, Neurology 63, 730-2.

Kocher, T., Schraml, P., Spagnoli, G. C., Harder, F., and Heberer, M. (2000). Identification of genes differentially expressed in melanoma sublines derived from a single surgical specimen characterised by different sensitivity to cytotoxic T-lymphocyte activity, Schweiz Med Wochenschr 130, 617-24.

Kocher, T., Zheng, M., Bolli, M., Simon, R., Forster, T., Schultz-Thater, E., Remmel, E., Noppen, C., Schmid, U., Ackermann, D., Mihatsch, M. J., Gasser, T., Heberer, M., Sauter, G., and Spagnoli, G. C. (2002). Prognostic relevance of MAGE-A4 tumor antigen expression in transitional cell carcinoma of the urinary bladder: a tissue microarray study, Int J Cancer 100, 702-5.

Koebbe, C. J., Horowitz, M., Jungreis, C., Levy, E., and Pless, M. (2003). Alcohol embolization of carotid-cavernous indirect fistulae, Neurosurgery 52, 1111-5; discussion 1115-6.

Koehler, M., and Merlo, A. (2001). [Treatment of brain metastases], Ther Umsch 58, 732-7.

Koleva, M., Schlaf, G., Landmann, R., Gotze, O., Jungermann, K., and Schieferdecker, H. L. (2002). Induction of anaphylatoxin C5a receptors in rat hepatocytes by lipopolysaccharide in vivo: mediation by interleukin-6 from Kupffer cells, Gastroen-

terology 122, 697-708.
Kon, E., Muraglia, A., Corsi, A., Bianco, P., Marcacci, M., Martin, I., Boyde, A., Ruspantini, I., Chistolini, P., Rocca, M., Giardino, R., Cancedda, R., and Quarto, R. (2000). Autologous bone marrow stromal cells loaded onto porous hydroxyapatite ceramic accelerate bone repair in critical-size defects of sheep long bones, J Biomed Mater Res 49, 328-37.
Krahenbuhl, L., Lang, C., Ludes, S., Seiler, C., Schafer, M., Zimmermann, A., and Krahenbuhl, S. (2003). Reduced hepatic glycogen stores in patients with liver cirrhosis, Liver 23, 101-9.
Krahenbuhl, S. (2003). [Abuse of benzodiazepines and similar substances], Ther Umsch 60, 335-40.
Kralovics, R., Buser, A. S., Teo, S. S., Coers, J., Tichelli, A., van der Maas, A. P., and Skoda, R. C. (2003). Comparison of molecular markers in a cohort of patients with chronic myeloproliferative disorders, Blood 102, 1869-71.
Kralovics, R., Skoda, R.C. (2004). Molecular pathogenesis of Philadelphia chromosome negative myeloproliferative disorders., Blood Reviews (in press).
Krapf, R. (2002). Development of Cushing's syndrome after use of a herbal remedy, Lancet 360, 1884.
Krenger, W., Rossi, S., and Hollander, G. A. (2000a). Apoptosis of thymocytes during acute graft-versus-host disease is independent of glucocorticoids, Transplantation 69, 2190-3.
Krenger, W., Rossi, S., Piali, L., and Hollander, G. A. (2000b). Thymic atrophy in murine acute graft-versus-host disease is effected by impaired cell cycle progression of host pro-T and pre-T cells, Blood 96, 347-54.
Krenger, W., Schmidlin, H., Cavadini, G., and Hollander, G. A. (2004). On the relevance of TCR rearrangement circles as molecular markers for thymic output during experimental graft-versus-host disease, J Immunol 172, 7359-67.
Kristian, S. A., Golda, T., Ferracin, F., Cramton, S. E., Neumeister, B., Peschel, A., Gotz, F., and Landmann, R. (2004). The ability of biofilm formation does not influence virulence of Staphylococcus aureus and host response in a mouse tissue cage infection model, Microb Pathog 36, 237-45.
Kristian, S. A., Lauth, X., Nizet, V., Goetz, F., Neumeister, B., Peschel, A., and Landmann, R. (2003). Alanylation of teichoic acids protects Staphylococcus aureus against Toll-like receptor 2-dependent host defense in a mouse tissue cage infection model, J Infect Dis 188, 414-23. Epub 2003 Jul 10.
Krummenacher, J., Muller, H. J., and Heller, D. (2001). Visual search for dimensionally redundant pop-out targets: evidence for parallel-coactive processing of dimensions, Percept Psychophys 63, 901-17.
Krummenacher, J., Muller, H. J., and Heller, D. (2002). Visual search for dimensionally redundant pop-out targets: parallel-coactive processing of dimensions is location specific, J Exp Psychol Hum Percept Perform 28, 1303-22.
Kuban, P., Reinhardt, M., Muller, B., and Hauser, P. C. (2004). On-site simultaneous determination of anions and cations in drainage water using a flow injection-capillary electrophoresis system with contactless conductivity detection, J Environ Monit 6, 169-74. Epub 2004 Feb 5.
Kudrjashova, E., Bashtrikov, P., Bochkov, V., Parfyonova, Y., Tkachuk, V., Antropova, J., Iljinskaya, O., Tararak, E., Erne, P., Ivanov, D., Philippova, M., and Resink, T. J. (2002). Expression of adhesion molecule T-cadherin is increased during neointima formation in experimental restenosis, Histochem Cell Biol 118, 281-90. Epub 2002 Sep 27.
Kuhn, C., Muller-Werdan, U., Schmitt, D. V., Lange, H., Pilz, G., Kreuzer, E., Mohr, F. W., Zerkowski, H. R., and Werdan, K. (2000). Improved outcome of APACHE II score-defined escalating systemic inflammatory response syndrome in patients post cardiac surgery in 1996 compared to 1988-1990: the ESSICS-study pilot project, Eur J Cardiothorac Surg 17, 30-7.
Kulik, A., Nakadate, K., Nyiri, G., Notomi, T., Malitschek, B., Bettler, B., and Shigemoto, R. (2002). Distinct localization of GABA(B) receptors relative to synaptic sites in the rat cerebellum and ventrobasal thalamus, Eur J Neurosci 15, 291-307.
Kuntzer, T., Antoine, J.C., Steck, A.J. (2004). Clinical features and pathophysiological bases of sensory neuronopathies (ganglionopathies). Muscle Nerve 2004 (in press).
Kuschel, B., Kochli, O. R., Niederacher, D., Muller, H., and Beckmann, M. W. (2000). [Hereditary cancer syndromes in gynecology: what the practitioner needs to know!], Schweiz Med Wochenschr 130, 362-75.
Kuster, G. M., Buser, P., Osswald, S., Kaiser, C., Schonenberger, R., Schindler, C., Amann, W., Rickenbacher, P., and Pfisterer, M. (2003). Comparison of presentation, perception, and six-month outcome between women and men or 75 years of age with angina pectoris, Am J Cardiol 91, 436-9.
Labuhn, M., Jones, G., Speel, E. J., Maier, D., Zweifel, C., Gratzl, O., Van Meir, E. G., Hegi, M. E., and Merlo, A. (2001). Quantitative real-time PCR does not show selective targeting of p14(ARF) but concomitant inactivation of both p16(INK4A) and p14(ARF) in 105 human primary gliomas, Oncogene 20, 1103-9.
Lacazette, E., Le Calvez, S., Gajendran, N., and Brenner, H. R. (2003). A novel pathway for MuSK to induce key genes in neuromuscular synapse formation, J Cell Biol 161, 727-36.
Laflamme, N., Echchannaoui, H., Landmann, R., and Rivest, S. (2003). Cooperation between toll-like receptor 2 and 4 in the brain of mice challenged with cell wall components derived from gram-negative and gram-positive bacteria, Eur J Immunol 33, 1127-38.
Laghi, L., Ranzani, G. N., Bianchi, P., Mori, A., Heinimann, K., Orbetegli, O., Spaudo, M. R., Luinetti, O., Francisconi, S., Roncalli, M., Solcia, E., and Malesci, A. (2002). Frameshift mutations of human gastrin receptor gene (hGARE) in gastrointestinal cancers with microsatellite instability, Lab Invest 82, 265-71.
Laifer, G., Widmer, A. F., Frei, R., Zimmerli, W., and Fluckiger, U. (2004). Polymerase chain reaction for Mycobacterium tuberculosis: impact on clinical management of refugees with pulmonary infiltrates, Chest 125, 981-6.
Landmann, L. (2002). Deconvolution improves colocalization analysis of multiple fluorochromes in 3D confocal data sets more than filtering techniques, J Microsc 208, 134-47.
Landmann, L., Marbet, P. (2004). Colocalization analysis yields superior results after image restoration., Micr Res Techn 2004 64: 103-112.
Landmann, R., Muller, B., and Zimmerli, W. (2000). CD14, new aspects of ligand and signal diversity, Microbes Infect 2, 295-304.
Landry, C., Brasseur, F., Spagnoli, G. C., Marbaix, E., Boon, T., Coulie, P., and Godelaine, D. (2000). Monoclonal antibody 57B stains tumor tissues that express gene MAGE-A4, Int J Cancer 86, 835-41.
Langemann, H., Alessandri, B., Mendelowitsch, A., Feuerstein, T., Landolt, H., and Gratzl, O. (2001a). Extracellular levels of glucose and lactate measured by quantitative microdialysis in the human brain, Neurol Res 23, 531-6.
Langemann, H., Feuerstein, T., Mendelowitsch, A., and Gratzl, O. (2001b). Microdialytical monitoring of uric and ascorbic acids in the brains of patients after severe brain injury and during neurovascular surgery, J Neurol Neurosurg Psychiatry 71, 169-74.
Lechner-Scott, J., Kappos, L., Hofman, M., Polman, C. H., Ronner, H., Montalban, X., Tintore, M., Frontoni, M., Buttinelli, C., Amato, M. P., Bartolozzi, M. L., Versavel, M., Dahlke, F., Kapp, J. F., and Gibberd, R. (2003). Can the Expanded Disability Status Scale be assessed by telephone?, Mult Scler 9, 154-9.
Lee, A. G., Tang, R. A., Feldon, S. E., Pless, M., Schiffman, J. S., Rubin, R. M., and Rao, N. (2001a). Orbital presentations of giant cell arteritis, Graefes Arch Clin Exp Ophthalmol 239, 509-13.
Lee, D. A., and Martin, I. (2004). Bioreactor culture techniques for cartilage-tissue engineering, Methods Mol Biol 238, 159-70.
Lee, J. H., Johnson, P. R., Roth, M., Hunt, N. H., and Black, J. L. (2001b). ERK activation and mitogenesis in human airway smooth muscle cells, Am J Physiol Lung Cell Mol Physiol 280, L1019-29.
Lee, M. S., and Pless, M. (2003). Apoplectic lymphocytic hypophysitis. Case report, J Neurosurg 98, 183-5.
Legendre, U., Battegay, M., Nuttli, I., Dalquen, P., and Nuesch, R. (2001). Simultaneous occurrence of 2 HIV-related immunereconstitution diseases after initiation of highly active antiretroviral therapy, Scand J Infect Dis 33, 388-9.
Lehmann, F., Hildebrand, P., and Beglinger, C. (2003). New molecular targets for treatment of peptic ulcer disease, Drugs 63, 1785-97.
Lehmann, F. S., and Beglinger, C. (2003). Current role of Helicobacter pylori stool tests, Digestion 68, 119-23. Epub 2003 Nov 7.
Lehmann, F. S., Drewe, J., Terracciano, L., and Beglinger, C. (2000a). Effect of ornidazole and clarithromycin resistance on eradication of Helicobacter pylori in peptic ulcer disease, Aliment Pharmacol Ther 14, 305-9.
Lehmann, F. S., Renner, E. L., Meyer-Wyss, B., Wilder-Smith, C. H., Mazzucchelli, L., Ruchti, C., Drewe, J., Beglinger, C., and Merki, H. S. (2000b). Helicobacter pylori and gastric erosions. Results of a prevalence study in asymptomatic volunteers, Digestion 62, 82-6.
Lehmann, F. S., Terracciano, L., Carena, I., Baeriswyl, C., Drewe, J., Tornillo, L., De Libero, G., and Beglinger, C. (2002). In situ correlation of cytokine secretion and apoptosis in Helicobacter pylori-associated gastritis, Am J Physiol Gastrointest Liver Physiol 283, G481-8.
Leib, S. L., Clements, J. M., Lindberg, R. L., Heimgartner, C., Loeffler, J. M., Pfister, L. A., Tauber, M. G., and Leppert, D. (2001). Inhibition of matrix metalloproteinases and tumour necrosis factor alpha converting enzyme as adjuvant therapy in pneumococcal meningitis, Brain 124, 1734-42.
Leib, S. L., Leppert, D., Clements, J., and Tauber, M. G. (2000). Matrix metalloproteinases contribute to brain damage in experimental pneumococcal meningitis, Infect Immun 68, 615-20.
Leishman, A. J., Gapin, L., Capone, M., Palmer, E., MacDonald, H. R., Kronenberg, M., and Cheroutre, H. (2002). Precursors of functional MHC class I- or class II-restricted CD8alphaalpha( ) T cells are positively selected in the thymus by agonist self-peptides, Immunity 16, 355-64.
Leppert, D., Goodin, D. S., and Aminoff, M. J. (2003). Stimulus recognition and its relationship to the cerebral event-related potential, Neurology 61, 1533-7.
Leppert, D., Leib, S. L., Grygar, C., Miller, K. M., Schaad, U. B., and Hollander, G. A. (2000). Matrix metalloproteinase (MMP)-8 and MMP-9 in cerebrospinal fluid during bacterial meningitis: association with blood-brain barrier damage and neurological sequelae, Clin Infect Dis 31, 80-4.
Leppert, D., Lindberg, R. L., Kappos, L., and Leib, S. L. (2001). Matrix metalloproteinases: multifunctional effectors of inflammation in multiple sclerosis and bacterial meningitis, Brain Res Brain Res Rev 36, 249-57.
Leppert, D., and Radue, E. W. (2001). Medial medullary syndrome due to vertebral artery dissection, J Neurol Neurosurg Psychiatry 70, 130-1.
Lerch, N., Boesch, N., Mueller, H.J., Malik, N.J. (2000). Prader-Willi- und Angelman-Syndrom. Molekulargenetische Diagnostik mittels methylierungsspezifischer Polymerasekettenreaktion., Monatsschr Kinderheilkd (2000) 148: 691-695.
Leu, M., Bellmunt, E., Schwander, M., Farinas, I., Brenner, H. R., and Muller, U. (2003). Erbb2 regulates neuromuscular synapse formation and is essential for muscle spindle development, Development 130, 2291-301.
Leuppi, J. D., Howarth, N., Janssens, J. P., and Tamm, M. (2003a). [Lung embolism in the elderly], Z Gerontol Geriatr 36, 143-8.
Leuppi, J. D., Salzberg, M., Meyer, L., Bucher, S. E., Nief, M., Brutsche, M. H., and Tamm, M. (2003b). An individualized, adjustable maintenance regimen of budesonide/formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing, Swiss Med Wkly 133, 302-9.
Li, Y., Hahn, D., Zhong, X. Y., Thomson, P. D., Holzgreve, W., and Hahn, S. (2003a). Detection of donor-specific DNA polymorphisms in the urine of renal transplant recipients, Clin Chem 49, 655-8.
Li, Y., Zhong, X. Y., Kang, A., Troeger, C., Holzgreve, W., and Hahn, S. (2003b). Inability to detect cell free fetal DNA in the urine of normal pregnant women nor in those affected by preeclampsia associated HELLP syndrome, J Soc Gynecol Investig 10, 503-8.
Li, Y., Zimmermann, B., Rusterholz, C., Kang, A., Holzgreve, W., and Hahn, S. (2004). Size separation of circulatory DNA in maternal plasma permits ready detection of fetal DNA polymorphisms, Clin Chem 50, 1002-11. Epub 2004 Apr 8.
Li, Y., Zimmermann, B., Zhong, X. Y., Gupta, A. K., Holzgreve, W., and Hahn, S. (2003c). Determination of RHD zygosity using real-time quantitative PCR, Swiss Med Wkly 133, 442-5.
Lindberg, R. L., De Groot, C. J., Certa, U., Ravid, R., Hoffmann, F., Kappos, L., and Leppert, D. (2004). Multiple sclerosis as a generalized CNS disease-comparative microarray analysis of normal appearing white matter and lesions in secondary progressive MS, J Neuroimmunol 152, 154-67.
Lindberg, R. L., De Groot, C. J., Montagne, L., Freitag, P., van der Valk, P., Kappos, L., and Leppert, D. (2001). The expression profile of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) in lesions and normal appearing white matter of multiple sclerosis, Brain 124, 1743-53.
Linscheid, P., Keller, U., Blau, N., Schaer, D. J., and Muller, B. (2003a). Diminished production of nitric oxide synthase cofactor tetrahydrobiopterin by rosiglitazone in adipocytes, Biochem Pharmacol 65, 593-8.
Linscheid, P., Seboek, D., Nylen, E. S., Langer, I., Schlatter, M., Becker, K. L., Keller, U., and Muller, B. (2003b). In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue, Endocrinology 144, 5578-84. Epub 2003 Aug 21.
Linscheid, P., Seboek, D., Nylen, E. S., Langer, I., Schlatter, M., Keller, U., Becker, K. L., and Muller, B. (2003c). In vitro and in vivo calcitonin-I gene expression in parenchymal cells: a novel product of human adipose tissue, Endocrinology 21, 21.
Linscheid, P., Seboek, D., Schaer, D. J., Zulewski, H., Keller, U., and Muller, B. (2004). Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes, Crit Care Med 32, 1715-21.
Liu, R., Hintermann, E., Erb, C., Tanner, H., Flammer, J., Eberle, A. N., and Haefliger, I. O. (2001). Modulation of Na/K-ATPase activity by isoproterenol and propranolol in human non-pigmented ciliary epithelial cells, Klin Monatsbl Augenheilkd 218, 363-5.
Liu, S., Asparuhova, M., Brondani, V., Ziekau, I., Klimkait, T., and Schumperli, D. (2004). Inhibition of HIV-1 multiplication by antisense U7 snRNAs and siRNAs targeting cyclophilin A, Nucleic Acids Res 32, 3752-9. Print 2004.
Look, M., van Putten, W., Duffy, M., Harbeck, N., Christensen, I. J., Thomssen, C., Kates, R., Spyratos, F., Ferno, M., Eppenberger-Castori, S., Fred Sweep, C. G., Ulm, K., Peyrat, J. P., Martin, P. M., Magdelenat, H., Brunner, N., Duggan, C., Lisboa, B. W., Bendahl, P. O., Quillien, V., Daver, A., Ricolleau, G., Meijer-van Gelder, M., Manders, P., Edward Fiets, W., Blankenstein, M., Broet, P., Romain, S., Daxenbichler, G., Windbichler, G., Cufer, T., Borstnar, S., Kueng, W., Beex, L., Klijn, J., O'Higgins, N., Eppenberger, U., Janicke, F., Schmitt, M., Foekens, J., and Bendah, P. O. (2003). Pooled analysis of prognostic impact of uPA and PAI-1 in breast cancer patients, Thromb Haemost 90, 538-48.
Look, M. P., van Putten, W. L., Duffy, M. J., Harbeck, N., Christensen, I. J., Thomssen, C., Kates, R., Spyratos, F., Ferno, M., Eppenberger-Castori, S., Sweep, C. G., Ulm, K., Peyrat, J. P., Martin, P. M., Magdelenat, H., Brunner, N., Duggan, C., Lisboa, B. W., Bendahl, P. O., Quillien, V., Daver, A., Ricolleau, G., Meijer-van Gelder, M. E., Manders, P., Fiets, W. E., Blankenstein, M. A., Broet, P., Romain, S., Daxenbichler, G., Windbichler, G., Cufer, T., Borstnar, S., Kueng, W., Beex, L. V., Klijn, J. G., O'Higgins, N., Eppenberger, U., Janicke, F., Schmitt, M., and Foekens, J. A. (2002). Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients, J Natl Cancer Inst 94, 116-28.
Lorente, P., Lacampagne, A., Pouzeratte, Y., Richards, S., Malitschek, B., Kuhn, R., Bettler, B., and Vassort, G. (2000). gamma-aminobutyric acid type B receptors are expressed and functional in mammalian cardiomyocytes, Proc Natl Acad Sci U S A 97, 8664-9.
Luft, T., Maraskovsky, E., Schnurr, M., Knebel, K., Kirsch, M., Gorner, M., Skoda, R., Ho, A. D., Nawroth, P., and Bierhaus, A. (2004). Tuning the volume of the immune response: strength and persistence of stimulation determine migration and cytokine secretion of dendritic cells, Blood 104, 1066-74. Epub 2004 Apr 27.
Luther-Wyrsch, A., Costello, E., Thali, M., Buetti, E., Nissen, C., Surbek, D., Holzgreve, W., Gratwohl, A., Tichelli, A., and Wodnar-Filipowicz, A. (2001a). Stable transduction with lentiviral vectors and amplification of immature hematopoietic progenitors from cord blood of preterm human fetuses, Hum Gene Ther 12, 377-89.
Luther-Wyrsch, A., Nissen, C., Surbek, D. V., Holzgreve, W., Costello, E., Thali, M., Buetti, E., and Wodnar-Filipowicz, A. (2001b). Fetal hematopoietic stem cells: in vitro expansion and transduction using lentiviral vectors, Ernst Schering Res Found Workshop, 123-44.
Luther-Wyrsch, A., Nissen, C., and Wodnar-Filipowicz, A. (2001c). Intracellular Fas ligand is elevated in T lymphocytes in severe aplastic anaemia, Br J Haematol 114, 884-90.
Luthy, M., Blumenthal, T. D., Langewitz, W., Kiss, A., Keller, U., and Schachinger, H. (2003). Prepulse inhibition of the human startle eye blink response by visual food cues, Appetite 41, 191-5.
Mackensen, A., Herbst, B., Chen, J. L., Kohler, G., Noppen, C., Herr, W., Spagnoli, G. C., Cerundolo, V., and Lindemann, A. (2000). Phase I study in melanoma patients of a vaccine with peptide-pulsed dendritic cells generated in vitro from CD34( ) hematopoietic progenitor cells, Int J Cancer 86, 385-92.
Maclachlan, D., Battegay, M., Jacob, A. L., and Tyndall, A. (2000). Successful treatment of hepatitis B-associated polyarteritis nodosa with a combination of lamivudine and conventional immunosuppressive therapy: a case report, Rheumatology (Oxford) 39, 106-8.
Mader, I., Roser, W., Kappos, L., Hagberg, G., Seelig, J., Radue, E. W., and Steinbrich, W. (2000). Serial proton MR spectroscopy of contrast-enhancing multiple sclerosis plaques: absolute metabolic values over 2 years during a clinical pharmacological study, AJNR Am J Neuroradiol 21, 1220-7.
Maetzler, W., Nitsch, C., Bendfeldt, K., Racay, P., Vollenweider, F., and Schwaller, B. (2004). Ectopic parvalbumin expression in mouse forebrain neurons increases excitotoxic injury provoked by ibotenic acid injection into the striatum, Exp Neurol 186, 78-88.
Mahboubi, K., Biedermann, B. C., Carroll, J. M., and Pober, J. S. (2000). IL-11 activates human endothelial cells to resist immune-mediated injury, J Immunol 164, 3837-46.
Maillet, P., Chappuis, P. O., Vaudan, G., Dobbie, Z., Muller, H., Hutter, P., and Sappino, A. P. (2000). A polymorphism in the ATM gene modulates the penetrance of hereditary non-polyposis colorectal cancer, Int J Cancer 88, 928-31.
Mak, T. W., Shahinian, A., Yoshinaga, S. K., Wakeham, A., Boucher, L. M., Pintilie, M., Duncan, G., Gajewska, B. U., Gronski, M., Eriksson, U., Odermatt, B., Ho, A., Bouchard, D., Whorisky, J. S., Jordana, M., Ohashi, P. S., Pawson, T., Bladt, F., and Tafuri, A. (2003). Costimulation through the inducible costimulator ligand is essential for both T helper and B cell functions in T cell-dependent B cell responses,

Nat Immunol 4, 765-72.
Mallion, J. M., Chamontin, B., Asmar, R., De Leeuw, P. W., O'Brien, E., Duprez, D., O'Rourke, M. F., Rahn, K. H., Romero, R., Battegay, E., Hitzenberger, G., and Safar, M. E. (2004). Twenty-four-hour ambulatory blood pressure monitoring efficacy of perindopril/indapamide first-line combination in hypertensive patients: the REASON study, Am J Hypertens 17, 245-51.
Maloy, K. J., Burkhart, C., Junt, T. M., Odermatt, B., Oxenius, A., Piali, L., Zinkernagel, R. M., and Hengartner, H. (2000). CD4( ) T cell subsets during virus infection. Protective capacity depends on effector cytokine secretion and on migratory capability, J Exp Med 191, 2159-70.
Mamot, C., Mild, G., Reuter, J., Laffer, U., Metzger, U., Terracciano, L., Boulay, J. L., Herrmann, R., and Rochlitz, C. (2003). Infrequent mutation of the tumour-suppressor gene Smad4 in early-stage colorectal cancer, Br J Cancer 88, 420-3.
Mandriota, S. J., Jussila, L., Jeltsch, M., Compagni, A., Baetens, D., Prevo, R., Banerji, S., Huarte, J., Montesano, R., Jackson, D. G., Orci, L., Alitalo, K., Christofori, G., and Pepper, M. S. (2001). Vascular endothelial growth factor-C-mediated lymphangiogenesis promotes tumour metastasis, Embo J 20, 672-82.
Manolova, V., Hirabayashi, Y., Mori, L., and De Libero, G. (2003). CD1a and CD1b surface expression is independent from de novo synthesized glycosphingolipids, Eur J Immunol 33, 29-37.
Mantamadiotis, T., Lemberger, T., Bleckmann, S. C., Kern, H., Kretz, O., Martin Villalba, A., Tronche, F., Kellendonk, C., Gau, D., Kapfhammer, J., Otto, C., Schmid, W., and Schutz, G. (2002). Disruption of CREB function in brain leads to neurodegeneration, Nat Genet 31, 47-54.
Marchetti, O., Bille, J., Fluckiger, U., Eggimann, P., Ruef, C., Garbino, J., Calandra, T., Glauser, M. P., Tauber, M. G., and Pittet, D. (2004). Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991-2000, Clin Infect Dis 38, 311-20. Epub 2004 Jan 14.
Marki, Y., Kaufmann, G. R., Battegay, M., and Klimkait, T. (2002). Impact of protease polymorphisms and viral fitness on human immunodeficiency virus (HIV) type 1 viremia in untreated HIV-1 infection, J Infect Dis 185, 1844-6.
Marra, G., D'Atri, S., Corti, C., Bonmassar, L., Catturazza, M. S., Schweizer, P., Heinimann, K., Bartosova, Z., Nystrom-Lahti, M., and Jiricny, J. (2001). Tolerance of human MSH2 /- lymphoblastoid cells to the methylating agent temozolomide, Proc Natl Acad Sci U S A 98, 7164-9.
Martin, I., and Frank, O. (2004). Real-time quantitative rt-PCR assays, Methods Mol Biol 238, 231-8.
Martin, I., Jakob, M., Schafer, D., Dick, W., Spagnoli, G., and Heberer, M. (2001a). Quantitative analysis of gene expression in human articular cartilage from normal and osteoarthritic joints, Osteoarthritis Cartilage 9, 112-8.
Martin, I., Mastrogiacomo, M., De Leo, G., Muraglia, A., Beltrame, F., Cancedda, R., and Quarto, R. (2002). Fluorescence microscopy imaging of bone for automated histomorphometry, Tissue Eng 8, 847-52.
Martin, I., Obradovic, B., Treppo, S., Grodzinsky, A. J., Langer, R., Freed, L. E., and Vunjak-Novakovic, G. (2000). Modulation of the mechanical properties of tissue engineered cartilage, Biorheology 37, 141-7.
Martin, I., Shastri, V. P., Padera, R. F., Yang, J., Mackay, A. J., Langer, R., Vunjak-Novakovic, G., and Freed, L. E. (2001b). Selective differentiation of mammalian bone marrow stromal cells cultured on three-dimensional polymer foams, J Biomed Mater Res 55, 229-35.
Martin, I., Suetterlin, R., Baschong, W., Heberer, M., Vunjak-Novakovic, G., and Freed, L. E. (2001c). Enhanced cartilage tissue engineering by sequential exposure of chondrocytes to FGF-2 during 2D expansion and BMP-2 during 3D cultivation, J Cell Biochem 83, 121-8.
Martin, I., Wendt, D., and Heberer, M. (2004). The role of bioreactors in tissue engineering, Trends Biotechnol 22, 80-6.
Martin, R., and Leppert, D. (2004). A plea for "omics" research in complex diseases such as multiple sclerosis--a change of mind is needed, J Neurol Sci 222, 3-5.
Martin-Facklam, M., Drewe, J., and Haefeli, W. E. (2000). [Drug interactions with the cytochrome P-450 system], Dtsch Med Wochenschr 125, 63-7.
Martina, B., Dieterle, T., Sigle, J. P., Surber, C., and Battegay, E. (2003). Effects of telmisartan and losartan on left ventricular mass in mild-to-moderate hypertension. A randomized, double-blind trial, Cardiology 99, 169-70.
Martinez, J. M., Wagner, K. E., Snider, R. H., Nylen, E. S., Muller, B., Sarani, B., Becker, K. L., and White, J. C. (2001). Late immunoneutralization of procalcitonin arrests the progression of lethal porcine sepsis, Surg Infect (Larchmt) 2, 193-202; discussion 202-3.
Marz, P., Ozbek, S., Fischer, M., Voltz, N., Otten, U., and Rose-John, S. (2002). Differential response of neuronal cells to a fusion protein of ciliary neurotrophic factor/soluble CNTF-receptor and leukemia inhibitory factor, Eur J Biochem 269, 3023-31.
Marz, P., Probst, A., Lang, S., Schwager, M., Rose-John, S., Otten, U., and Ozbek, S. (2004). Ataxin-10, the spinocerebellar ataxia type 10 neurodegenerative disorder protein, is essential for survival of cerebellar neurons, J Biol Chem 279, 35542-50. Epub 2004 Jun 16.
Matt, P., Bernet, F., Habicht, J., Gambazzi, F., Passweg, J., Gratwohl, A., Tamm, M., and Zerkowski, H. R. (2003). Short- and long-term outcome after lung resection for invasive pulmonary aspergillosis, Thorac Cardiovasc Surg 51, 221-5.
Matt, P., Todorov, A., Grapow, M., and Zerkowski, H. R. (2004). Ascending aortic thrombus causing stroke, Eur J Cardiothorac Surg 25, 286.
Matzinger, D., Degen, L., Drewe, J., Meuli, J., Duebendorfer, R., Ruckstuhl, N., D'Amato, M., Rovati, L., and Beglinger, C. (2000). The role of long chain fatty acids in regulating food intake and cholecystokinin release in humans, Gut 46, 688-693.
Maurer, M., Riesen, W., Muser, J., Hulter, H. N., and Krapf, R. (2003). Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans, Am J Physiol Renal Physiol 284, F32-40.
Maymon, R., Tercanli, S., Dreazen, E., Sartorius, G., Holzgreve, W., and Herman, A. (2004). Comparison of pregnancy outcome of euploid fetuses with increased nuchal translucency (NT) expressed in NT MoM or delta-NT, Ultrasound Obstet Gynecol 23, 477-81.
Mayr, M., Nickeleit, V., Hirsch, H. H., Dickenmann, M., Mihatsch, M. J., and Steiger, J. (2001). Polyomavirus BK nephropathy in a kidney transplant recipient: critical issues of diagnosis and management, Am J Kidney Dis 38, E13.
McKallip, R. J., Fisher, M., Do, Y., Szakal, A. K., Gunthert, U., Nagarkatti, P. S., and Nagarkatti, M. (2003). Targeted deletion of CD44v7 exon leads to decreased endothelial cell injury but not tumor cell killing mediated by interleukin-2-activated cytolytic lymphocytes, J Biol Chem 278, 43818-30. Epub 2003 Aug 6.
Meienberg, F., Battegay, E., Bucher, H. C., and Battegay, M. (2001). The use of lipid-lowering agents in HIV-infected patients, J HIV Ther 6, 40-4.
Meienberg, F., Bucher, H. C., Sponagel, L., Zinkernagel, C., Gyr, N., and Battegay, M. (2002). Anxiety in health care workers after exposure to potentially HIV-contaminated blood or body fluids, Swiss Med Wkly 132, 321-4.
Meier, C., Beat, M., Guglielmetti, M., Christ-Crain, M., Staub, J. J., and Kraenzlin, M. (2004a). Restoration of euthyroidism accelerates bone turnover in patients with subclinical hypothyroidism: a randomized controlled trial, Osteoporos Int 15, 209-16. Epub 2004 Jan 16.
Meier, C., Christ-Crain, M., Guglielmetti, M., Huber, P., Staub, J. J., and Muller, B. (2003a). Prolactin dysregulation in women with subclinical hypothyroidism: effect of levothyroxine replacement therapy, Thyroid 13, 979-85.
Meier, C., Christ-Crain, M., Keller, U., and Staub, J. J. (2002a). [Mental changes in hypo- and hyperthyroidism], Dtsch Med Wochenschr 127, 1145-50.
Meier, C., Staub, J. J., Roth, C. B., Guglielmetti, M., Kunz, M., Miserez, A. R., Drewe, J., Huber, P., Herzog, R., and Muller, B. (2001a). TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study), J Clin Endocrinol Metab 86, 4860-6.
Meier, C., Trittibach, P., Guglielmetti, M., Staub, J. J., and Muller, B. (2003b). Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey, Bmj 326, 311-2.
Meier, C. R., Krahenbuhl, S., Schlienger, R. G., and Jick, H. (2002b). Association between body mass index and liver disorders: an epidemiological study, J Hepatol 37, 741-7.
Meier, G., Waldherr, C., Herrmann, R., Maecke, H., Mueller-Brand, J., and Pless, M. (2004b). Successful targeted radiotherapy with 90Y-DOTATOC in a patient with Merkel cell carcinoma. A Case Report, Oncology 66, 160-3.
Meier, R., Wettstein, A., Drewe, J., and Geiser, H. R. (2001b). Fish oil (Eicosapen) is less effective than metronidazole, in combination with pantoprazole and clarithromycin, for Helicobacter pylori eradication, Aliment Pharmacol Ther 15, 851-5.
Meins, M., Piosik, P., Schaeren-Wiemers, N., Franzoni, S., Troncoso, E., Kiss, J. Z., Brosamle, C., Schwab, M. E., Molnar, Z., and Monard, D. (2001). Progressive neuronal and motor dysfunction in mice overexpressing the serine protease inhibitor protease nexin-1 in postmitotic neurons, J Neurosci 21, 8830-41.
Melchers, F., ten Boekel, E., Seidl, T., Kong, X. C., Yamagami, T., Onishi, K., Shimizu, T., Rolink, A. G., and Andersson, J. (2000). Repertoire selection by pre-B-cell receptors and B-cell receptors, and genetic control of B-cell development from immature to mature B cells, Immunol Rev 175, 33-46.
Meli, D. N., Loeffler, J. M., Baumann, P., Neumann, U., Buhl, T., Leppert, D., and Leib, S. L. (2004). In pneumococcal meningitis a novel water-soluble inhibitor of matrix metalloproteinases and TNF-alpha converting enzyme attenuates seizures and injury of the cerebral cortex, J Neuroimmunol 151, 6-11.
Mendelowitsch, A. (2001). Microdialysis: intraoperative and posttraumatic applications in neurosurgery, Methods 23, 73-81.
Mendelowitsch, A., Ritz, M. F., Ros, J., Langemann, H., and Gratzl, O. (2001). 17beta-Estradiol reduces cortical lesion size in the glutamate excitotoxicity model by enhancing extracellular lactate: a new neuroprotective pathway, Brain Res 901, 230-6.
Mendelowitsch, A., Taussky, P., Rem, J. A., and Gratzl, O. (2004). Clinical outcome of standard extracranial-intracranial bypass surgery in patients with symptomatic atherosclerotic occlusion of the internal carotid artery, Acta Neurochir (Wien) 146, 95-101. Epub 2004 Jan 30.
Merlin, T., Woelky-Bruggmann, R., Fearns, C., Freudenberg, M., and Landmann, R. (2002). Expression and role of CD14 in mice sensitized to lipopolysaccharide by Propionibacterium acnes, Eur J Immunol 32, 761-72.
Merlo, A. (2003). Genes and pathways driving glioblastomas in humans and murine disease models, Neurosurg Rev 26, 145-58.
Merlo, A., and Bettler, B. (2004). Glioblastomas on the move, Sci STKE 2004, pe18.
Merlo, A., Mueller-Brand, J., and Maecke, H. R. (2003). Comparing monoclonal antibodies and small peptidic hormones for local targeting of malignant gliomas, Acta Neurochir Suppl 88, 83-91.
Metzger, F., and Kapfhammer, J. P. (2000). Protein kinase C activity modulates dendritic differentiation of rat Purkinje cells in cerebellar slice cultures, Eur J Neurosci 12, 1993-2005.
Metzger, F., and Kapfhammer, J. P. (2003). Protein kinase C: its role in activity-dependent Purkinje cell dendritic development and plasticity, Cerebellum 2, 206-14.
Metzger, J., Degen, L. P., Beglinger, C., Siegemund, M., Studer, W., Heberer, M., Harder, F., and von Flue, M. O. (2002). Ileocecal valve as substitute for the missing pyloric sphincter after partial distal gastrectomy, Ann Surg 236, 28-36.
Meyer, M., Belke, D. D., Trost, S. U., Swanson, E., Dieterle, T., Scott, B., Cary, S. P., Ho, P., Bluhm, W. F., McDonough, P. M., Silverman, G. J., and Dillmann, W. H. (2004). A recombinant antibody increases cardiac contractility by mimicking phospholamban phosphorylation, Faseb J 18, 1312-4. Epub 2004 Jun 4.
Meyer, T., Gabriel, H. H., Ratz, M., Muller, H. J., and Kindermann, W. (2001). Anaerobic exercise induces moderate acute phase response, Med Sci Sports Exerc 33, 549-55.
Michael, S., Thole, M., Dillmann, R., Fahr, A., Drewe, J., and Fricker, G. (2000). Improvement of intestinal peptide absorption by a synthetic bile acid derivative, cholylsarcosine, Eur J Pharm Sci 10, 133-40.
Michos, O., Panman, L., Vintersten, K., Beier, K., Zeller, R., and Zuniga, A. (2004). Gremlin-mediated BMP antagonism induces the epithelial-mesenchymal feedback signaling controlling metanephric kidney and limb organogenesis, Development 131, 3401-10. Epub 2004 Jun 16.
Mild, G., Bachmann, F., Boulay, J. L., Glatz, K., Laffer, U., Lowy, A., Metzger, U., Reuter, J., Terracciano, L., Herrmann, R., and Rochlitz, C. (2002). DCR3 locus is a predictive marker for 5-fluorouracil-based adjuvant chemotherapy in colorectal cancer, Int J Cancer 102, 254-7.
Miller, D. H., Thompson, A. J., and Kappos, L. (2001). MRI and assessment of treatment in multiple sclerosis, Brain 124, 1052-3.
Miller, D. S., Nobmann, S. N., Gutmann, H., Toeroek, M., Drewe, J., and Fricker, G. (2000). Xenobiotic transport across isolated brain microvessels studied by confocal microscopy, Mol Pharmacol 58, 1357-67.
Milo-Landesman, D., Surana, M., Berkovich, I., Compagni, A., Christofori, G., Fleischer, N., and Efrat, S. (2001). Correction of hyperglycemia in diabetic mice transplanted with reversibly immortalized pancreatic beta cells controlled by the tet-on regulatory system, Cell Transplant 10, 645-50.
Milting, H., Janssen, P. M., Wangemann, T., Kogler, H., Domeier, E., Seidler, T., Hakim, K., Grapow, M., Zeitz, O., Prestle, J., and Zerkowski, H. R. (2001). FK506 does not affect cardiac contractility and adrenergic response in vitro, Eur J Pharmacol 430, 299-304.
Ming, X. F., Stoecklin, G., Lu, M., Looser, R., and Moroni, C. (2001). Parallel and independent regulation of interleukin-3 mRNA turnover by phosphatidylinositol 3-kinase and p38 mitogen-activated protein kinase, Mol Cell Biol 21, 5778-89.
Miny, P., Heinimann, K., Tercanli, S., and Holzgreve, W. (2003). [Genetic testing in pregnancy], Ther Umsch 60, 455-61.
Miny, P., Tercanli, S., and Holzgreve, W. (2002). Developments in laboratory techniques for prenatal diagnosis, Curr Opin Obstet Gynecol 14, 161-8.
Miot, S., Crespo, S., and Schifferli, J. A. (2002a). Distinct forms of DAF in urine and blood, J Immunol Methods 260, 43-53.
Miot, S., Marfurt, J., Lach-Trifilieff, E., Gonzalez-Rubio, C., Lopez-Trascasa, M., Sadallah, S., and Schifferli, J. A. (2002b). The Mechanism of Loss of CR1 during Maturation of Erythrocytes Is Different between Factor I Deficient Patients and Healthy Donors, Blood Cells Mol Dis 29, 200-12.
Miserez, A. R., Clavaguera, F., Monsch, A. U., Probst, A., and Tolnay, M. (2003). Argyrophilic grain disease: molecular genetic difference to other four-repeat tauopathies, Acta Neuropathol 29, 29.
Miserez, A. R., Muller, P. Y., Barella, L., Barella, S., Staehelin, H. B., Leitersdorf, E., Kark, J. D., and Friedlander, Y. (2002a). Sterol-regulatory element-binding protein (SREBP)-2 contributes to polygenic hypercholesterolaemia, Atherosclerosis 164, 15-26.
Miserez, A. R., Muller, P. Y., Barella, L., Schwietert, M., Erb, P., Vernazza, P. L., and Battegay, M. (2001). A single-nucleotide polymorphism in the sterol-regulatory element-binding protein 1c gene is predictive of HIV-related hyperlipoproteinaemia, Aids 15, 2045-9.
Miserez, A. R., Muller, P. Y., and Spaniol, V. (2002b). Indinavir inhibits sterol-regulatory element-binding protein-1c-dependent lipoprotein lipase and fatty acid synthase gene activations, Aids 16, 1587-94.
Moalem, G., Gdalyahu, A., Shani, Y., Otten, U., Lazarovici, P., Cohen, I. R., and Schwartz, M. (2000). Production of neurotrophins by activated T cells: implications for neuroprotective autoimmunity, J Autoimmun 15, 331-45.
Moll, S., Miot, S., Sadallah, S., Gudat, F., Mihatsch, M. J., and Schifferli, J. A. (2001). No complement receptor 1 stumps on podocytes in human glomerulopathies, Kidney Int 59, 160-8.
Molyneux, P. D., Barker, G. J., Barkhof, F., Beckmann, K., Dahlke, F., Filippi, M., Ghazi, M., Hahn, D., MacManus, D., Polman, C., Pozzilli, C., Kappos, L., Thompson, A. J., Wagner, K., Yousry, T., and Miller, D. H. (2001). Clinical-MRI correlations in a European trial of interferon beta-1b in secondary progressive MS, Neurology 57, 2191-7.
Molyneux, P. D., Kappos, L., Polman, C., Pozzilli, C., Barkhof, F., Filippi, M., Yousry, T., Hahn, D., Wagner, K., Ghazi, M., Beckmann, K., Dahlke, F., Losseff, N., Barker, G. J., Thompson, A. J., and Miller, D. H. (2000). The effect of interferon beta-1b treatment on MRI measures of cerebral atrophy in secondary progressive multiple sclerosis. European Study Group on Interferon beta-1b in secondary progressive multiple sclerosis, Brain 123, 2256-63.
Moore, C., Leu, M., Muller, U., and Brenner, H. R. (2001). Induction of multiple signaling loops by MuSK during neuromuscular synapse formation, Proc Natl Acad Sci U S A 98, 14655-60.
Moransard, M., Borges, L. S., Willmann, R., Marangi, P. A., Brenner, H. R., Ferns, M. J., and Fuhrer, C. (2003). Agrin regulates rapsyn interaction with surface acetylcholine receptors, and this underlies cytoskeletal anchoring and clustering, J Biol Chem 278, 7350-9. Epub 2002 Dec 16.
Morant, R., Bernhard, J., Dietrich, D., Gillessen, S., Bonomo, M., Borner, M., Bauer, J., Cerny, T., Rochlitz, C., Wernli, M., Gschwend, A., Hanselmann, S., Hering, F., and Schmid, H. P. (2004). Capecitabine in hormone-resistant metastatic prostatic carcinoma – a phase II trial, Br J Cancer 90, 1312-7.
Morawietz, H., Goettsch, W., Szibor, M., Barton, M., Shaw, S., Hakim, K., Zerkowski, H. R., and Holtz, J. (2002a). Angiotensin-converting enzyme inhibitor therapy prevents upregulation of endothelin-converting enzyme-1 in failing human myocardium, Biochem Biophys Res Commun 295, 1057-61.
Morawietz, H., Goettsch, W., Szibor, M., Barton, M., Shaw, S., Hakim, K., Zerkowski, H. R., and Holtz, J. (2002b). Increased expression of endothelin-converting enzyme-1 in failing human myocardium, Clin Sci (Lond) 103, 237S-240S.
Morawietz, H., Szibor, M., Goettsch, W., Bartling, B., Barton, M., Shaw, S., Koerfer, R., Zerkowski, H. R., and Holtz, J. (2000). Deloading of the left ventricle by ventricular assist device normalizes increased expression of endothelin ET(A) receptors but not endothelin-converting enzyme-1 in patients with end-stage heart failure, Circulation 102, III188-93.
Mordasini, M. R., Krahenbuhl, S., and Schlienger, R. G. (2002). Appropriateness of digoxin level monitoring, Swiss Med Wkly 132, 506-12.
Morgenthaler, N. G., Struck, J., Chancerelle, Y., Weglohner, W., Agay, D., Bohuon, C., Suarez-Domenech, V., Bergmann, A., and Muller, B. (2003). Production of procalcitonin (PCT) in non-thyroidal tissue after LPS injection, Horm Metab Res 35, 290-5.
Mpandi, M., Otten, L. A., Lavanchy, C., Acha-Orbea, H., and Finke, D. (2003). Passive immunization with neutralizing antibodies interrupts the mouse mammary tumor virus life cycle, J Virol 77, 9369-77.
Mueller, C., Buerkle, G., Buettner, H. J., Petersen, J., Perruchoud, A. P., Eriksson, U., Marsch, S., and Roskamm, H. (2002). Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty, Arch Intern Med 162, 329-36.
Mueller, C., and Buser, P. (2002). B-type natriuretic peptide (BNP): can it improve our management of patients with congestive heart failure?, Swiss Med Wkly 132, 618-22.
Mueller, C., Huber, P., Laifer, G., Mueller, B., and Perruchoud, A. P. (2004a). Procalcitonin and the early diagnosis of infective endocarditis, Circulation 109,

1707-10. Epub 2004 Apr 5.
Mueller, C., Scholer, A., Laule-Kilian, K., Martina, B., Schindler, C., Buser, P., Pfisterer, M., and Perruchoud, A. P. (2004b). Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea, N Engl J Med 350, 647-54.
Mueller, H., Flury, N., Eppenberger-Castori, S., Kueng, W., David, F., and Eppenberger, U. (2000). Potential prognostic value of mitogen-activated protein kinase activity for disease-free survival of primary breast cancer patients, Int J Cancer 89, 384-8.
Mueller, H. J., Dobbie, Z., Heiinimann, K. (2000). Familiäres Kolorektalkarzinom und genetisches Screening., Chir Gastroenterol 2000 16:206-212.
Mulle, C., Sailer, A., Swanson, G. T., Brana, C., O'Gorman, S., Bettler, B., and Heinemann, S. F. (2000). Subunit composition of kainate receptors in hippocampal interneurons, Neuron 28, 475-84.
Muller, B. (2003). [Weight loss cures advertised in the media: only quackery?], Schweiz Rundsch Med Prax 92, 279-83.
Muller, B., and Abelin, T. (1994). [Evaluation of advertisements of weight-reducing cures in the press], Schweiz Med Wochenschr 124, 749-58.
Muller, B., and Becker, K. L. (2001). Procalcitonin: how a hormone became a marker and mediator of sepsis, Swiss Med Wkly 131, 595-602.
Muller, B., Becker, K. L., Kranzlin, M., Schachinger, H., Huber, P. R., Nylen, E. S., Snider, R. H., White, J. C., Schmidt-Gayk, H., Zimmerli, W., and Ritz, R. (2000a). Disordered calcium homeostasis of sepsis: association with calcitonin precursors, Eur J Clin Invest 30, 823-31.
Muller, B., Becker, K. L., Schachinger, H., Rickenbacher, P. R., Huber, P. R., Zimmerli, W., and Ritz, R. (2000b). Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit, Crit Care Med 28, 977-83.
Muller, B., Christ-Crain, M., Snider, R., Nylen, E., Becker, K.L. (2004). Procalcitonin and C-reactive Protein – a dusty way to the holy grail (letter). Clin Infect Dis 2004 (in press).
Muller, B., Kasper, M., Surber, C., and Imanidis, G. (2003a). Permeation, metabolism and site of action concentration of nicotinic acid derivatives in human skin. Correlation with topical pharmacological effect, Eur J Pharm Sci 20, 181-95.
Muller, B., Peri, G., Doni, A., Perruchoud, A. P., Landmann, R., Pasqualini, F., and Mantovani, A. (2002a). High circulating levels of the IL-1 type II decoy receptor in critically ill patients with sepsis: association of high decoy receptor levels with glucocorticoid administration, J Leukoc Biol 72, 643-9.
Muller, B., Peri, G., Doni, A., Torri, V., Landmann, R., Bottazzi, B., and Mantovani, A. (2001a). Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients, Crit Care Med 29, 1404-7.
Muller, B., Suarez Domenech, V., White, J.C., Wagner, K.E., Snider, R.S., Nylen, E.S., Becker, K.L. (2001). Calcitonin precursors: prototypes of hormokines., Journal Anästes Intensivbeh 2001 2: 60-2.
Muller, B., Tsakiris, D. A., Roth, C. B., Guglielmetti, M., Staub, J. J., and Marbet, G. A. (2001b). Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease, Eur J Clin Invest 31, 131-7.
Muller, B., White, J. C., Nylen, E. S., Snider, R. H., Becker, K. L., and Habener, J. F. (2001c). Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis, J Clin Endocrinol Metab 86, 396-404.
Muller, B., Zulewski, H., Huber, P., Ratcliffe, J. G., and Staub, J. J. (1995). Impaired action of thyroid hormone associated with smoking in women with hypothyroidism, N Engl J Med 333, 964-9.
Muller, C., Kuster, G., Buttner, H. J., and Buser, P. (2003b). [B-type natriuretic peptide--current use in the diagnosis and management of heart failure], Herz 28, 374-9.
Muller, H., Plasilova, M., Russell, A. M., and Heinimann, K. (2003c). Genetic predisposition as a basis for chemoprevention, surgical and other interventions in colorectal cancer, Recent Results Cancer Res 163, 235-47; discussion 264-6.
Muller, H. H., Heinimann, K., and Dobbie, Z. (2000c). Genetics of hereditary colon cancer – a basis for prevention?, Eur J Cancer 36, 1215-23.
Muller, H. J., Beier, R., da Palma, J. C., Lanvers, C., Ahlke, E., von Schutz, V., Gunkel, M., Horn, A., Schrappe, M., Henze, G., Kranz, K., and Boos, J. (2002b). PEG-asparaginase (Oncaspar) 2500 U/m(2) BSA in reinduction and relapse treatment in the ALL/NHL-BFM protocols, Cancer Chemother Pharmacol 49, 149-54. Epub 2001 Nov 16.
Muller, H. J., Beier, R., Loning, L., Blutters-Sawatzki, R., Dorffel, W., Maass, E., Muller-Weihrich, S., Scheel-Walter, H. G., Scherer, F., Stahnke, K., Schrappe, M., Horn, A., Lumkemann, K., and Boos, J. (2001d). Pharmacokinetics of native Escherichia coli asparaginase (Asparaginase medac) and hypersensitivity reactions in ALL-BFM 95 reinduction treatment, Br J Haematol 114, 794-9.
Muller, H. J., Grubert, M., Hilger, R., Richly, H., Port, R., Scheulen, M., and Mross, K. (2002c). The influence of elevated liver function parameters on the pharmacokinetics of doxorubicin and epirubicin--a population based pharmacokinetic study of CESAR-APOH. Central European Society for Anticancer Drug Research. Working Group for Pharmacology in Oncology and Hematology, Int J Clin Pharmacol Ther 40, 575-7.
Muller, H. J., Loning, L., Horn, A., Schwabe, D., Gunkel, M., Schrappe, M., von Schutz, V., Henze, G., Casimiro da Palma, J., Ritter, J., Pinheiro, J. P., Winkelhorst, M., and Boos, J. (2000d). Pegylated asparaginase (Oncaspar) in children with ALL: drug monitoring in reinduction according to the ALL/NHL-BFM 95 protocols, Br J Haematol 110, 379-84.
Muller, H. J., and O'Grady, R. B. (2000). Dimension-based visual attention modulates dual-judgment accuracy in Duncan's (1984) one- versus two-object report paradigm, J Exp Psychol Hum Percept Perform 26, 1332-51.
Muller, H. J., Port, R. E., Grubert, M., Hilger, R. A., Scheulen, M., and Mross, K. (2003d). The influence of liver metastases on the pharmacokinetics of doxorubicin---a population-based pharmacokinetic project of the CESAR-APOH, Int J Clin Pharmacol Ther 41, 598-9.
Muller, H. J., Reimann, B., and Krummenacher, J. (2003e). Visual search for singleton feature targets across dimensions: Stimulus- and expectancy-driven effects in dimensional weighting, J Exp Psychol Hum Percept Perform 29, 1021-35.
Muller, H. J., and von Muhlenen, A. (2000). Probing distractor inhibition in visual search: inhibition of return, J Exp Psychol Hum Percept Perform 26, 1591-605.
Muller, H. J., Weckesser, M., and Schober, O. (2000e). Bilateral renal metastasis in follicular thyroid carcinoma, Nuklearmedizin 39, 45-7.
Muller, P. Y., Janovjak, H., Miserez, A. R., and Dobbie, Z. (2002d). Processing of gene expression data generated by quantitative real-time RT-PCR, Biotechniques 32, 1372-4, 1376, 1378-9.
Muller, P. Y., and Miserez, A. R. (2002). Identification of mutations in the gene encoding sterol regulatory element binding protein (SREBP)-2 in hypercholesterolaemic subjects, J Med Genet 39, 271-5.
Muller-Schweinitzer, E., Brett, W., Zerkowski, H. R., and Haefeli, W. E. (2000). The mechanism of cryoinjury: In vitro studies on human internal mammary arteries, Br J Pharmacol 130, 636-40.
Munsch, S., Biedert, E., and Keller, U. (2003). Evaluation of a lifestyle change programme for the treatment of obesity in general practice, Swiss Med Wkly 133, 148-54.
Muruganathan, R., Krustev, R., Muller, H. J., Mohwald, H., Kolaric, B., and Klitzing, R. V. (2004). Foam Films Stabilized by Dodecyl Maltoside. 1. Film Thickness and Free Energy of Film Formation, Langmuir 20, 6352-6358.
Myhr, K. M., Sadallah, S., Mollnes, T. E., Meri, S., Nyland, H. I., Schifferli, J., and Vedeler, C. A. (2000). Interferon-alpha2a effects on complement activation and regulation in MS patients, Acta Neurol Scand 101, 30-5.
Naeher, D., Luescher, I. F., and Palmer, E. (2002). A role for the alpha-chain connecting peptide motif in mediating TCR-CD8 cooperation, J Immunol 169, 2964-70.
Naguib, M., Flood, P., McArdle, J. J., and Brenner, H. R. (2002). Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist, Anesthesiology 96, 202-31.
Netsch, M., Gutmann, H., Luescher, S., Brill, S., Schmidlin, C.B., Kreuter, M.H., Drewe, J. (2004). Inhibitory activity of a geen tea extract and some of its constituents on multidrug resistance-associated protein 2 functionality., Planta Medica 2004 (in press).
Neuhaus, P., Oustanina, S., Loch, T., Kruger, M., Bober, E., Dono, R., Zeller, R., and Braun, T. (2003). Reduced mobility of fibroblast growth factor (FGF)-deficient myoblasts might contribute to dystrophic changes in the musculature of FGF2/FGF6/mdx triple-mutant mice, Mol Cell Biol 23, 6037-48.
Neumann, U., Kubota, H., Frei, K., Ganu, V., and Leppert, D. (2004). Characterization of Mca-Lys-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH2, a fluorogenic substrate with increased specificity constants for collagenases and tumor necrosis factor converting enzyme, Anal Biochem 328, 166-73.
Neven, P., Quail, D., Levrier, M., Aguas, F., The, H. S., De Geyter, C., Glant, M. D., Beck, H., Bosio-LeGoux, B., Schmitt, H., Hottgenroth, A., and Nickelsen, T. (2004). Uterine effects of estrogen plus progestin therapy and raloxifene: adjudicated results from the EURALOX study, Obstet Gynecol 103, 881-91.
Nickeleit, V., Hirsch, H. H., Zeiler, M., Gudat, F., Prince, O., Thiel, G., and Mihatsch, M. J. (2000a). BK-virus nephropathy in renal transplants-tubular necrosis, MHC-class II expression and rejection in a puzzling game, Nephrol Dial Transplant 15, 324-32.
Nickeleit, V., Klimkait, T., Binet, I. F., Dalquen, P., Del Zenero, V., Thiel, G., Mihatsch, M. J., and Hirsch, H. H. (2000b). Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with viral nephropathy, N Engl J Med 342, 1309-15.
Niemann, B., Rochlitz, C., Herrmann, R., and Pless, M. (2004). Toxic encephalopathy induced by capecitabine, Oncology 66, 331-5.
Niermann, T., Kern, F., Erne, P., and Resink, T. (2000). The glycosyl phosphatidylinositol anchor of human T-cadherin binds lipoproteins, Biochem Biophys Res Commun 276, 1240-7.
Niermann, T., Schmutz, S., Erne, P., and Resink, T. (2003). Aryl hydrocarbon receptor ligands repress T-cadherin expression in vascular smooth muscle cells, Biochem Biophys Res Commun 300, 943-9.
Nikolova, Z., Peng, B., Hubert, M., Seiberling, M., Keller, U., Ho, Y. Y., Schran, H., and Capdeville, R. (2004a). Bioequivalence, safety, and tolerability of imatinib tablets compared with capsules, Cancer Chemother Pharmacol 23, 23.
Nikolova, Z., Peng, B., Hubert, M., Sieberling, M., Keller, U., Ho, Y. Y., Schran, H., and Capdeville, R. (2004b). Bioequivalence, safety, and tolerability of imatinib tablets compared with capsules, Cancer Chemother Pharmacol 53, 433-8.
Nissen, C., Genitsch, A., Sendelov, S., Dalle Carbonare, V., and Wodnar-Filipowicz, A. (2000). Cell cycling stress in the monocyte line as a risk factor for progression of the aplastic anaemia/paroxysmal nocturnal haemoglobinuria syndrome to myelodysplastic syndrome, Acta Haematol 103, 33-40.
Noppen, C., Levy, F., Burri, L., Zajac, P., Remmel, E., Schaefer, C., Luscher, U., Heberer, M., and Spagnoli, G. C. (2000). Naturally processed and concealed HLA-A2.1-restricted epitopes from tumor-associated antigen tyrosinase-related protein-2, Int J Cancer 87, 241-6.
Nordmann, A., Blattmann, L., Gallino, A., Khetari, R., Martina, B., Muller, P., Plebani, G., Schmid, H., and Battegay, E. (2000a). Systematic, immediate in-hospital initiation of lipid-lowering drugs during acute coronary events improves lipid control, Eur J Intern Med 11, 309-316.
Nordmann, A., Frach, B., Walker, T., Martina, B., and Battegay, E. (2000b). Comparison of self-reported home blood pressure measurements with automatically stored values and ambulatory blood pressure, Blood Press 9, 200-5.
Nordmann, A., Heilmbauer, I., Walker, T., Martina, B., and Battegay, E. (2001). A case-management program of medium intensity does not improve cardiovascular risk factor control in coronary artery disease patients: the Heartcare I trial, Am J Med 110, 543-50.
Noseworthy, J., Kappos, L., and Daumer, M. (2003). Competing interests in multiple sclerosis research, Lancet 361, 350-1.
Noue, P., Bernabe, J., Rampin, O., Vidament, M., Dumas, T., Palmer, E., and Magistrini, M. (2001). Sexual behavior of stallions during in-hand natural service and semen collection: an observation in French studs, Anim Reprod Sci 68, 161-9.
Nuesch, R., Geigy, N., Schaedler, E., and Battegay, M. (2002a). Effect of highly active antiretroviral therapy on hospitalization characteristics of HIV-infected patients, Eur J Clin Microbiol Infect Dis 21, 684-7.
Nuesch, R., Rahm, G., Rudin, W., Steffen, I., Frei, R., Rufli, T., and Zimmerli, W. (2002b). Clustering of bloodstream infections during maggot debridement therapy using contaminated larvae of Protophormia terraenovae, Infection 30, 306-9.
Nuesch, R., Schroeder, K., Dieterle, T., Martina, B., and Battegay, E. (2001). Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study, Bmj 323, 142-6.
Nutt, S. L., Eberhard, D., Horcher, M., Rolink, A. G., and Busslinger, M. (2001). Pax5 determines the identity of B cells from the beginning to the end of B-lymphopoiesis, Int Rev Immunol 20, 65-82.
Nylen, E., Muller, B., Becker, K. L., and Snider, R. (2003). The future diagnostic role of procalcitonin levels: the need for improved sensitivity, Clin Infect Dis 36, 823-4; author reply 826-7.
Nylen, E. S., and Muller, B. (2004). Endocrine changes in critical illness, J Intensive Care Med 19, 67-82.
O'Grady, R. B., and Muller, H. J. (2000). Object-based selection operates on a grouped array of locations, Percept Psychophys 62, 1655-67.
O'Rourke, D. A., Liu, Z. X., Sellin, L., Spokes, K., Zeller, R., and Cantley, L. G. (2000). Hepatocyte growth factor induces MAPK-dependent formin IV translocation in renal epithelial cells, J Am Soc Nephrol 11, 2212-21.
Obradovic, B., Martin, I., Padera, R. F., Treppo, S., Freed, L. E., and Vunjak-Novakovic, G. (2001). Integration of engineered cartilage, J Orthop Res 19, 1089-97.
Oertli, D., Marti, W. R., Zajac, P., Noppen, C., Kocher, T., Padovan, E., Adamina, M., Schumacher, R., Harder, F., Heberer, M., and Spagnoli, G. C. (2002). Rapid induction of specific cytotoxic T lymphocytes against melanoma-associated antigens by a recombinant vaccinia virus vector expressing multiple immunodominant epitopes and costimulatory molecules in vivo, Hum Gene Ther 13, 569-75.
Okura, Y., Brink, M., Itabe, H., Scheidegger, K. J., Kalangos, A., and Delafontaine, P. (2000). Oxidized low-density lipoprotein is associated with apoptosis of vascular smooth muscle cells in human atherosclerotic plaques, Circulation 102, 2680-6.
Okura, Y., Brink, M., Zahid, A. A., Anwar, A., and Delafontaine, P. (2001). Decreased expression of insulin-like growth factor-1 and apoptosis of vascular smooth muscle cells in human atherosclerotic plaque, J Mol Cell Cardiol 33, 1777-89.
Olivieri, G., Hess, C., Savaskan, E., Ly, C., Meier, F., Baysang, G., Brockhaus, M., and Muller-Spahn, F. (2001). Melatonin protects SHSY5Y neuroblastoma cells from cobalt-induced oxidative stress, neurotoxicity and increased beta-amyloid secretion, J Pineal Res 31, 320-5.
Opravil, M., Hirschel, B., Lazzarin, A., Furrer, H., Chave, J. P., Yerly, S., Bisset, L. R., Fischer, M., Vernazza, P., Bernasconi, E., Battegay, M., Ledergerber, B., Gunthard, H., Howe, C., Weber, R., and Perrin, L. (2002). A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in human immunodeficiency virus infection, J Infect Dis 185, 1251-60. Epub 2002 Apr 1.
Otten, L. A., Finke, D., and Acha-Orbea, H. (2002). Can MMTV exploit TLR4?, Trends Microbiol 10, 303-5; discussion 305-6.
Otten, U., Marz, P., Heese, K., Hock, C., Kunz, D., and Rose-John, S. (2001). Signals regulating neurotrophin expression in glial cells, Prog Brain Res 132, 545-54.
Oudit, G. Y., Crackower, M. A., Eriksson, U., Sarao, R., Kozieradzki, I., Sasaki, T., Irie-Sasaki, J., Gidrewicz, D., Rybin, V. O., Wada, T., Steinberg, S. F., Backx, P. H., and Penninger, J. M. (2003). Phosphoinositide 3-kinase gamma-deficient mice are protected from isoproterenol-induced heart failure, Circulation 108, 2147-52. Epub 2003 Sep 8.
Pache, M., Kaiser, H. J., Akhalbedashvili, N., Lienert, C., Dubler, B., Kappos, L., and Flammer, J. (2003). Extraocular blood flow and endothelin-1 plasma levels in patients with multiple sclerosis, Eur Neurol 49, 164-8.
Padovan, E., Spagnoli, G. C., Ferrantini, M., and Heberer, M. (2002a). IFN-alpha2a induces IP-10/CXCL10 and MIG/CXCL9 production in monocyte-derived dendritic cells and enhances their capacity to attract and stimulate CD8 effector T cells, J Leukoc Biol 71, 669-76.
Padovan, E., Terracciano, L., Certa, U., Jacobs, B., Reschner, A., Bolli, M., Spagnoli, G. C., Borden, E. C., and Heberer, M. (2002b). Interferon stimulated gene 15 constitutively produced by melanoma cells induces e-cadherin expression on human dendritic cells, Cancer Res 62, 3453-8.
Pagano, A., Rovelli, G., Mosbacher, J., Lohmann, T., Duthey, B., Stauffer, D., Ristig, D., Schuler, V., Meigel, I., Lampert, C., Stein, T., Prezeau, L., Blahos, J., Pin, J., Froestl, W., Kuhn, R., Heid, J., Kaupmann, K., and Bettler, B. (2001). C-terminal interaction is essential for surface trafficking but not for heteromeric assembly of GABA(b) receptors, J Neurosci 21, 1189-202.
Palmer, E. (2000). Reader interested in increased paclitaxel reactions, Oncol Nurs Forum 27, 1353.
Palmer, E. (2002a). Is Swedish pension reform the right medicine for aging Europe?, J Aging Soc Policy 14, 35-52.
Palmer, E. (2002b). Shc: a dominant player after ten seasons, Nat Immunol 3, 710-1.
Palmer, E. (2003). Negative selection--clearing out the bad apples from the T-cell repertoire, Nat Rev Immunol 3, 383-91.
Panman, L., and Zeller, R. (2003). Patterning the limb before and after SHH signalling, J Anat 202, 3-12.
Panozzo, L., Battegay, M., Friedl, A., and Vernazza, P. L. (2003). High risk behaviour and fertility desires among heterosexual HIV-positive patients with a serodiscordant partner--two challenging issues, Swiss Med Wkly 133, 124-7.
Pansky, A., Hildebrand, P., Fasler-Kan, E., Baselgia, L., Ketterer, S., Beglinger, C., and Heim, M. H. (2000). Defective Jak-STAT signal transduction pathway in melanoma cells resistant to growth inhibition by interferon-alpha, Int J Cancer 85, 720-5.
Papakonstantinou, E., Aletras, A. J., Roth, M., Tamm, M., and Karakiulakis, G. (2003). Hypoxia modulates the effects of transforming growth factor-beta isoforms on matrix-formation by primary human lung fibroblasts, Cytokine 24, 25-35.
Papakonstantinou, E., Karakiulakis, G., Tamm, M., Perruchoud, A. P., and Roth, M. (2000). Hypoxia modifies the effect of PDGF on glycosaminoglycan synthesis by primary human lung cells, Am J Physiol Lung Cell Mol Physiol 279, L825-34.
Papakonstantinou, E., Roth, M., Kokkas, B., Papadopoulos, C., and Karakiulakis, G. (2001). Losartan inhibits the angiotensin II-induced modifications on fibrinolysis and matrix deposition by primary human vascular smooth muscle cells, J Cardiovasc Pharmacol 38, 715-28.
Papakonstantinou, E., Roth, M., Tamm, M., Eickelberg, O., Perruchoud, A. P., and Karakiulakis, G. (2002). Hypoxia differentially enhances the effects of transforming growth factor-beta isoforms on the synthesis and secretion of glycosaminoglycans by human lung fibroblasts, J Pharmacol Exp Ther 301, 830-7.
Penner, I. K., Rausch, M., Kappos, L., Opwis, K., and Radu, E. W. (2003). Analysis of impairment related functional architecture in MS patients during performance of different attention tasks, J Neurol 250, 461-72.
Perl, A. K., Hokuto, I., Impagnatiello, M. A., Christofori, G., and Whitsett, J. A. (2003). Temporal effects of Sprouty on lung morphogenesis, Dev Biol 258,

154-68.
Peters, F., Ruszat, R., Hirsch, H. H., Bachmann, A., and Spicher, T. (2004). ["It's moving inside!" Bladder schistosomiasis], Schweiz Rundsch Med Prax 93, 116-9.
Petersen, T. R., Gulland, S., Bettelli, E., Kuchroo, V., Palmer, E., and Backstrom, B. T. (2004). A chimeric T cell receptor with super-signaling properties, Int Immunol 16, 889-94. Epub 2004 May 17.
Pfister, O., Chklovskaia, E., Jansen, W., Meszaros, K., Nissen, C., Rahner, C., Hurwitz, N., Bogatcheva, N., Lyman, S. D., and Wodnar-Filipowicz, A. (2000). Chronic overexpression of membrane-bound flt3 ligand by T lymphocytes in severe aplastic anaemia, Br J Haematol 109, 211-20.
Pfisterer, M., Buser, P., Osswald, S., Allemann, U., Amann, W., Angehrn, W., Eeckhout, E., Erne, P., Estlinbaum, W., Kuster, G., Moccetti, T., Naegeli, B., and Rickenbacher, P. (2003). Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial, Jama 289, 1117-23.
Pfrunder, A., Gutmann, H., Beglinger, C., and Drewe, J. (2003a). Gene expression of CYP3A4, ABC-transporters (MDR1 and MRP1-MRP5) and hPXR in three different human colon carcinoma cell lines, J Pharm Pharmacol 55, 59-66.
Pfrunder, A., Schiesser, M., Gerber, S., Haschke, M., Bitzer, J., and Drewe, J. (2003b). Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial, Br J Clin Pharmacol 56, 683-90.
Philippova, M., Ivanov, D., Tkachuk, V., Erne, P., and Resink, T. J. (2003). Polarisation of T-cadherin to the leading edge of migrating vascular cells in vitro: a function in vascular cell motility?, Histochem Cell Biol 120, 353-60. Epub 2003 Oct 25.
Pilcher, C. D., Eron, J. J., Jr., Vemazza, P. L., Battegay, M., Harr, T., Yerly, S., Vom, S., and Perrin, L. (2001). Sexual transmission during the incubation period of primary HIV infection, Jama 286, 1713-4.
Pirovino, S., Zehnder-Gerber, B., Christ-Crain, M., Keller, U., and Muller, B. (2004). [In Process Citation], Schweiz Rundsch Med Prax 93, 428-30.
Plasilova, M., Chattopadhyay, C., Pal, P., Schaub, N. A., Buechner, S. A., Mueller, H., Miny, P., Ghosh, A., and Heinimann, K. (2004a). Homozygous missense mutation in the lamin A/C gene causes autosomal recessive Hutchinson-Gilford progeria syndrome, J Med Genet 41, 609-14.
Plasilova, M., Russell, A. M., Wanner, A., Wolf, A., Dobbie, Z., Muller, H. J., and Heinimann, K. (2004b). Exclusion of an extracolonic disease modifier locus on chromosome 1p33-36 in a large Swiss familial adenomatous polyposis kindred, Eur J Hum Genet 12, 365-71.
Plekhanova, O. S., Parfyonova, Y. V., Bibilashvily, R., Stepanova, V. V., Erne, P., Bobik, A., and Tkachuk, V. A. (2000). Urokinase plasminogen activator enhances neointima growth and reduces lumen size in injured carotid arteries, J Hypertens 18, 1065-9.
Pless, M. (2000). [Value of chemotherapy in curative therapy of head and neck therapy], Hno 48, 873-6.
Pless, M., Belhadj, K., Menssen, H. D., Kern, W., Coiffier, B., Wolf, J., Herrmann, R., Thiel, E., Bootle, D., Sklenar, I., Muller, C., Choi, L., Porter, C., and Capdeville, R. (2004). Clinical efficacy, tolerability, and safety of SAM486A, a novel polyamine biosynthesis inhibitor, in patients with relapsed or refractory non-Hodgkin's lymphoma: results from a phase II multicenter study, Clin Cancer Res 10, 1299-305.
Pless, M., Carlsson, M., Sundelin, C., and Persson, K. (2001). Pre-school children with developmental co-ordination disorder: self-perceived competence and group motor skill intervention, Acta Paediatr 90, 532-8.
Pless, M., Carlsson, M., Sundelin, C., and Persson, K. (2002a). Preschool children with developmental coordination disorder: a short-term follow-up of motor status at seven to eight years of age, Acta Paediatr 91, 521-8.
Pless, M., and Chang, B. M. (2003). Rosai-Dorfman disease. Extranodal sinus histiocytosis in three co-existing sites. A case report, J Neurooncol 61, 137-41.
Pless, M., Rizzo, J. F., 3rd, Lamkin, J. C., and Lessell, S. (2000). Concordance of bilateral temporal artery biopsy in giant cell arteritis, J Neuroophthalmol 20, 216-8.
Pless, M., Rizzo, J. F., 3rd, and Shang, J. (2002b). Orbital apex syndrome: a rare presentation of extramedullary hematopoiesis: case report and review of literature, J Neurooncol 57, 37-40.
Pless, M., and Zivkovic, S. A. (2002). Neurologic complications of transplantation, Neurologist 8, 107-20.
Pletz, M. W., Duda, P. W., Kappos, L., and Steck, A. J. (2003). Immune-mediated neuropathies: etiology and pathogenic relationship to aging processes, J Neuroimmunol 137, 1-11.
Pollmann, S., Weidner, R., Muller, H. J., and von Cramon, D. Y. (2000). A fronto-posterior network involved in visual dimension changes, J Cogn Neurosci 12, 480-94.
Polman, C., Barkhof, F., Kappos, L., Pozzilli, C., Sandbrink, R., Dahlke, F., Jakobs, P., and Lorenz, A. (2003a). Oral interferon beta-1a in relapsing-remitting multiple sclerosis: a double-blind randomized study, Mult Scler 9, 342-8.
Polman, C., Kappos, L., White, R., Dahlke, F., Beckmann, K., Pozzilli, C., Thompson, A., Petkau, J., and Miller, D. (2003b). Neutralizing antibodies during treatment of secondary progressive MS with interferon beta-1b, Neurology 60, 37-43.
Polman, C. H., Kappos, L., Petkau, J., and Thompson, A. (2003c). Neutralising antibodies to interferon beta during the treatment of multiple sclerosis, J Neurol Neurosurg Psychiatry 74, 1162; author reply 1162-3.
Polyakov, A., Palmer, E., Devitt, P. G., and Coventry, B. J. (2000). Clinicians and computers: friends or foes?, Teach Learn Med 12, 91-5.
Prang, P., Del Turco, D., and Kapfhammer, J. P. (2001). Regeneration of entorhinal fibers in mouse slice cultures is age dependent and can be stimulated by NT-4, GDNF, and modulators of G-proteins and protein kinase C, Exp Neurol 169, 135-47.
Preiss, M., Besler, K., and Zerkowski, H. R. (2003). Suicidal crossbow bolt cardiac injury, Surgery 133, 228-9.
Preiss, M., Brett, W., and Zerkowski, H. R. (2001a). Extreme annuloaortic dilation of the ascending aorta, Tex Heart Inst J 28, 160.
Preiss, M., Habicht, J., Bongartz, G., and Zerkowski, H. R. (2001b). Aneurysmal and partially thrombosed orifice of a coronary artery fistula into the right atrium combined with patent foramen ovale, Thorac Cardiovasc Surg 49, 120-1.
Preiss, M., Hosli, I., Holzgreve, W., and Zerkowski, H. R. (2001c). [Aortic dissection in pregnancy in Marfan syndrome--case report and treatment concept], Z Geburtshilfe Neonatol 205, 110-3.
PRISMS, T., and 2001., P. o. R. a. D. b. I.-B.-a. S. i. M. S. S. G. (2001). Long-term efficacy of interfeeron-B-1a in relapsing multiple sclerosis., Neurology 56(12): 1628-1636.
Puder, J. J., Atar, M., Muller, B., Pavan, M., Keller, U. (2004). Using insulin pen needles up to five times does not increase pain intensity nor affect needle tip shape., Diab Res Clin Pract 2004 (in press).
Puder, J. J., and Keller, U. (2003). Quality of diabetes care: problem of patient or doctor adherence?, Swiss Med Wkly 133, 530-4.
Quinlivan, E. B., Wang, R. X., Stewart, P. W., Kolmoltri, C., Regamey, N., Erb, P., and Vernazza, P. L. (2001). Longitudinal sero-reactivity to human herpesvirus 8 (KSHV) in the Swiss HIV Cohort 4.7 years before KS, J Med Virol 64, 157-66.
Quong, J., Eppenberger-Castori, S., Moore, D., 3rd, Scott, G. K., Birrer, M. J., Kueng, W., Eppenberger, U., and Benz, C. C. (2002). Age-dependent changes in breast cancer hormone receptors and oxidant stress markers, Breast Cancer Res Treat 76, 221-36.
Radojevic, V., and Kapfhammer, J. P. (2004). Repair of the entorhino-hippocampal projection in vitro, Exp Neurol 188, 11-9.
Radue, E. W., and Kappos, L. (2003). Vancouver Consortium of MS Centers' Magnetic Resonance Imaging Guidelines, Int MS J 10, 131-3.
Radziwill, A. J., Kappos, L., Battegay, M., and Steck, A. J. (2000). [Neurological complications of HIV infection. Review: new diagnostic, therapeutic and prognostic aspects], Schweiz Med Wochenschr 130, 457-70.
Radziwill, A. J., Kuntzer, T., and Steck, A. J. (2002). [Immunopathology and treatments of Guillain-Barre syndrome and of chronic inflammatory demyelinating polyneuropathy], Rev Neurol (Paris) 158, 301-10.
Radziwill, A. J., Steck, A. J., Renaud, S., and Fuhr, P. (2003). Distal motor latency and residual latency as sensitive markers of anti-MAG polyneuropathy, J Neurol 250, 962-6.
Rahner, C., Stieger, B., and Landmann, L. (2000). Apical endocytosis in rat hepatocytes In situ involves clathrin, traverses a subapical compartment, and leads to lysosomes, Gastroenterology 119, 1692-707.
Raineri, I., Wegmueller, D., Gross, B., Certa, U., and Moroni, C. (2004). Roles of AUF1 isoforms, HuR and BRF1 in ARE-dependent mRNA turnover studied by RNA interference, Nucleic Acids Res 32, 1279-88. Print 2004.
Ramirez, J. C., Finke, D., Esteban, M., Kraehenbuhl, J. P., and Acha-Orbea, H. (2003). Tissue distribution of the Ankara strain of vaccinia virus (MVA) after mucosal or systemic administration, Arch Virol 148, 827-39.
Ramos, E., Drachenberg, C. B., Portocarrero, M., Wali, R., Klassen, D. K., Fink, J. C., Farney, A., Hirsch, H., Papadimitriou, J. C., Cangro, C. B., Weir, M. R., and Bartlett, S. T. (2002). BK virus nephropathy diagnosis and treatment: experience at the University of Maryland Renal Transplant Program, Clin Transpl, 143-53.
Ramseier, E., Fehr, J., and Hirsch, H. H. (2004). [In Process Citation], Schweiz Rundsch Med Prax 93, 1055-7.
Ratz, A. E., von Moos, M., and Drewe, J. (2001). [St. John's wort: a pharmaceutical with potentially dangerous interactions], Schweiz Rundsch Med Prax 90, 843-9.
Regamey, N., Hess, V., Passweg, J., Hess, C., Steiger, J., Erb, P., Cathomas, G., and Tamm, M. (2004). Infection with human herpesvirus 8 and transplant-associated gammopathy, Transplantation 77, 1551-4.
Regeniter, A., Siede, W. H., Scholer, A., Huber, P., Frischmuth, N., and Steiger, J. U. (2000a). Erratum to "Interpreting complex urinary patterns with MDI LABLINK: a statistical evaluation", Clin Chim Acta 301, 229-30.
Regeniter, A., Siede, W. H., Scholer, A., Huber, P., Frischmuth, N., and Steiger, J. U. (2000b). Interpreting complex urinary patterns with MDI LABLINK: a statistical evaluation, Clin Chim Acta 297, 261-73.
Regeniter, A., Steiger, J. U., Scholer, A., Huber, P. R., and Siede, W. H. (2003). Windows to the ward: graphically oriented report forms. Presentation of complex, interrelated laboratory data for electrophoresis/immunofixation, cerebrospinal fluid, and urinary protein profiles, Clin Chem 49, 41-50.
Reichenberger, F., Cathomas, G., Weber, R., Schoenenberger, R., and Tamm, M. (2001a). Recurrent fever and pulmonary infiltrates in an HIV-positive patient, Respiration 68, 548-54.
Reichenberger, F., Dickenmann, M., Binet, I., Soler, M., Bolliger, C., Steiger, J., Brunner, F., Thiel, G., and Tamm, M. (2001b). Diagnostic yield of bronchoalveolar lavage following renal transplantation, Transpl Infect Dis 3, 2-7.
Reichenberger, F., Eickelberg, O., Wyser, C., Perruchoud, A. P., Roth, M., and Tamm, M. (2001c). Distinct endobronchial expression of matrix-metalloproteinases (MMP) and their endogenous inhibitors in lung cancer, Swiss Med Wkly 131, 273-9.
Reichenberger, F., and Tamm, M. (2002). [N-acetylcystein in the therapy of chronic bronchitis], Pneumologie 56, 793-7.
Reichenberger, F., Wyser, C., Gonon, M., Cathomas, G., and Tamm, M. (2001d). Pulmonary mucosa-associated lymphoid tissue lymphoma in a patient with common variable immunodeficiency syndrome, Respiration 68, 109-12.
Reichlin, S., Dyson, A., Muller, D., Fischer, A., Fischer, H. R., and Beglinger, C. (2003). Potential of telemedicine in primary care, Curr Probl Dermatol 32, 76-81.
Remmel, E., Terracciano, L., Noppen, C., Zajac, P., Heberer, M., Spagnoli, G. C., and Padovan, E. (2001). Modulation of dendritic cell phenotype and mobility by tumor cells in vitro, Hum Immunol 62, 39-49.
Renaud, S., Erne, B., Fuhr, P., Said, G., Lacroix, C., Steck, A. J., and Leppert, D. (2003a). Matrix metalloproteinases-9 and -2 in secondary vasculitic neuropathies, Acta Neuropathol (Berl) 105, 37-42.
Renaud, S., Gregor, M., Fuhr, P., Lorenz, D., Deuschl, G., Gratwohl, A., and Steck, A. J. (2003b). Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies, Muscle Nerve 27, 611-5.
Rende, M., Brizi, E., Conner, J., Treves, S., Censier, K., Provenzano, C., Taglialatela, G., Sanna, P. P., and Donato, R. (2000). Nerve growth factor (NGF) influences differentiation and proliferation of myogenic cells in vitro via TrKA, Int J Dev Neurosci 18, 869-85.
Reschner, A., Moretta, A., Landmann, R., Heberer, M., Spagnoli, G. C., and Padovan, E. (2003). The esterbonded palmitoyl side chains of Pam3CysSerLys4 lipopeptide account for its powerful adjuvanticity to HLA class I-restricted CD8 T lymphocytes, Eur J Immunol 33, 2044-52.
Resnick, M. B., Sabo, E., Kondratev, S., Kerner, H., Spagnoli, G. C., and Yakirevich, E. (2002). Cancer-testis antigen expression in uterine malignancies with an emphasis on carcinosarcomas and papillary serous carcinomas, Int J Cancer 101, 190-5.
Rimoldi, D., Rubio-Godoy, V., Dutoit, V., Lienard, D., Salvi, S., Guillaume, P., Speiser, D., Stockert, E., Spagnoli, G., Servis, C., Cerottini, J. C., Lejeune, F., Romero, P., and Valmori, D. (2000a). Efficient simultaneous presentation of NY-ESO-1/LAGE-1 primary and nonprimary open reading frame-derived CTL epitopes in melanoma, J Immunol 165, 7253-61.
Rimoldi, D., Salvi, S., Schultz-Thater, E., Spagnoli, G. C., and Cerottini, J. C. (2000b). Anti-MAGE-3 antibody 57B and anti-MAGE-1 antibody 6C1 can be used to study different proteins of the MAGE-A family, Int J Cancer 86, 749-51.
Rinnova, M., Hradilek, M., Barinka, C., Weber, J., Soucek, M., Vondrasek, J., Klimkait, T., and Konvalinka, J. (2000). A picomolar inhibitor of resistant strains of human immunodeficiency virus protease identified by a combinatorial approach, Arch Biochem Biophys 382, 22-30.
Ritz, M. F., Lechner-Scott, J., Scott, R. J., Fuhr, P., Malik, N., Erne, B., Taylor, V., Suter, U., Schaeren-Wiemers, N., and Steck, A. J. (2000). Characterisation of autoantibodies to peripheral myelin protein 22 in patients with hereditary and acquired neuropathies, J Neuroimmunol 104, 155-63.
Robinson, R. L., Anetseder, M. J., Brancadoro, V., van Broekhoven, C., Carsana, A., Censier, K., Fortunato, G., Girard, T., Heytens, L., Hopkins, P. M., Jurkat-Rott, K., Klinger, W., Kozak-Ribbens, G., Krivosic, R., Monnier, N., Nivoche, Y., Olthoff, D., Rueffert, H., Sorrentino, V., Tegazzin, V., and Mueller, C. R. (2003). Recent advances in the diagnosis of malignant hyperthermia susceptibility: how confident can we be of genetic testing?, Eur J Hum Genet 11, 342-8.
Rochlitz, C., Dreno, B., Jantscheff, P., Cavalli, F., Squiban, P., Acres, B., Baudin, M., Escudier, B., Heinzerling, L., Morant, R., Herrmann, R., Dietrich, P. Y., and Dummer, R. (2002). Immunotherapy of metastatic melanoma by intratumoral injections of Vero cells producing human IL-2: phase II randomized study comparing two dose levels, Cancer Gene Ther 9, 289-95.
Rochlitz, C., Figlin, R., Squiban, P., Salzberg, M., Pless, M., Herrmann, R., Tartour, E., Zhao, Y., Bizouarne, N., Baudin, M., and Acres, B. (2003). Phase I immunotherapy with a modified vaccinia virus (MVA) expressing human MUC1 as antigen-specific immunotherapy in patients with MUC1-positive advanced cancer, J Gene Med 5, 690-9.
Roelcke, U., Eschle, D., Kappos, L., Moschopulos, M., Laeng, R. H., and Buettner, U. W. (2002a). Meningoradiculitis associated with giant cell arteritis, Neurology 59, 1811-2.
Roelcke, U., Hausmann, O., Merlo, A., Missimer, J., Maguire, R. P., Freitag, P., Radu, E. W., Weinreich, R., Gratzl, O., and Leenders, K. L. (2002b). PET imaging drug distribution after intratumoral injection: the case for (124)I-iododeoxyuridine in malignant gliomas, J Nucl Med 43, 1444-51.
Rolink, A. G. (2004). B-cell development and pre-B-1 cell plasticity in vitro, Methods Mol Biol 271, 271-81.
Rolink, A. G., Andersson, J., and Melchers, F. (2004). Molecular mechanisms guiding late stages of B-cell development, Immunol Rev 197, 41-50.
Rolink, A. G., and Melchers, F. (2000). Precursor B cells from Pax-5-deficient mice--stem cells for macrophages, granulocytes, osteoclasts, dendritic cells, natural killer cells, thymocytes and T cells, Curr Top Microbiol Immunol 251, 21-6.
Rolink, A. G., and Melchers, F. (2002). BAFFled B cells survive and thrive: roles of BAFF in B-cell development, Curr Opin Immunol 14, 266-75.
Rolink, A. G., Schaniel, C., Andersson, J., and Melchers, F. (2001). Selection events operating at various stages in B cell development, Curr Opin Immunol 13, 202-7.
Rolink, A. G., Schaniel, C., Bruno, L., and Melchers, F. (2002a). In vitro and in vivo plasticity of Pax5-deficient pre-B I cells, Immunol Lett 82, 35-40.
Rolink, A. G., Schaniel, C., Busslinger, M., Nutt, S. L., and Melchers, F. (2000a). Fidelity and infidelity in commitment to B-lymphocyte lineage development, Immunol Rev 175, 104-11.
Rolink, A. G., Schaniel, C., and Melchers, F. (2002b). Stability and plasticity of wild-type and Pax5-deficient precursor B cells, Immunol Rev 187, 87-95.
Rolink, A. G., Tschopp, J., Schneider, P., and Melchers, F. (2002c). BAFF is a survival and maturation factor for mouse B cells, Eur J Immunol 32, 2004-10.
Rolink, A. G., Winkler, T., Melchers, F., and Andersson, J. (2000b). Precursor B cell receptor-dependent B cell proliferation and differentiation does not require the bone marrow or fetal liver environment, J Exp Med 191, 23-32.
Rosen, O., Muller, H. J., Gokbuget, N., Langer, W., Peter, N., Schwartz, S., Hahling, D., Hartmann, F., Ittel, T. H., Muck, R., Rothmann, F., Arnold, R., Boos, J., and Hoelzer, D. (2003). Pegylated asparaginase in combination with high-dose methotrexate for consolidation in adult acute lymphoblastic leukaemia in first remission: a pilot study, Br J Haematol 123, 836-41.
Rosette, C., Werlen, G., Daniels, M. A., Holman, P. O., Alam, S. M., Travers, P. J., Gascoigne, N. R., Palmer, E., and Jameson, S. C. (2001). The impact of duration versus extent of TCR occupancy on T cell activation: a revision of the kinetic proofreading model, Immunity 15, 59-70.
Roskoden, T., Otten, U., and Schwegler, H. (2004). Early postnatal corticosterone administration regulates neurotrophins and their receptors in septum and hippocampus of the rat, Exp Brain Res 154, 183-91. Epub 2003 Oct 14.
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, 682-91.
Roth, M. (2004). Budesonide/Formoterol: a viewpoint., Drugs 2004 64(4): 443-4.
Roth, M., and Block, L. H. (2000). Distinct effects of Broncho-Vaxom (OM-85 BV) on gp130 binding cytokines, Thorax 55, 678-84.
Roth, M., Johnson, P. R., Borger, P., Bihl, M. P., Rudiger, J. J., King, G. G., Ge, Q., Hostettler, K., Burgess, J. K., Black, J. L., and Tamm, M. (2004). Dysfunctional interaction of C/EBPalpha and the glucocorticoid receptor in asthmatic bronchial smooth-muscle cells, N Engl J Med 351, 560-74.
Roth, M., Johnson, P. R., Rudiger, J. J., King, G. G., Ge, Q., Burgess, J. K., Anderson, G., Tamm, M., and Black, J. L. (2002). Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular

signalling, Lancet 360, 1293-9.
Rudiger, J. J., Eriksson, U., Schiller, P., and Leuppi, J. D. (2002a). [Henoch-Schoenlein syndrome in an 80-year-old patient], Dtsch Med Wochenschr 127, 1382-4.
Rudiger, J. J., Roth, M., Bihl, M. P., Cornelius, B. C., Johnson, M., Ziesche, R., and Block, L. H. (2002b). Interaction of C/EBPalpha and the glucocorticoid receptor in vivo and in nontransformed human cells, Faseb J 16, 177-84.
Rueckschloss, U., Galle, J., Holtz, J., Zerkowski, H. R., and Morawietz, H. (2001). Induction of NAD(P)H oxidase by oxidized low-density lipoprotein in human endothelial cells: antioxidative potential of hydroxymethylglutaryl coenzyme A reductase inhibitor therapy, Circulation 104, 1767-72.
Ruegg, S., Engelter, S., Jeanneret, C., Hetzel, A., Probst, A., Steck, A. J., and Lyrer, P. (2003). Bilateral vertebral artery occlusion resulting from giant cell arteritis: report of 3 cases and review of the literature, Medicine (Baltimore) 82, 1-12.
Ruegg, S., Stahl, M., Buhlmann, M., Dupont, A., Lyrer, P. A., Humbel, R. L., and Steck, A. J. (2002). Cerebellar degeneration and polyglandular autoimmune syndrome with anti-glutamic acid decarboxylase antibodies, J Neurol 249, 348-50.
Ruegg, S. J., Steck, A. J., and Fuhr, P. (2004). Levetiracetam improves paroxysmal symptoms in a patient with stiff-person syndrome, Neurology 62, 338.
Rueter, F., Hirsch, H. H., Kunz, F., Buser, P., Habicht, J. M., Moch, H., Fluckiger, U., and Zerkowski, H. R. (2002). Late Aspergillus fumigatus endomyocarditis with brain abscess as a lethal complication after heart transplantation, J Heart Lung Transplant 21, 1242-5.
Ruettimann, E., Vacher, C.-M., van der Putten, H., Kaupmann, K., Gassmann, M., Bettler, B. (2003). Altered hippocampal expression of calbindin D-28k and calretinin in GABA B(1)-deficient mice., Biochem Pharmacol.
Rufli, T. (2000). 82nd annual meeting of the swiss society for dermatology and venereology. september 14-16, 2000, basel, Dermatology 201, 84-100.
Ruiz-Deya, G., Cheng, S., Palmer, E., Thomas, R., and Slakey, D. (2001). Open donor, laparoscopic donor and hand assisted laparoscopic donor nephrectomy: a comparison of outcomes, J Urol 166, 1270-3; discussion 1273-4.
Rulifson, I. C., Szot, G. L., Palmer, E., and Bluestone, J. A. (2002). Inability to induce tolerance through direct antigen presentation, Am J Transplant 2, 510-9.
Rumbo, M., Sierro, F., Debard, N., Kraehenbuhl, J. P., and Finke, D. (2004). Lymphotoxin beta receptor signaling induces the chemokine CCL20 in intestinal epithelium, Gastroenterology 127, 213-23.
Ruschitzka, F. T., Wenger, R. H., Stallmach, T., Quaschning, T., de Wit, C., Wagner, K., Labugger, R., Kelm, M., Noll, G., Rulicke, T., Shaw, S., Lindberg, R. L., Rodenwaldt, B., Lutz, H., Bauer, C., Luscher, T. F., and Gassmann, M. (2000). Nitric oxide prevents cardiovascular disease and determines survival in polyglobulic mice overexpressing erythropoietin, Proc Natl Acad Sci U S A 97, 11609-13.
Rust, R. C., Landmann, L., Gosert, R., Tang, B. L., Hong, W., Hauri, H. P., Egger, D., and Bienz, K. (2001). Cellular COPII proteins are involved in production of the vesicles that form the poliovirus replication complex, J Virol 75, 9808-18.
Sadallah, S., Heim, M., Hess, C., Klimkait, T., Doppler, N., Battegay, M., Schifferli, J.A. (2004a). Contrary to HIV, Hepatitis C Virus (HCV) is not associated with erythrocytes., J Hepatol 2004 (in press).
Sadallah, S., Heim, M., Hess, C., Klimkait, T., Doppler, N., Battegay, M., Schifferli, J.A. (2004b). Differing association of HCV and HIV-1 with erythrocytes in vivo., J of Hepatology (in press).
Sadallah, S., Hess, C., Trendelenburg, M., Vedeler, C., Lopez-Trascasa, M., and Schifferli, J. A. (2003). Autoantibodies against complement receptor 1 (CD35) in SLE, liver cirrhosis and HIV-infected patients, Clin Exp Immunol 131, 174-81.
Saghatelyan, A. K., Snapyan, M., Gorissen, S., Meigel, I., Mosbacher, J., Kaupmann, K., Bettler, B., Kornilov, A. V., Nifantiev, N. E., Sakanyan, V., Schachner, M., and Dityatev, A. (2003). Recognition molecule associated carbohydrate inhibits postsynaptic GABA(B) receptors: a mechanism for homeostatic regulation of GABA release in perisomatic synapses, Mol Cell Neurosci 24, 271-82.
Sander, A., Guth, A., Brenner, H. R., and Witzemann, V. (2000). Gene transfer into individual muscle fibers and conditional gene expression in living animals, Cell Tissue Res 301, 397-403.
Sandner, S. E., Salama, A. D., Houser, S. L., Palmer, E., Turka, L. A., and Sayegh, M. H. (2003). New TCR transgenic model for tracking allospecific CD4 T-cell activation and tolerance in vivo, Am J Transplant 3, 1242-50.
Saravanan, K., Schaeren-Wiemers, N., Klein, D., Sandhoff, R., Schwarz, A., Yaghootfam, A., Gieselmann, V., and Franken, S. (2004). Specific downregulation and mistargeting of the lipid raft-associated protein MAL in a glycolipid storage disorder, Neurobiol Dis 16, 396-406.
Sarcevic, B., Spagnoli, G. C., Terracciano, L., Schultz-Thater, E., Heberer, M., Gamulin, M., Krajina, Z., Oresic, T., Separovic, R., and Juretic, A. (2003). Expression of cancer/testis tumor associated antigens in cervical squamous cell carcinoma, Oncology 64, 443-9.
Sartori, A. A., Schar, P., Fitz-Gibbon, S., Miller, J. H., and Jiricny, J. (2001). Biochemical characterization of uracil processing activities in the hyperthermophilic archaeon Pyrobaculum aerophilum, J Biol Chem 276, 29979-86. Epub 2001 Jun 8.
Satie, A. P., Rajpert-De Meyts, E., Spagnoli, G. C., Henno, S., Olivo, L., Jacobsen, G. K., Rioux-Leclercq, N., Jegou, B., and Samson, M. (2002). The cancer-testis gene, NY-ESO-1, is expressed in normal fetal and adult testes and in spermatocytic seminomas and testicular carcinoma in situ, Lab Invest 82, 775-80.
Sayegh, M. H., Wu, Z., Hancock, W. W., Langmuir, P. B., Mata, M., Sandner, S., Kishimoto, K., Sho, M., Palmer, E., Mitchell, R. N., and Turka, L. A. (2003). Allograft rejection in a new allospecific CD4 TCR transgenic mouse, Am J Transplant 3, 381-9.
Schachinger, H., Cox, D., Linder, L., Brody, S., and Keller, U. (2003). Cognitive and psychomotor function in hypoglycemia: response error patterns and retest reliability, Pharmacol Biochem Behav 75, 915-20.
Schachinger, H., Dieterle, T., Martina, B., Haberthur, C., Huber, P. R., Bock, A., Drewe, J., and Gyr, K. (2004a). Increased renovascular response to angiotensin II in persons genetically predisposed to arterial hypertension disappears after chronic angiotensin-converting enzyme inhibition, J Hypertens 22, 175-80.
Schachinger, H., Muller, B. U., Strobel, W., Drewe, J., and Ritz, R. (2000). Effect of midazolam on transfer function between beat-to-beat arterial pressure and inter-beat interval length, Br J Anaesth 84, 316-22.
Schachinger, H., Port, J., Brody, S., Linder, L., Wilhelm, F. H., Huber, P. R., Cox, D., and Keller, U. (2004b). Increased high-frequency heart rate variability during insulin-induced hypoglycaemia in healthy humans, Clin Sci (Lond) 106, 583-8.
Schaefer, D., Martin, I., Jundt, G., Seidel, J., Heberer, M., Grodzinsky, A., Bergin, I., Vunjak-Novakovic, G., and Freed, L. E. (2002). Tissue-engineered composites for the repair of large osteochondral defects, Arthritis Rheum 46, 2524-34.
Schaefer, D., Martin, I., Shastri, P., Padera, R. F., Langer, R., Freed, L. E., and Vunjak-Novakovic, G. (2000). In vitro generation of osteochondral composites, Biomaterials 21, 2599-606.
Schaefer, D. B., Wendt, D., Moretti, M., Jakob, M., Jay, G. D., Heberer, M., and Martin, I. (2004). Lubricin reduces cartilage-cartilage integration, Biorheology 41, 503-8.
Schaer, L., Osswald, S., Fuhr, P., Leppert, D. (2004). AV block III recognised by a neurolist., Neurology 2004 (in press).
Schaeren-Wiemers, N., Bonnet, A., Erb, M., Erne, B., Bartsch, U., Kern, F., Mantei, N., Sherman, D., and Suter, U. (2004). The raft-associated protein MAL is required for maintenance of proper axon-glia interactions in the central nervous system, J Cell Biol 166, 731-42.
Schafer, D., Rosso, R., Fricker, R., Spagnoli, G., Jundt, G., Gerber, H., and Heberer, M. (2000). Functional outcome of transplanted knee joints in dogs, Arch Orthop Trauma Surg 120, 426-31.
Schafer, D., Seidel, J., Martin, I., Jundt, G., Heberer, M., Grozinsky, A., Vunjak-Novakovic, G., and Freed, L. (2004). [Engineering and characterization of functional osteochondral repair tissue], Orthopade 33, 721-6.
Schaller, B., Radziwill, A. J., and Steck, A. J. (2001). Successful treatment of Guillain-Barre syndrome with combined administration of interferon-beta-1a and intravenous immunoglobulin, Eur Neurol 46, 167-8.
Schaniel, C., Bruno, L., Melchers, F., and Rolink, A. G. (2002a). Multiple hematopoietic cell lineages develop in vivo from transplanted Pax5-deficient pre-B I-cell clones, Blood 99, 472-8.
Schaniel, C., Gottar, M., Roosnek, E., Melchers, F., and Rolink, A. G. (2002b). Extensive in vivo self-renewal, long-term reconstitution capacity, and hematopoietic multipotency of Pax5-deficient precursor B-cell clones, Blood 99, 2760-6.
Schaniel, C., Melchers, F., and Rolink, A. G. (2000). The cluster of ABCD chemokines which organizes T cell-dependent B cell responses, Curr Top Microbiol Immunol 251, 181-9.
Schaniel, C., Rolink, A. G., and Melchers, F. (2001). Attractions and migrations of lymphoid cells in the organization of humoral immune responses, Adv Immunol 78, 111-68.
Schar, P. (2001). Spontaneous DNA damage, genome instability, and cancer--when DNA replication escapes control, Cell 104, 329-32.
Schar, P., Fasi, M., and Jessberger, R. (2004). SMC1 coordinates DNA double-strand break repair pathways, Nucleic Acids Res 32, 3921-9. Print 2004.
Schatz, O., Monini, P., Bugarini, R., Neipel, F., Schulz, T. F., Andreoni, M., Erb, P., Eggers, M., Haas, J., Butto, S., Lukwiya, M., Bogner, J. R., Yaguboglu, S., Sheldon, J., Sarmati, L., Goebel, F. D., Hintermaier, R., Enders, G., Regamey, N., Wernli, M., Sturzl, M., Rezza, G., and Ensoli, B. (2001). Kaposi's sarcoma-associated herpesvirus serology in Europe and Uganda: multicentre study with multiple and novel assays, J Med Virol 65, 123-32.
Schaub, S., Dickenmann, M., Cynke, E., Bircher, A., and Steiger, J. (2002). Prednisone-induced neutropenia after cadaveric kidney transplantation, Nephrol Dial Transplant 17, 1119-21.
Scheubel, R. J., Bartling, B., Stein, S., Darmer, D., Holtz, J., Pregla, R., Hetzer, R., Koerfer, R., Zerkowski, H. R., and Silber, R. E. (2001). Age-dependent myocardial reinduction of apoptosis inhibitors under VAD in heart failure, Thorac Cardiovasc Surg 49, 268-72.
Schiedermaier, P., Harrison, P., Arthur, M., Grandt, D., Sutton, R., Drewe, J., Larsen, F., and Sieber, C. (2002). Effect of the somatostatin analogue lanreotide on meal-stimulated portal blood flow in patients with liver cirrhosis, Digestion 65, 56-60.
Schiesser, M., Holzgreve, W., Lapaire, O., Willi, N., Luthi, H., Lopez, R., and Tercanli, S. (2003a). Sirenomelia, the mermaid syndrome--detection in the first trimester, Prenat Diagn 23, 493-5.
Schiesser, M., Lapaire, O., Holzgreve, W., and Tercanli, S. (2003b). Umbilical cord edema associated with patent urachus, Ultrasound Obstet Gynecol 22, 646-7.
Schiesser, M., Lapaire, O., Tercanli, S., and Holzgreve, W. (2004). Lost intrauterine devices during pregnancy: maternal and fetal outcome after ultrasound-guided extraction. An analysis of 82 cases, Ultrasound Obstet Gynecol 23, 486-9.
Schlienger, R., Kurmann, M., Drewe, J., Muller-Spahn, F., and Seifritz, E. (2000a). Inhibition of phenprocoumon anticoagulation by carbamazepine, Eur Neuropsychopharmacol 10, 219-21.
Schlienger, R. G., Keller, M. J., and Krahenbuhl, S. (2002). Tolterodine-associated acute mixed liver injury, Ann Pharmacother 36, 817-9.
Schlienger, R. G., Klink, M. H., Eggenberger, C., and Drewe, J. (2000b). Seizures associated with therapeutic doses of venlafaxine and trimipramine, Ann Pharmacother 34, 1402-5.
Schlumberger, S. E., Jaggin, V., Tanner, H., and Eberle, A. N. (2002a). Endogenous receptor for melanin-concentrating hormone in human neuroblastoma Kelly cells, Biochem Biophys Res Commun 298, 54-9.
Schlumberger, S. E., Saito, Y., Giller, T., Hintermann, E., Tanner, H., Jaggin, V., Zumsteg, U., Civelli, O., and Eberle, A. N. (2003). Different structural requirements for melanin-concentrating hormone (MCH) interacting with rat MCH-R1 (SLC-1) and mouse B16 cell MCH-R, J Recept Signal Transduct Res 23, 69-81.
Schlumberger, S. E., Talke-Messerer, C., Zumsteg, U., and Eberle, A. N. (2002b). Expression of receptors for melanin-concentrating hormone (MCH) in different tissues and cell lines, J Recept Signal Transduct Res 22, 509-31.
Schmid, A., and Hirsch, H. H. (2003). [Highly active antiretroviral therapy of HIV patients. ART Cohort Collaboration], Internist (Berl) 44, 1597-600.
Schneider, A., Suman, A., Rossi, L., Barmada, M. M., Beglinger, C., Parvin, S., Sattar, S., Ali, L., Khan, A. K., Gyr, N., and Whitcomb, D. C. (2002). SPINK1/PSTI mutations are associated with tropical pancreatitis and type II diabetes mellitus in Bangladesh, Gastroenterology 123, 1026-30.
Schneider, P., Takatsuka, H., Wilson, A., Mackay, F., Tardivel, A., Lens, S., Cachero, T. G., Finke, D., Beermann, F., and Tschopp, J. (2001). Maturation of marginal zone and follicular B cells requires B cell activating factor of the tumor necrosis factor family and is independent of B cell maturation antigen, J Exp Med 194, 1691-7.
Schnyder, A., Krahenbuhl, S., Torok, M., Drewe, J., and Huwyler, J. (2004). Targeting of skeletal muscle in vitro using biotinylated immunoliposomes, Biochem J 377, 61-7.
Schomber, T., Kalberer, C. P., Wodnar-Filipowicz, A., and Skoda, R. C. (2004). Gene silencing by lentivirus-mediated delivery of siRNA in human CD34 cells, Blood 103, 4511-3. Epub 2004 Feb 26.
Schoumacher, F., Glaus, A., Mueller, H., Eppenberger, U., Bolliger, B., and Senn, H. J. (2001). BRCA1/2 mutations in Swiss patients with familial or early-onset breast and ovarian cancer, Swiss Med Wkly 131, 223-6.
Schrenk, K., Kapfhammer, J. P., and Metzger, F. (2002). Altered dendritic development of cerebellar Purkinje cells in slice cultures from protein kinase Cgamma-deficient mice, Neuroscience 110, 675-89.
Schrum, A. G., Turka, L. A., and Palmer, E. (2003). Surface T-cell antigen receptor expression and availability for long-term antigenic signaling, Immunol Rev 196, 7-24.
Schubart, D. B., Rolink, A., Schubart, K., and Matthias, P. (2000). Cutting edge: lack of peripheral B cells and severe agammaglobulinemia in mice simultaneously lacking Bruton's tyrosine kinase and the B cell-specific transcriptional coactivator OBF-1, J Immunol 164, 18-22.
Schubart, K., Massa, S., Schubart, D., Corcoran, L. M., Rolink, A. G., and Matthias, P. (2001). B cell development and immunoglobulin gene transcription in the absence of Oct-2 and OBF-1, Nat Immunol 2, 69-74.
Schuler, M., Herrmann, R., De Greve, J. L., Stewart, A. K., Gatzemeier, U., Stewart, D. J., Laufman, L., Gralla, R., Kuball, J., Buhl, R., Heussel, C. P., Kommoss, F., Perruchoud, A. P., Shepherd, F. A., Fritz, M. A., Horowitz, J. A., Huber, C., and Rochlitz, C. (2001a). Adenovirus-mediated wild-type p53 gene transfer in patients receiving chemotherapy for advanced non-small-cell lung cancer: results of a multicenter phase II study, J Clin Oncol 19, 1750-8.
Schuler, V., Luscher, C., Blanchet, C., Klix, N., Sansig, G., Klebs, K., Schmutz, M., Heid, J., Gentry, C., Urban, L., Fox, A., Spooren, W., Jaton, A. L., Vigouret, J., Pozza, M., Kelly, P. H., Mosbacher, J., Froestl, W., Kaslin, E., Korn, R., Bischoff, S., Kaupmann, K., van der Putten, H., and Bettler, B. (2001b). Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA(B) responses in mice lacking GABA(B(1)), Neuron 31, 47-58.
Schultz-Thater, E., Noppen, C., Gudat, F., Durmuller, U., Zajac, P., Kocher, T., Heberer, M., and Spagnoli, G. C. (2000). NY-ESO-1 tumour associated antigen is a cytoplasmic protein detectable by specific monoclonal antibodies in cell lines and clinical specimens, Br J Cancer 83, 204-8.
Schumacher, R., Adamina, M., Zurbriggen, R., Bolli, M., Padovan, E., Zajac, P., Heberer, M., and Spagnoli, G. C. (2004). Influenza virosomes enhance class I restricted CTL induction through CD4 T cell activation, Vaccine 22, 714-23.
Schumacher, T., Hofer, S., Eichhorn, K., Wasner, M., Zimmerer, S., Freitag, P., Probst, A., Gratzl, O., Reubi, J. C., Maecke, R., Mueller-Brand, J., and Merlo, A. (2002). Local injection of the 90Y-labelled peptidic vector DOTATOC to control gliomas of WHO grades II and III: an extended pilot study, Eur J Nucl Med Mol Imaging 29, 486-93.
Schumann, H., Holtz, J., Zerkowski, H. R., and Hatzfeld, M. (2000). Expression of secreted frizzled related proteins 3 and 4 in human ventricular myocardium correlates with apoptosis related gene expression, Cardiovasc Res 45, 720-8.
Schutz, A., Oertli, D., Marti, W. R., Noppen, C., Padovan, E., Spagnoli, G. C., Heberer, M., and Zajac, P. (2001). Immunogenicity of nonreplicating recombinant vaccinia expressing HLA-A201 targeted or complete MART-1/Melan-A antigen, Cancer Gene Ther 8, 655-61.
Schuurmans, M. M., Hoffmann, F., Lindberg, R. L., and Meyer, U. A. (2001). Zinc mesoporphyrin represses induced hepatic 5-aminolevulinic acid synthase and reduces heme oxygenase activity in a mouse model of acute hepatic porphyria, Hepatology 33, 1217-22.
Schwab, R. E., Froidevaux, S., Paku, S., Tejeda, M., Szende, B., Pap, A., Beglinger, C., Eberle, A. N., and Keri, G. (2001). Antiproliferative efficacy of the somatostatin analogue TT-232 in human melanoma cells and tumours, Anticancer Res 21, 71-5.
Schwarzler, C., Oliferenko, S., and Gunthert, U. (2001). Variant isoforms of CD44 are required in early thymocyte development, Eur J Immunol 31, 2997-3005.
Seboek, D., Linscheid, P., Zulewski, H., Langer, I., Christ-Crain, M., Keller, U., Muller, B. (2004). Somatostatin is expressed and secreted by human adipose tissue upon infection and inflammation., J Clin Endocrinol Metab 2004 (in press).
Seidl, T., Rolink, A., and Melchers, F. (2001). The VpreB protein of the surrogate light-chain can pair with some mu heavy-chains in the absence of the lambda 5 protein, Eur J Immunol 31, 1999-2006.
Sell, S. M., White, T., Johnson, P., Johnson, J., Palmer, E., Tullis, C., and Lugemwa, P. R. (2002). An improved assay for genotyping the common Alu insertion in the tissue-type plasminogen activation gene PLAT, Genet Test 6, 67-8.
Sendi, P., Al Maiwenn, J., and Battegay, M. (2004a). Optimising the performance of an outpatient setting, Swiss Med Wkly 134, 44-9.
Sendi, P., Hoffmann, M., Bucher, H. C., Erb, P., Haller, P., Gyr, N., and Battegay, M. (2003). Intravenous opiate maintenance in a cohort of injecting drug addicts, Drug Alcohol Depend 69, 183-8.
Sendi, P., Locher, R., Bucheli, B., and Battegay, M. (2004b). The decision to get vaccinated against influenza, Am J Med 116, 856-8.
Sendi, P., Locher, R., Bucheli, B., and Battegay, M. (2004c). Intranasal influenza vaccine in a working population, Clin Infect Dis 38, 974-80. Epub 2004 Mar 15.
Sendi, P., Palmer, A. J., Gafni, A., and Battegay, M. (2001). Highly active antiretroviral therapy: pharmacoeconomic issues in the management of HIV infection, Pharmacoeconomics 19, 709-13.
Sendi, P., Schellenberg, F., Ungsedhapand, C., Kaufmann, G. R., Bucher, H. C., Weber, R., and Battegay, M. (2004d). Productivity costs and determinants of productivity in HIV-infected patients, Clin Ther 26, 791-800.
Shamshiev, A., Donda, A., Prigozy, T. I., Mori, L., Chigorno, V., Benedict, C. A., Kappos, L., Sonnino, S., Kronenberg, M., and De Libero, G. (2000). The alphabeta T cell response to self-glycolipids shows a novel mechanism of CD1b loading and a requirement for complex oligosaccharides, Immunity 13, 255-64.
Shamshiev, A., Gober, H. J., Donda, A., Mazorra, Z., Mori, L., and De Libero, G. (2002). Presentation of the same glycolipid by different CD1 molecules, J Exp Med 195, 1013-21.
Shastri, V. P., Martin, I., and Langer, R. (2000). Macroporous polymer foams by hydrocarbon templating,

Proc Natl Acad Sci U S A 97, 1970-5.
Sieber, C. C., Beglinger, C., Bart, S., Tschoepl, M., Currie, G., Larsen, F., and Drewe, J. (2004). Lanreotide effect on splanchnic blood flow in healthy subjects: effect of the rate of infusion, Clin Pharmacol Ther 75, 70-9.
Sieber, C. C., Sumanovski, L. T., Stumm, M., van der Kooij, M., and Battegay, E. (2001). In vivo angiogenesis in normal and portal hypertensive rats: role of basic fibroblast growth factor and nitric oxide, J Hepatol 34, 644-50.
Sieber, O. M., Heinimann, K., Gorman, P., Lamlum, H., Crabtree, M., Simpson, C. A., Davies, D., Neale, K., Hodgson, S. V., Roylance, R. R., Phillips, R. K., Bodmer, W. F., and Tomlinson, I. P. (2002a). Analysis of chromosomal instability in human colorectal adenomas with two mutational hits at APC, Proc Natl Acad Sci U S A 99, 16910-5. Epub 2002 Dec 16.
Sieber, O. M., Heinimann, K., and Tomlinson, I. P. (2003a). Genomic instability--the engine of tumorigenesis?, Nat Rev Cancer 3, 701-8.
Sieber, O. M., Lamlum, H., Crabtree, M. D., Rowan, A. J., Barclay, E., Lipton, L., Hodgson, S., Thomas, H. J., Neale, K., Phillips, R. K., Farrington, S. M., Dunlop, M. G., Mueller, H. J., Bisgaard, M. L., Bulow, S., Fidalgo, P., Albuquerque, C., Scarano, M. I., Bodmer, W., Tomlinson, I. P., and Heinimann, K. (2002b). Whole-gene APC deletions cause classical familial adenomatous polyposis, but not attenuated polyposis or "multiple" colorectal adenomas, Proc Natl Acad Sci U S A 99, 2954-8. Epub 2002 Feb 26.
Sieber, O. M., Lipton, L., Crabtree, M., Heinimann, K., Fidalgo, P., Phillips, R. K., Bisgaard, M. L., Orntoft, T. F., Aaltonen, L. A., Hodgson, S. V., Thomas, H. J., and Tomlinson, I. P. (2003b). Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH, N Engl J Med 348, 791-9.
Simon-Vermot, I., and Keller, U. (2000). [Consequences and complications of obesity], Ther Umsch 57, 493-7.
Skeie, G. O., Mygland, A., Treves, S., Gilhus, N. E., Aarli, J. A., and Zorzato, F. (2003). Ryanodine receptor antibodies in myasthenia gravis: epitope mapping and effect on calcium release in vitro, Muscle Nerve 27, 81-9.
Skoda, R. C. (2004). Chronic myeloproliferative disorders: molecular markers and pathogenesis, Hematol J 5, S122-5.
Sollberger, M., Erne, B., Sansano, S., Steck, A. J., and Schaeren-Wiemers, N. (2002). Characterization of human nerve basal lamina for their binding properties of anti-MAG antibodies, J Neurocytol 31, 5-14.
Sollberger, M., Fluri, F., Baumann, T., Sonnet, S., Tamm, M., Steck, A. J., and Brutsche, M. (2004). Successful treatment of steroid-refractory neurosarcoidosis with infliximab, J Neurol 251, 760-1.
Sormani, M. P., Bruzzi, P., Beckmann, K., Wagner, K., Miller, D. H., Kappos, L., and Filippi, M. (2003). MRI metrics as surrogate endpoints for EDSS progression in SPMS patients treated with IFN beta-1b, Neurology 60, 1462-6.
Spagnoli, G. C., Kloth, J., Terracciano, L., Trutmann, M., Chklovskaia, E., Remmel, E., Noppen, C., Zajac, P., Kocher, T., and Heberer, M. (2000). FLT3 ligand gene expression and protein production in human colorectal cancer cell lines and clinical tumor specimens, Int J Cancer 86, 238-43.
Spagnoli, G. C., Zajac, P., Marti, W. R., Oertli, D., Padovan, E., Noppen, C., Kocher, T., Adamina, M., and Heberer, M. (2002). Cytotoxic T-cell induction in metastatic melanoma patients undergoing recombinant vaccinia virus-based immuno-gene therapy, Recent Results Cancer Res 160, 195-201.
Span, P. N., Lindberg, R. L., Manders, P., Tjan-Heijnen, V. C., Heuvel, J. J., Beex, L. V., and Sweep, C. G. (2004). Tissue inhibitors of metalloproteinase expression in human breast cancer: TIMP-3 is associated with adjuvant endocrine therapy success, J Pathol 202, 395-402.
Span, P. N., Sweep, C. G., Manders, P., Beex, L. V., Leppert, D., and Lindberg, R. L. (2003). Matrix metalloproteinase inhibitor reversion-inducing cysteine-rich protein with Kazal motifs: a prognostic marker for good clinical outcome in human breast carcinoma, Cancer 97, 2710-5.
Spaniol, M., Bracher, R., Ha, H. R., Follath, F., and Krahenbuhl, S. (2001a). Toxicity of amiodarone and amiodarone analogues on isolated rat liver mitochondria, J Hepatol 35, 628-36.
Spaniol, M., Brooks, H., Auer, L., Zimmermann, A., Solioz, M., Stieger, B., and Krahenbuhl, S. (2001b). Development and characterization of an animal model of carnitine deficiency, Eur J Biochem 268, 1876-87.
Spaniol, M., Kaufmann, P., Beier, K., Wuthrich, J., Torok, M., Scharnagl, H., Marz, W., and Krahenbuhl, S. (2003). Mechanisms of liver steatosis in rats with systemic carnitine deficiency due to treatment with trimethylhydraziniumpropionate, J Lipid Res 44, 144-53.
Spiegel, I., Salomon, D., Erne, B., Schaeren-Wiemers, N., and Peles, E. (2002). Caspr3 and caspr4, two novel members of the caspr family are expressed in the nervous system and interact with PDZ domains, Mol Cell Neurosci 20, 283-97.
Spirig, R., Nicca, D., Werder, V., Voggensperger, J., Unger, M., Bischofberger, I., Kesselring, A., Battegay, M., and De Geest, S. (2002). [Developing and establishing an expanded and more comprehensive HIV/AIDS nursing practice], Pflege 15, 293-9.
Spycher, C., Klonis, N., Spielmann, T., Kump, E., Steiger, S., Tilley, L., and Beck, H. P. (2003). MAHRP-1, a novel Plasmodium falciparum histidine-rich protein, binds ferriprotoporphyrin IX and localizes to the Maurer's clefts, J Biol Chem 278, 35373-83. Epub 2003 Jun 18.
Staehelin, C., Rickenbach, M., Low, N., Egger, M., Ledergerber, B., Hirschel, B., D'Acremont, V., Battegay, M., Wagels, T., Bernasconi, E., Kopp, C., and Furrer, H. (2003). Migrants from Sub-Saharan Africa in the Swiss HIV Cohort Study: access to antiretroviral therapy, disease progression and survival, Aids 17, 2237-44.
Steck, A. J. (2000). Auto-antibody tests in peripheral neuropathies: pros and cons, J Neurol 247, 423-8.
Steck, B., Amsler, F., Kappos, L., and Burgin, D. (2001). Gender-specific differences in the process of coping in families with a parent affected by a chronic somatic disease (e.g. multiple sclerosis), Psychopathology 34, 236-44.
Steffen, I., Bienz, K., and Klimkait, T. (2003). [Modern methods of virus diagnosis], Ther Umsch 60, 589-94.
Steiger, D., Bubendorf, L., Oberholzer, M., Tamm, M., and Leuppi, J. D. (2004). Ciprofloxacin-induced acute interstitial pneumonitis, Eur Respir J 23, 172-4.
Steiger, J. (2000). [In Process Citation], Schweiz Med Wochenschr Suppl 120, 11S.
Steiger, J., Habicht, J., Dalquen, P., and Tamm, M. (2000). Pulmonary nodules following kidney transplantation, Respiration 67, 104-7.
Steinhauer, S. R., Siegle, G. J., Condray, R., and Pless, M. (2004). Sympathetic and parasympathetic innervation of pupillary dilation during sustained processing, Int J Psychophysiol 52, 77-86.
Stevens, M. M., Marini, R. P., Martin, I., Langer, R., and Prasad Shastri, V. (2004). FGF-2 enhances TGF-beta1-induced periosteal chondrogenesis, J Orthop Res 22, 1114-9.
Stockli, R., and Battegay, M. (2001). [Generalized lymphadenopathy in a 43-year-old patient], Schweiz Rundsch Med Prax 90, 747-9.
Stockli, R., and Keller, U. (2002). [From obesity to diabetes], Ther Umsch 59, 388-92.
Stockli, R., and Keller, U. (2003). [Effectiveness of therapeutic interventions in obesity], Schweiz Rundsch Med Prax 92, 1999-2006.
Stoeckli, R., Chanda, R., Langer, I., and Keller, U. (2004). Changes of body weight and plasma ghrelin levels after gastric banding and gastric bypass, Obes Res 12, 346-50.
Stoeckli, T. C., Steffen-Klopfstein, I., Erb, P., Brown, T. M., and Kalish, M. L. (2000). Molecular epidemiology of HIV-1 in Switzerland: evidence for a silent mutation in the C2V3 region distinguishing intravenous drug users from homosexual men. Swiss HIV Cohort Study, J Acquir Immune Defic Syndr 23, 58-67.
Stoecklin, G., Colombi, M., Raineri, I., Leuenberger, S., Mallaun, M., Schmidlin, M., Gross, B., Lu, M., Kitamura, T., and Moroni, C. (2002). Functional cloning of BRF1, a regulator of ARE-dependent mRNA turnover, Embo J 21, 4709-18.
Stoecklin, G., Gross, B., Ming, X. F., and Moroni, C. (2003a). A novel mechanism of tumor suppression by destabilizing AU-rich growth factor mRNA, Oncogene 22, 3554-61.
Stoecklin, G., Lu, M., Rattenbacher, B., and Moroni, C. (2003b). A constitutive decay element promotes tumor necrosis factor alpha mRNA degradation via an AU-rich element-independent pathway, Mol Cell Biol 23, 3506-15.
Stoecklin, G., Ming, X. F., Looser, R., and Moroni, C. (2000). Somatic mRNA turnover mutants implicate tristetraprolin in the interleukin-3 mRNA degradation pathway, Mol Cell Biol 20, 3753-63.
Stoecklin, G., Stoeckle, P., Lu, M., Muehlemann, O., and Moroni, C. (2001). Cellular mutants define a common mRNA degradation pathway targeting cytokine AU-rich elements, Rna 7, 1578-88.
Stoermer, R., Drewe, J., Dursteler-Mac Farland, K. M., Hock, C., Mueller-Spahn, F., Ladewig, D., Stohler, R., and Mager, R. (2003). Safety of injectable opioid maintenance treatment for heroin dependence, Biol Psychiatry 54, 854-61.
Stoffel, F., Forster, T. H., Steiger, J., Gasser, T. C., and Sulser, T. (2002). [Manually-assisted laparoscopic donor nephrectomy], Urologe A 41, 258-62.
Stotz, M., Albrecht, R., Zwicker, G., Drewe, J., and Ummenhofer, W. (2003). EMS defibrillation-first policy may not improve outcome in out-of-hospital cardiac arrest, Resuscitation 58, 277-82.
Straumann, A., Rossi, L., Simon, H. U., Heer, P., Spichtin, H. P., and Beglinger, C. (2003a). Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis?, Gastrointest Endosc 57, 407-12.
Straumann, A., Spichtin, H. P., Grize, L., Bucher, K. A., Beglinger, C., and Simon, H. U. (2003b). Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years, Gastroenterology 125, 1660-9.
Strebel, A., Bachmann, F., Wernli, M., and Erb, P. (2002). Tumor necrosis factor-related, apoptosis-inducing ligand supports growth of mouse mastocytoma tumors by killing tumor-infiltrating macrophages, Int J Cancer 100, 627-34.
Strebel, A., Harr, T., Bachmann, F., Wernli, M., and Erb, P. (2001). Green fluorescent protein as a novel tool to measure apoptosis and necrosis, Cytometry 43, 126-33.
Strub, M., Fuhr, P., and Kappos, L. (2000). [Late manifestation of radiation injury to the plexus brachialis and plexus lumbosacralis], Schweiz Med Wochenschr 130, 1407-12.
Stubiger, N., Crane, I. J., Kotter, I., Lamont, G. R., Zoeller, M., Gunthert, U., Forrester, J. V., Zierhut, M., and Stiemer, R. H. (2003). Interferon alpha 2a in IRPB-derived peptide-induced EAU--part I, Adv Exp Med Biol 528, 537-40.
Stuen, S., Bergstrom, K., and Palmer, E. (2002). Reduced weight gain due to subclinical Anaplasma phagocytophilum (formerly Ehrlichia phagocytophila) infection, Exp Appl Acarol 28, 209-15.
Sturm, J., Keese, M., Zhang, H., Bonninghoff, R., Magdeburg, R., Vajkoczy, P., Dono, R., Zeller, R., and Gretz, N. (2004). Liver regeneration in FGF-2-deficient mice: VEGF acts as potential functional substitute for FGF-2, Liver Int 24, 161-8.
Suarez, J., Belke, D. D., Gloss, B., Dieterle, T., McDonough, P. M., Kim, Y. K., Brunton, L. L., and Dillmann, W. H. (2004). In vivo adenoviral transfer of sorcin reverses cardiac contractile abnormalities of diabetic cardiomyopathy, Am J Physiol Heart Circ Physiol 286, H68-75. Epub 2003 Sep 4.
Sulser, T., Gurke, L., Langer, I., Dickenmann, M., Steiger, J., Gasser, T. C., and Bachmann, A. (2004). Retroperitoneoscopic living-donor nephrectomy: first clinical experiences in 19 operations, J Endourol 18, 257-62.
Sun, Y., Marz, P., Otten, U., Ge, J., and Rose-John, S. (2002). The effect of gp130 stimulation on glutamate-induced excitotoxicity in primary hippocampal neurons, Biochem Biophys Res Commun 295, 532-9.
Sune, C., Brennan, L., Stover, D. R., and Klimkait, T. (2004). Effect of polymorphisms on the replicative capacity of protease inhibitor-resistant HIV-1 variants under drug pressure, Clin Microbiol Infect 10, 119-26.
Surbek, D., Seelmann, K., Gratwohl, A., Tichelli, A., Drack, G., Hohlfeld, P., Chapuis, B., Schneider, H., Holzgreve, W. (2003). Nabelschnurblutspende: unverwandte Spende, familiäre (gerichtete) Spende und autologe Spende ("Private Banking"). Gynäkol Geburtsh Rundsch 2003 43: 118-21.
Surbek, D. V., Aufderhaar, U., and Holzgreve, W. (2000a). Umbilical cord blood collection for transplantation: which technique should be preferred?, Am J Obstet Gynecol 183, 1587-8.
Surbek, D. V., Danzer, E., Steinmann, C., Tichelli, A., Wodnar-Filipowicz, A., Hahn, S., and Holzgreve, W. (2001a). Effect of preeclampsia on umbilical cord blood hematopoietic progenitor-stem cells, Am J Obstet Gynecol 185, 725-9.
Surbek, D. V., Glanzmann, R., Senn, H. P., Hoesli, I., and Holzgreve, W. (2000b). Can cord blood be used for autologous transfusion in preterm neonates?, Eur J Pediatr 159, 790-1.
Surbek, D. V., Hoesli, I. M., and Holzgreve, W. (2000c). Morphology assessed by transvaginal ultrasonography differs in patients in preterm labor with vs. without bacterial vaginosis, Ultrasound Obstet Gynecol 15, 242-5.
Surbek, D. V., and Holzgreve, W. (2001a). Fetal cells from cord blood as stem cell source: current status and possible implications in gynaecologic oncology, Eur J Gynaecol Oncol 22, 6-12.
Surbek, D. V., and Holzgreve, W. (2001b). Prenatal transplantation of hematopoietic stem cells: overview, Ernst Schering Res Found Workshop, 115-22.
Surbek, D. V., Holzgreve, W., and Nicolaides, K. H. (2001b). Haematopoietic stem cell transplantation and gene therapy in the fetus: ready for clinical use?, Hum Reprod Update 7, 85-91.
Surbek, D. V., Holzgreve, W., Steinmann, C., Hahn, S., Gratwohl, A., Wodnar-Filipowicz, A., and Tichelli, A. (2000d). Preterm birth and the availability of cord blood for HPC transplantation, Transfusion 40, 817-20.
Surbek, D. V., Schatt, S., Holzgreve, W. (2001). Stem Cell Transplantation and gene therapy inuetro., Infusion Therapy and Transfusion Medicine 2001 28: 150-8.
Surbek, D. V., Steinmann, C., Burk, M., Hahn, S., Tichelli, A., and Holzgreve, W. (2000e). Developmental changes in adhesion molecule expressions in umbilical cord blood CD34 hematopoietic progenitor and stem cells, Am J Obstet Gynecol 183, 1152-7.
Surbek, D. V., Steinmann, C., Tichelli, A., Wodnar-Filipowicz, A., and Holzgreve, W. (2000f). Decreased cord blood yield in post-term pregnancy: a comparative study, Br J Haematol 110, 235-7.
Surbek, D. V., Tercanli, S., and Holzgreve, W. (2000g). Transabdominal first trimester embryofetoscopy as a potential approach to early in utero stem cell transplantation and gene therapy, Ultrasound Obstet Gynecol 15, 302-7.
Surbek, D. V., Visca, E., Steinmann, C., Tichelli, A., Schatt, S., Hahn, S., Gratwohl, A., and Holzgreve, W. (2000h). Umbilical cord blood collection before placental delivery during cesarean delivery increases cord blood volume and nucleated cell number available for transplantation, Am J Obstet Gynecol 183, 218-21.
Surbek, D. V., Young, A., Danzer, E., Schoeberlein, A., Dudler, L., and Holzgreve, W. (2002). Ultrasound-guided stem cell sampling from the early ovine fetus for prenatal ex vivo gene therapy, Am J Obstet Gynecol 187, 960-3.
Szinnai, C., Mottet, C., Gutzwiller, J. P., Drewe, J., Beglinger, C., and Sieber, C. C. (2001). Role of gender upon basal and postprandial systemic and splanchnic haemodynamics in humans, Scand J Gastroenterol 36, 540-4.
Szinnai, G., Meier, C., Komminoth, P., and Zumsteg, U. W. (2003). Review of multiple endocrine neoplasia type 2A in children: therapeutic results of early thyroidectomy and prognostic value of codon analysis, Pediatrics 111, E132-9.
Taillard, C., Greub, G., Weber, R., Pfyffer, G. E., Bodmer, T., Zimmerli, S., Frei, R., Bassetti, S., Rohner, P., Piffaretti, J. C., Bernasconi, E., Bille, J., Telenti, A., and Prod'hom, G. (2003). Clinical implications of Mycobacterium kansasii species heterogeneity: Swiss National Survey, J Clin Microbiol 41, 1240-4.
Tamm, M., Eich, C., Frei, R., Gilgen, S., Breitenbucher, A., and Mordasini, C. (2000). [Inhaled colistin in cystic fibrosis], Schweiz Med Wochenschr 130, 1366-72.
Tamm, M., Traenkle, P., Grilli, B., Soler, M., Bolliger, C. T., Dalquen, P., and Cathomas, G. (2001). Pulmonary cytomegalovirus infection in immunocompromised patients, Chest 119, 838-43.
Tardivel, A., Tinel, A., Lens, S., Steiner, Q. G., Sauberli, E., Wilson, A., Mackay, F., Rolink, A. G., Beermann, F., Tschopp, J., and Schneider, P. (2004). The anti-apoptotic factor Bcl-2 can functionally substitute for the B cell survival but not for the marginal zone B cell differentiation activity of BAFF, Eur J Immunol 34, 509-18.
Tartour, E., Mehtali, M., Sastre-Garau, X., Joyeux, I., Mathiot, C., Pleau, J. M., Squiban, P., Rochlitz, C., Courtney, M., Jantscheff, P., Herrmann, R., Pouillart, P., Fridman, W. H., and Dorval, T. (2000). Phase I clinical trial with IL-2-transfected xenogeneic cells administered in subcutaneous metastatic tumours: clinical and immunological findings, Br J Cancer 83, 1454-61.
Tay, A. G., Farhadi, J., Suetterlin, R., Pierer, G., Heberer, M., and Martin, I. (2004). Cell yield, proliferation, and postexpansion differentiation capacity of human ear, nasal, and rib chondrocytes, Tissue Eng 10, 762-70.
te Welscher, P., Fernandez-Teran, M., Ros, M. A., and Zeller, R. (2002a). Mutual genetic antagonism involving GLI3 and dHAND prepatterns the vertebrate limb bud mesenchyme prior to SHH signaling, Genes Dev 16, 421-6.
te Welscher, P., Zuniga, A., Kuijper, S., Drenth, T., Goedemans, H. J., Meijlink, F., and Zeller, R. (2002b). Progression of vertebrate limb development through SHH-mediated counteraction of GLI3, Science 298, 827-30. Epub 2002 Sep 5.
Terada, N., Ohno, N., Yamakawa, H., Baba, T., Fujii, Y., Christofori, G., Ohara, O., and Ohno, S. (2003). Protein 4.1B in mouse islets of Langerhans and beta-cell tumorigenesis, Histochem Cell Biol 120, 277-83. Epub 2003 Sep 9.
Tercanli, S., Miny, P., Siebert, M. S., Hosli, I., Surbek, D. V., and Holzgreve, W. (2001). Fanconi anemia associated with increased nuchal translucency detected by first-trimester ultrasound, Ultrasound Obstet Gynecol 17, 160-2.
Terszowski, G., Jankowski, A., Hendriks, W. J., Rolink, A. G., and Kisielow, P. (2001). Within the hemopoietic system, LAR phosphatase is a T cell lineage-specific adhesion receptor-like protein whose phosphatase activity appears dispensable for T cell development, repertoire selection and function, Eur J Immunol 31, 832-40.
Thomas, S. Y., Hou, R., Boyson, J. E., Means, T. K., Hess, C., Olson, D. P., Strominger, J. L., Brenner, M. B., Gumperz, J. E., Wilson, S. B., and Luster, A. D. (2003). CD1d-restricted NKT cells express a chemokine receptor profile indicative of Th1-type inflammatory homing cells, J Immunol 171, 2571-80.
Thurlimann, B., Hess, D., Koberle, D., Senn, I., Ballabeni, P., Pagani, O., Perey, L., Aebi, S., Rochlitz, C., and Goldhirsch, A. (2004). Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95--a sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial, Breast Cancer Res Treat 85, 247-54.
Thut, M. P., Uehlinger, D., Steiger, J., and Mihatsch, M. J. (2002). [Renal biopsy: standard procedure of modern nephrology], Ther Umsch 59, 110-6.
Tietz, A., Heim, M. H., Eriksson, U., Marsch, S., Terracciano, L., and Krahenbuhl, S. (2003). Fulminant liver failure associated with clarithromycin, Ann Pharmacother 37, 57-60.
Tietz, A., Tamm, M., and Battegay, M. (2000). Mycobacterium kansasii abscess of the chest wall after drainage of bacterial empyema, Eur J Clin Microbiol

Infect Dis 19, 72-3.
Tissot, J. D., Sanchez, J. C., Vuadens, F., Scherl, A., Schifferli, J. A., Hochstrasser, D. F., Schneider, P., and Duchosal, M. A. (2002). IgM are associated to Sp alpha (CD5 antigen-like), Electrophoresis 23, 1203-6.
Todesco, L., Torok, M., Krahenbuhl, S., and Wenk, M. (2003). Determination of -3858G-- A and -164C-- A genetic polymorphisms of CYP1A2 in blood and saliva by rapid allelic discrimination: large difference in the prevalence of the -3858G-- A mutation between Caucasians and Asians, Eur J Clin Pharmacol 59, 343-6.
Torok, M., Huwyler, J., Gutmann, H., Fricker, G., and Drewe, J. (2003). Modulation of transendothelial permeability and expression of ATP-binding cassette transporters in cultured brain capillary endothelial cells by astrocytic factors and cell-culture conditions, Exp Brain Res 153, 356-65. Epub 2003 Sep 12.
Towers, S., Principalle, A., Billinton, A., Edmunds, M., Bettler, B., Urban, L., Castro-Lopes, J., and Bowery, N. G. (2000). GABAB receptor protein and mRNA distribution in rat spinal cord and dorsal root ganglia, Eur J Neurosci 12, 3201-10.
Trampuz, A., Widmer, A. F., Fluckiger, U., Haenggi, M., Frei, R., and Zimmerli, W. (2004). Changes in the epidemiology of pneumococcal bacteremia in a Swiss university hospital during a 15-year period, 1986-2000, Mayo Clin Proc 79, 604-12.
Trendelenburg, M., Lutz, H. U., Tissot, J. D., Moll, S., Hoffmann, T., and Schifferli, J. A. (2003). Cryoglobulin/albumin complexes in a patient with severe autoimmune syndrome, Scand J Rheumatol 32, 367-73.
Trendelenburg, M., and Schifferli, J. A. (2000a). [Apoptosis and C1q: possible explanations for the pathogenesis of systemic lupus erythematosus], Z Rheumatol 59, 172-5.
Trendelenburg, M., and Schifferli, J. A. (2000b). [New physiopathological findings in paraproteinemias], Schweiz Med Wochenschr 130, 1639-42.
Trendelenburg, M., and Schifferli, J. A. (2003). Cryoglobulins in chronic hepatitis C virus infection, Clin Exp Immunol 133, 153-5.
Treves, S., Feriotto, G., Moccagatta, L., Gambari, R., and Zorzato, F. (2000). Molecular cloning, expression, functional characterization, chromosomal localization, and gene structure of junctate, a novel integral calcium binding protein of sarco(endo)plasmic reticulum membrane, J Biol Chem 275, 39555-68.
Treves, S., Franzini-Armstrong, C., Moccagatta, L., Arnoult, C., Grasso, C., Schrum, A., Ducreux, S., Zhu, M. X., Mikoshiba, K., Girard, T., Smida-Rezgui, S., Ronjat, M., and Zorzato, F. (2004). Junctate is a key element in calcium entry induced by activation of InsP3 receptors and/or calcium store depletion, J Cell Biol 166, 537-48. Epub 2004 Aug 9.
Treves, S., Pouliquin, R., Moccagatta, L., and Zorzato, F. (2002). Functional properties of EGFP-tagged skeletal muscle calcium-release channel (ryanodine receptor) expressed in COS-7 cells: sensitivity to caffeine and 4-chloro-m-cresol, Cell Calcium 31, 1-12.
Trkola, A., Kuster, H., Leemann, C., Oxenius, A., Fagard, C., Furrer, H., Battegay, M., Vernazza, P., Bernasconi, E., Weber, R., Hirschel, B., Bonhoeffer, S., and Guenthard, H. F. (2004). Humoral immunity to HIV-1: Kinetics of antibody responses in chronic infection reflect capacity of immune system to improve viral set point, Blood 8, 8.
Troeger, C., Gugger, M., Holzgreve, W., and Wight, E. (2003a). Correlation of perineal ultrasound and lateral chain urethrocystography in the anatomical evaluation of the bladder neck, Int Urogynecol J Pelvic Floor Dysfunct 14, 380-4. Epub 2003 Nov 20.
Troeger, C., Schaub, A. F., Bernasconi, P., Hosli, I., and Holzgreve, W. (2003b). Spectral analysis of fetal heart rate variability in fetuses with supraventricular extrasystoles, Fetal Diagn Ther 18, 284-8.
Truninger, K., Malik, N., Ammann, R. W., Muellhaupt, B., Seifert, B., Muller, H. J., and Blum, H. E. (2001). Mutations of the cystic fibrosis gene in patients with chronic pancreatitis, Am J Gastroenterol 96, 2657-61.
Tsakiris, J. D., Battegay, E., Heilmbauer, I., Walker, T., Lindberg, R.L.P., Nordmann, A., Martina, B., Leppert, D. (2004). Inverse regulation of MMP-9 and MMP-2 in long-term follow-up after acute coronary syndrome: lack of correlation with platelet and endothelial cell activation markers., Vasc Dis Prevention 2004 (in press).
Ulivieri, C., Peter, A., Orsini, E., Palmer, E., and Baldari, C. T. (2001). Defective signaling to Fyn by a T cell antigen receptor lacking the alpha -chain connecting peptide motif, J Biol Chem 276, 3574-80. Epub 2000 Oct 31.
Ullmer, E., Mayr, M., Binet, I., Ebnother-Staub, C., Dalquen, P., Soler, M., and Tamm, M. (2000). Granulomatous Pneumocystis carinii pneumonia in Wegener's granulomatosis, Eur Respir J 15, 213-6.
Unterweger, M., De Geyter, C., Frohlich, J. M., Bongartz, G., and Wiesner, W. (2002). Three-dimensional dynamic MR-hysterosalpingography; a new, low invasive, radiation-free and less painful radiological approach to female infertility, Hum Reprod 17, 3138-41.
Urwyler, S., Mosbacher, J., Lingenhoehl, K., Heid, J., Hofstetter, K., Froestl, W., Bettler, B., and Kaupmann, K. (2001). Positive allosteric modulation of native and recombinant gamma-aminobutyric acid(B) receptors by 2,6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol (CGP7930) and its aldehyde analog CGP13501, Mol Pharmacol 60, 963-71.
Vacher, C. M., and Bettler, B. (2003). GABA(B) receptors as potential therapeutic targets, Curr Drug Target CNS Neurol Disord 2, 248-59.
Valencia, M., Bentele, M., Vaze, M. B., Herrmann, G., Kraus, E., Lee, S. E., Schar, P., and Haber, J. E. (2001). NEJ1 controls non-homologous end joining in Saccharomyces cerevisiae, Nature 414, 666-9.
Vallat, J. M., Tabaraud, F., Sindou, P., Preux, P. M., Vandenberghe, A., and Steck, A. (2000). Myelin widenings and MGUS-IgA: an immunoelectron microscopic study, Ann Neurol 47, 808-11.
Valmori, D., Levy, F., Miconnet, I., Zajac, P., Spagnoli, G. C., Rimoldi, D., Lienard, D., Cerundolo, V., Cerottini, J. C., and Romero, P. (2000). Induction of potent antitumor CTL responses by recombinant vaccinia encoding a melan-A peptide analogue, J Immunol 164, 1125-31.
Van Driel, M., Gunthert, U., van Kessel, A. C., Joling, P., Stauder, R., Lokhorst, H. M., and Bloem, A. C. (2002). CD44 variant isoforms are involved in plasma cell adhesion to bone marrow stromal cells, Leukemia 16, 135-43.
Vernez, L., Hopfgartner, G., Wenk, M., and Krahenbuhl, S. (2003). Determination of carnitine and acylcarnitines in urine by high-performance liquid chromatography-electrospray ionization ion trap tandem mass spectrometry, J Chromatogr A 984, 203-13.
Vernez, L., Wenk, M., and Krahenbuhl, S. (2004). Determination of carnitine and acylcarnitines in plasma by high-performance liquid chromatography/electrospray ionization ion trap tandem mass spectrometry, Rapid Commun Mass Spectrom 18, 1233-8.
Viardot, A., and Muller, B. (2003). [Vertigo and arterial hypertension in younger patients. Hyperaldosteronism (Conn syndrome) in diastolic arterial hypertension, chronic hypokalemia, right adrenal gland adenoma], Schweiz Rundsch Med Prax 92, 821-2.
Vidament, M., Ecot, P., Noue, P., Bourgeois, C., Magistrini, M., and Palmer, E. (2000). Centrifugation and addition of glycerol at 22 degres C instead of 4 degrees C improve post-thaw motility and fertility of stallion spermatozoa, Theriogenology 54, 907-19.
Vidament, M., Yvon, J. M., Couty, I., Arnaud, G., Nguekam-Feugang, J., Noue, P., Cottron, S., Le Tellier, A., Noel, F., Palmer, E., and Magistrini, M. (2001). Advances in cryopreservation of stallion semen in modified INRA82, Anim Reprod Sci 68, 201-18.
Vieira Pinheiro, J. P., Muller, H. J., Schwabe, D., Gunkel, M., Casimiro da Palma, J., Henze, G., von Schutz, V., Winkelhorst, M., Wurthwein, G., and Boos, J. (2001). Drug monitoring of low-dose PEG-asparaginase (Oncaspar) in children with relapsed acute lymphoblastic leukaemia, Br J Haematol 113, 115-9.
Vital, A., Lagueny, A., Julien, J., Ferrer, X., Barat, M., Hermosilla, E., Rouanet-Larriviere, M., Henry, P., Bredin, A., Louiset, P., Herbelleau, T., Boisseau, C., Guiraud-Chaumeil, B., Steck, A., and Vital, C. (2000). Chronic inflammatory demyelinating polyneuropathy associated with dysglobulinemia: a peripheral nerve biopsy study in 18 cases, Acta Neuropathol (Berl) 100, 63-8.
Voggensperger, J., Nicca, D., Battegay, M., Zellweger, J. P., and Spirig, R. (2003). [Smoking cessation for HIV infected patients], Pflege 16, 283-8.
Vollenweider, F., Herrmann, M., Otten, U., and Nitsch, C. (2003). Interleukin-6 receptor expression and localization after transient global ischemia in gerbil hippocampus, Neurosci Lett 341, 49-52.
Vollmer, M., Wenzel, F., DeGeyter, C., Zhang, H., Holzgreve, W., and Miny, P. (2000). Assessing the chromosome copy number in metaphase II oocytes by sequential fluorescence in situ hybridization, J Assist Reprod Genet 17, 596-602.
von Mach, M. A., and Keller, U. (2001). [Comorbidity and physical complaints in morbid obesity], Schweiz Rundsch Med Prax 90, 1569-74.
von Meyenburg, C., Hrupka, B. H., Arsenijevic, D., Schwartz, G. J., Landmann, R., and Langhans, W. (2004). Role for CD14, TLR2, and TLR4 in bacterial product-induced anorexia, Am J Physiol Regul Integr Comp Physiol 287, R298-305.
von Muhlenen, A., and Muller, H. J. (2000). Perceptual integration of motion and form information: evidence of parallel-continuous processing, Percept Psychophys 62, 517-31.
von Muhlenen, A., and Muller, H. J. (2001). Visual search for motion-form conjunctions: is form discriminated within the motion system?, J Exp Psychol Hum Percept Perform 27, 707-18.
von Muhlenen, A., Muller, H. J., and Muller, D. (2003). Sit-and-wait strategies in dynamic visual search, Psychol Sci 14, 309-14.
Voss, S., Quail, D., Dawson, A., Backstrom, T., Aguas, F., Erenus, M., The, H. S., Bonnar, J., De Geyter, C., Hunter, M., and Nickelsen, T. (2002). A randomised, double-blind trial comparing raloxifene HCl and continuous combined hormone replacement therapy in postmenopausal women: effects on compliance and quality of life, Bjog 109, 874-85.
Vrtic, F., Haefeli, W. E., Drewe, J., Krahenbuhl, S., and Wenk, M. (2003). Interaction of ibuprofen and probenecid with drug metabolizing enzyme phenotyping procedures using caffeine as the probe drug, Br J Clin Pharmacol 55, 191-8.
Vunjak-Novakovic, G., Obradovic, B., Martin, I., and Freed, L. E. (2002). Bioreactor studies of native and tissue engineered cartilage, Biorheology 39, 259-68.
Wacker, A., Stadler, P., and Pless, M. (2002). [Chordomas--diagnostic steps and therapeutic consequences], Dtsch Med Wochenschr 127, 1389-91.
Wagner, K. E., Martinez, J. M., Vath, S. D., Snider, R. H., Nylen, E. S., Becker, K. L., Muller, B., and White, J. C. (2002). Early immunoneutralization of calcitonin precursors attenuates the adverse physiologic response to sepsis in pigs, Crit Care Med 30, 2313-21.
Waldburger, J. M., Rossi, S., Hollander, G. A., Rodewald, H. R., Reith, W., and Acha-Orbea, H. (2003). Promoter IV of the class II transactivator gene is essential for positive selection of CD4 T cells, Blood 101, 3550-9. Epub 2002 Dec 27.
Waldherr, C., Pless, M., Maecke, H. R., Haldemann, A., and Mueller-Brand, J. (2001a). The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study, Ann Oncol 12, 941-5.
Waldherr, C., Pless, M., Maecke, H. R., Schumacher, T., Crazzolara, A., Nitzsche, E. U., Haldemann, A., and Mueller-Brand, J. (2002). Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC, J Nucl Med 43, 610-6.
Waldherr, C., Schumacher, T., Pless, M., Crazzolara, A., Maecke, H. R., Nitzsche, E. U., Haldemann, A., and Mueller-Brand, J. (2001b). Radiopeptide transmitted internal irradiation of non-iodophil thyroid cancer and conventionally untreatable medullary thyroid cancer using, Nucl Med Commun 22, 673-8.
Walker, G., Pfeilschifter, J., Otten, U., and Kunz, D. (2001). Proteolytic cleavage of inducible nitric oxide synthase (iNOS) by calpain I, Biochim Biophys Acta 1568, 216-24.
Walter, M. A., Christ-Crain, M., Eckard, B., Schindler, C., Nitzsche, E. U., Muller-Brand, J., and Muller, B. (2004). Radioiodine therapy in hyperthyroidism: inverse correlation of pretherapeutic iodine uptake level and post-therapeutic outcome, Eur J Clin Invest 34, 365-70.
Walter, M. A., Christ-Crain, M., Muller, B., Muller-Brand, J. (2004). The Detrimental Effect of Antithyroid Drugs on the Outcome of Radioiodine Therapy is not directly due to a Decreased Radioiodine Uptake., Nucl Med Commun 2004 (in press).
Walter, M. A., Muller, B., and Muller-Brand, J. (2003). [Does an individual estimation of halflife improve the results of radioiodine therapy of Graves' disease?], Nuklearmedizin 42, N29; author reply N29.
Waubant, E., Goodkin, D., Bostrom, A., Bacchetti, P., Hietpas, J., Lindberg, R., and Leppert, D. (2003). IFNbeta lowers MMP-9/TIMP-1 ratio, which predicts new enhancing lesions in patients with SPMS, Neurology 60, 52-7.
Weber, C., Collet, S., Fried, R., Lambrecht, J.T., Erb, P., Meyer, J. (2001). Low prevalence of hepatitis C virus antibody among Swiss dental health care workers., J Hepatol 2004 (in press) 34:963-4.
Weber, J., Mesters, J. R., Lepsik, M., Prejdova, J., Svec, M., Sponarova, J., Mlcochova, P., Skalicka, K., Strisovsky, K., Uhlikova, T., Soucek, M., Machala, L., Stankova, M., Vondrasek, J., Klimkait, T., Kraeusslich, H. G., Hilgenfeld, R., and Konvalinka, J. (2002). Unusual binding mode of an HIV-1 protease inhibitor explains its potency against multi-drug-resistant virus strains, J Mol Biol 324, 739-54.
Weber, J. F., Kirsch, E., Radu, E. W., Steck, A. J., Kaiser, H. J., and Lyrer, P. A. (2003). Angioplasty in a patient with ocular ischemia due to occlusion of the internal and stenosis of the external carotid artery, Cerebrovasc Dis 16, 436-9.
Wehrli, N., Legler, D. F., Finke, D., Toellner, K. M., Loetscher, P., Baggiolini, M., MacLennan, I. C., and Acha-Orbea, H. (2001). Changing responsiveness to chemokines allows medullary plasmablasts to leave lymph nodes, Eur J Immunol 31, 609-16.
Weidner, R., Pollmann, S., Muller, H. J., and von Cramon, D. Y. (2002). Top-down controlled visual dimension weighting: an event-related fMRI study, Cereb Cortex 12, 318-28.
Welge-Luessen, A., Hauser, R., Schmid, N., Kappos, L., and Probst, R. (2003). Endonasal surgery for contact point headaches: a 10-year longitudinal study, Laryngoscope 113, 2151-6.
Wellinger, R. E., Schar, P., and Sogo, J. M. (2003). Rad52-independent accumulation of joint circular minichromosomes during S phase in Saccharomyces cerevisiae, Mol Cell Biol 23, 6363-72.
Wendt, D., Marsano, A., Jakob, M., Heberer, M., and Martin, I. (2003). Oscillating perfusion of cell suspensions through three-dimensional scaffolds enhances cell seeding efficiency and uniformity, Biotechnol Bioeng 84, 205-14.
Wenk, M., Todesco, L., and Krahenbuhl, S. (2004). Effect of St John's wort on the activities of CYP1A2, CYP3A4, CYP2D6, N-acetyltransferase 2, and xanthine oxidase in healthy males and females, Br J Clin Pharmacol 57, 495-9.
Werlen, G., Hausmann, B., Naeher, D., and Palmer, E. (2003). Signaling life and death in the thymus: timing is everything, Science 299, 1859-63.
Werlen, G., Hausmann, B., and Palmer, E. (2000). A motif in the alphabeta T-cell receptor controls positive selection by modulating ERK activity, Nature 406, 422-6.
Werlen, G., and Palmer, E. (2002). The T-cell receptor signalosome: a dynamic structure with expanding complexity, Curr Opin Immunol 14, 299-305.
Whang, K. T., Vath, S. D., Becker, K. L., Snider, R. H., Nylen, E. S., Muller, B., Li, Q., Tamarkin, L., and White, J. C. (2000). Procalcitonin and proinflammatory cytokine interactions in sepsis, Shock 14, 73-8.
Wicki, A., Malik, N., Gratwohl, A., Tichelli, A., Meyer-Monard, S., and Muller, H. (2002). Determination of the donor:host blood cell ratio after haematological stem cell transplant by means of semiquantitative detection of short tandem repeat polymorphisms, Swiss Med Wkly 132, 288-95.
Widmer, I., Wernli, M., Bachmann, F., Gudat, F., Cathomas, G., and Erb, P. (2002). Differential expression of viral Bcl-2 encoded by Kaposi's sarcoma-associated herpesvirus and human Bcl-2 in primary effusion lymphoma cells and Kaposi's sarcoma lesions, J Virol 76, 2551-6.
Wiederkehr, M., and Krapf, R. (2001). Metabolic and endocrine effects of metabolic acidosis in humans, Swiss Med Wkly 131, 127-32.
Wiederkehr, M. R., Kalogiros, J., and Krapf, R. (2004). Correction of metabolic acidosis improves thyroid and growth hormone axes in haemodialysis patients, Nephrol Dial Transplant 19, 1190-7. Epub 2004 Feb 19.
Wiederkehr-Adam, M., Ernst, P., Muller, K., Bieck, E., Gombert, F. O., Ottl, J., Graff, P., Grossmuller, F., and Heim, M. H. (2003). Characterization of phosphopeptide motifs specific for the Src homology 2 domains of signal transducer and activator of transcription 1 (STAT1) and STAT3, J Biol Chem 278, 16117-28.
Wiederseiner, J. M., Muser, J., Lutz, T., Hulter, H. N., and Krapf, R. (2004). Acute metabolic acidosis: characterization and diagnosis of the disorder and the plasma potassium response, J Am Soc Nephrol 15, 1589-96.
Wiendl, H., Neuhaus, O., Kappos, L., and Hohlfeld, R. (2000). [Multiple sclerosis. Current review of failed and discontinued clinical trials of drug treatment], Nervenarzt 71, 597-610.
Wiesner, W., Ruehm, S. G., Bongartz, G., Kaim, A., Reese, E., and De Geyter, C. (2001). Three-dimensional dynamic MR hysterosalpingography: a preliminary report, Eur Radiol 11, 1439-44.
Wiesner, W., Wetzel, S. G., Kappos, L., Hoshi, M. M., Witte, U., Radue, E. W., and Steinbrich, W. (2002). Swallowing abnormalities in multiple sclerosis: correlation between videofluoroscopy and subjective symptoms, Eur Radiol 12, 789-92.
Wiestner, A., Padosch, S. A., Ghilardi, N., Cesar, J. M., Odriozola, J., Shapiro, A., and Skoda, R. C. (2000). Hereditary thrombocythaemia is a genetically heterogeneous disorder: exclusion of TPO and MPL in two families with hereditary thrombocythaemia, Br J Haematol 110, 104-9.
Williams, P. L., Leib, S. L., Kamberi, P., Leppert, D., Sobel, R. A., Bifrare, Y. D., Clemons, K. V., and Stevens, D. A. (2002). Levels of matrix metalloproteinase-9 within cerebrospinal fluid in a rabbit model of coccidioidal meningitis and vasculitis, J Infect Dis 186, 1692-5. Epub 2002 Nov 1.
Willison, H. J., O'Leary, C. P., Veitch, J., Blumhardt, L. D., Busby, M., Donaghy, M., Fuhr, P., Ford, H., Hahn, A., Renaud, S., Katifi, H. A., Ponsford, S., Reuber, M., Steck, A., Sutton, I., Schady, W., Thomas, P. K., Thompson, A. J., Vallat, J. M., and Winer, J. (2001). The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies, Brain 124, 1968-77.
Winkler, D. T., Scotti, A. L., and Nitsch, C. (2001). Ischemia-induced degeneration of CA1 pyramidal cells decreases seizure severity in a subgroup of epileptic gerbils and affects parvalbumin immunoreactivity of CA1 interneurons, Exp Neurol 168, 364-72.
Witschi, A., Widmer, A. F., Schnider, B. F., Wehrle, J., Zerkowski, H. R., and Bernet, F. (2003). Safety of heart-lung machines during prolonged standby, Infection 31, 350-2.
Wittig, B. M., Johansson, B., Zoller, M., Schwarzler, C., and Gunthert, U. (2000). Abrogation of experimental colitis correlates with increased apoptosis in mice deficient for CD44 variant exon 7 (CD44v7), J Exp Med 191, 2053-64.
Wodnar-Filipowicz, A. (2002). [Plasticity of stem cells: a change of paradigm?], Ther Umsch 59, 565-70.
Wodnar-Filipowicz, A. (2003). Flt3 ligand: role in control of hematopoietic and immune functions of the

bone marrow, News Physiol Sci 18, 247-51.
Wolf, K., Kirsch, E. C., Sponagel, L., Rufenacht, D. A., and Battegay, M. (2002a). Disappearance of an intracerebral arteriovenous malformation in an HIV-infected patient after initiation of HAART, Infection 30, 101-3.
Wolf, K., Tichelli, A., and Battegay, M. (2001). [Anemia, neutropenia and thrombocytopenia: hematological findings and HIV], Schweiz Rundsch Med Prax 90, 1775-9.
Wolf, K., Tsakiris, D. A., Weber, R., Erb, P., and Battegay, M. (2002b). Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1, J Infect Dis 185, 456-62. Epub 2002 Jan 18.
Wolinsky, J. S., Toyka, K. V., Kappos, L., and Grossberg, S. E. (2003). Interferon-beta antibodies: implications for the treatment of MS, Lancet Neurol 2, 528.
Wolz, C., Goerke, C., Landmann, R., Zimmerli, W., and Fluckiger, U. (2002). Transcription of clumping factor A in attached and unattached Staphylococcus aureus in vitro and during device-related infection, Infect Immun 70, 2758-62.
Wunderlich, K., Golubnitschaja, O., Pache, M., Eberle, A. N., and Flammer, J. (2002). Increased plasma levels of 20S proteasome alpha-subunit in glaucoma patients: an observational pilot study, Mol Vis 8, 431-5.
Wunderlich, K., Pech, M., Eberle, A. N., Mihatsch, M., Flammer, J., and Meyer, P. (2000). Expression of connective tissue growth factor (CTGF) mRNA in plaques of human anterior subcapsular cataracts and membranes of posterior capsule opacification, Curr Eye Res 21, 627-36.
Wunderlich, K., Zimmerman, C., Gutmann, H., Teuchner, B., Flammer, J., and Drewe, J. (2003). Vasospastic persons exhibit differential expression of ABC-transport proteins, Mol Vis 9, 756-61.
Wyss, A., and Moroni, C. (2000). Calcium-dependent and oncogenic IL-3 mRNA stabilization can be distinguished pharmacologically and by sequence requirements in the 3'UTR, Growth Factors 18, 109-18.
Yakirevich, E., Sabo, E., Dirnfeld, M., Sova, Y., Spagnoli, G. C., and Resnick, M. B. (2003a). Morphometrical Quantification of Spermatogonial Germ Cells With the 57B Anti-MAGE-A4 Antibody in the Evaluation of Testicular Biopsies for Azoospermia, Appl Immunohistochem Mol Morphol 11, 37-44.
Yakirevich, E., Sabo, E., Lavie, O., Mazareb, S., Spagnoli, G. C., and Resnick, M. B. (2003b). Expression of the MAGE-A4 and NY-ESO-1 cancer-testis antigens in serous ovarian neoplasms, Clin Cancer Res 9, 6453-60.
Yao, M., Dieterle, T., Hale, S. L., Dow, J. S., Kedes, L. H., Peterson, K. L., and Kloner, R. A. (2003). Long-term outcome of fetal cell transplantation on postinfarction ventricular remodeling and function, J Mol Cell Cardiol 35, 661-70.
Yerly, S., Vora, S., Rizzardi, P., Chave, J. P., Vernazza, P. L., Flepp, M., Telenti, A., Battegay, M., Veuthey, A. L., Bru, J. P., Rickenbach, M., Hirschel, B., and Perrin, L. (2001). Acute HIV infection: impact on the spread of HIV and transmission of drug resistance, Aids 15, 2287-92.
You, Z., Hester, J., Rollins, L., Spagnoli, G. C., van der Bruggen, P., and Chen, S. Y. (2001). A retrogen strategy for presentation of an intracellular tumor antigen as an exogenous antigen by dendritic cells induces potent antitumor T helper and CTL responses, Cancer Res 61, 197-205.
Young, A. J., Holzgreve, W., Dudler, L., Schoeberlein, A., and Surbek, D. V. (2003). Engraftment of human cord blood-derived stem cells in preimmune ovine fetuses after ultrasound-guided in utero transplantation, Am J Obstet Gynecol 189, 698-701.
Young, J., De Geest, S., Spirig, R., Flepp, M., Rickenbach, M., Furrer, H., Bernasconi, E., Hirschel, B., Telenti, A., Vernazza, P., Battegay, M., and Bucher, H. C. (2004). Stable partnership and progression to AIDS or death in HIV infected patients receiving highly active antiretroviral therapy: Swiss HIV cohort study, Bmj 328, 15.
Zajac, P., Oertli, D., Marti, W., Adamina, M., Bolli, M., Guller, U., Noppen, C., Padovan, E., Schultz-Thater, E., Heberer, M., and Spagnoli, G. (2003). Phase I/II clinical trial of a nonreplicative vaccinia virus expressing multiple HLA-A0201-restricted tumor-associated epitopes and costimulatory molecules in metastatic melanoma patients, Hum Gene Ther 14, 1497-510.
Zanetti Dallenbach, R., and De Geyter, C. (2001). [What is your diagnosis? Relative hypergonadotrophic ovarian insufficiency after chemotherapy for Hodgkin disease], Schweiz Rundsch Med Prax 90, 47-9.
Zaugg, C. E. (2002). [Circadian rhythm of cardiovascular emergencies], Schweiz Rundsch Med Prax 91, 1553-5.
Zaugg, C. E. (2003a). [Common biostatistical errors in clinical studies], Schweiz Rundsch Med Prax 92, 218-24.
Zaugg, C. E. (2003b). Standard error as standard?, Circulation 107, e89.
Zaugg, C. E., and Buser, P. T. (2001). When calcium turns arrhythmogenic: intracellular calcium handling during the development of hypertrophy and heart failure, Croat Med J 42, 24-32.
Zaugg, C. E., Spaniol, M., Kaufmann, P., Bellahcene, M., Barbosa, V., Tolnay, M., Buser, P. T., and Krahenbuhl, S. (2003). Myocardial function and energy metabolism in carnitine-deficient rats, Cell Mol Life Sci 60, 767-75.
Zaugg, C. E., Ziegler, A., Lee, R. J., Barbosa, V., and Buser, P. T. (2002). Postresuscitation stunning: postfibrillatory myocardial dysfunction caused by reduced myofilament Ca2 responsiveness after ventricular fibrillation-induced myocyte Ca2 overload, J Cardiovasc Electrophysiol 13, 1017-24.
Zelikin, A. N., Lynn, D. M., Farhadi, J., Martin, I., Shastri, V., and Langer, R. (2002). Erodible conducting polymers for potential biomedical applications, Angew Chem Int Ed Engl 41, 141-4.
Zeller, A., Battegay, M., Gyr, N., and Battegay, E. (2003a). Evaluation of unstructured medical school examinations: prospective observational study, Swiss Med Wkly 133, 184-7.
Zeller, A., Handschin, D., Gyr, N., Martina, B., and Battegay, E. (2004). Blood pressure and heart rate of students undergoing a medical licensing examination, Blood Press 13, 20-4.
Zeller, A., Schaub, N., Steffen, I., Battegay, E., Hirsch, H. H., and Bircher, A. J. (2003b). Drug hypersensitivity syndrome to carbamazepine and human herpes virus 6 infection: case report and literature review, Infection 31, 254-6.
Zeller, R., and Deschamps, J. (2002). Developmental biology: first come, first served, Nature 420, 138-9.
Zerbini, A., Pilli, M., Soliani, P., Ziegler, S., Pelosi, G., Orlandini, A., Cavallo, C., Uggeri, J., Scandroglio, R., Crafa, P., Spagnoli, G. C., Ferrari, C., and Missale, G. (2004). Ex vivo characterization of tumor-derived melanoma antigen encoding gene-specific CD8 cells in patients with hepatocellular carcinoma, J Hepatol 40, 102-9.
Zerkowski, H. R., Grapow, M. T., Todorov, A., and Morawietz, H. (2000). [Reverse remodeling by surgery--fact or fiction?], Z Kardiol 89, 76-84.
Zerkowski, H. R., Grussenmeyer, T., Matt, P., Grapow, M., Engelhardt, S., and Lefkovits, I. (2004). Proteomics strategies in cardiovascular research, J Proteome Res 3, 200-8.
Zerkowski, H. R., and Preiss, M. (2001). [Multiple heart valve diseases: differential therapeutic considerations], Z Kardiol 90, 65-9.
Zhang, H., Holzgreve, W., and De Geyter, C. (2001). Bcl2-L-10, a novel anti-apoptotic member of the Bcl-2 family, blocks apoptosis in the mitochondria death pathway but not in the death receptor pathway, Hum Mol Genet 10, 2329-39.
Zhang, H., Vollmer, M., De Geyter, M., Litzistorf, Y., Ladewig, A., Durrenberger, M., Guggenheim, R., Miny, P., Holzgreve, W., and De Geyter, C. (2000). Characterization of an immortalized human granulosa cell line (COV434), Mol Hum Reprod 6, 146-53.
Zhang, J. Q., Biedermann, B., Nitschke, L., and Crocker, P. R. (2004). The murine inhibitory receptor mSiglec-E is expressed broadly on cells of the innate immune system whereas mSiglec-F is restricted to eosinophils, Eur J Immunol 34, 1175-84.
Zhong, X. Y., Hahn, D., Troeger, C., Klemm, A., Stein, G., Thomson, P., Holzgreve, W., and Hahn, S. (2001a). Cell-free DNA in urine: a marker for kidney graft rejection, but not for prenatal diagnosis?, Ann N Y Acad Sci 945, 250-7.
Zhong, X. Y., Holzgreve, W., and Hahn, S. (2001b). Circulatory fetal and maternal DNA in pregnancies at risk and those affected by preeclampsia, Ann N Y Acad Sci 945, 138-40.
Zhong, X. Y., Holzgreve, W., and Hahn, S. (2002a). Cell-free fetal DNA in the maternal circulation does not stem from the transplacental passage of fetal erythroblasts, Mol Hum Reprod 8, 864-70.
Zhong, X. Y., Holzgreve, W., and Hahn, S. (2002b). The levels of circulatory cell free fetal DNA in maternal plasma are elevated prior to the onset of preeclampsia, Hypertens Pregnancy 21, 77-83.
Zhong, X. Y., Wang, Y., Chen, S., Labu, Pubuzhuoma, Gesangzhuogab, Ouzhuwangmu, Hahn, C., Holzgreve, W., and Hahn, S. (2004). Can Circulatory Fetal DNA Be Used to Study Placentation at High Altitude?, Ann N Y Acad Sci 1022, 124-128.
Ziegler, A., Zaugg, C. E., Buser, P. T., Seelig, J., and Kunnecke, B. (2002a). Non-invasive measurements of myocardial carbon metabolism using in vivo 13C NMR spectroscopy, NMR Biomed 15, 222-34.
Ziegler, S., Burki, K., and Skoda, R. C. (2002b). A 2-kb c-mpl promoter fragment is sufficient to direct expression to the megakaryocytic lineage and sites of embryonic hematopoiesis in transgenic mice, Blood 100, 1072-4.
Zimmerli, L., and Leppert, D. (2004). [Polyneuropathy seropositive for anti-Hu antibodies], Schweiz Rundsch Med Prax 93, 570-2.
Zimmerman, C., Drewe, J., Flammer, J., and Shaarawy, T. (2004). In vitro release of mitomycin C from collagen implants, Curr Eye Res 28, 1-4.
Zimmermann, B., Holzgreve, W., Wenzel, F., and Hahn, S. (2002a). Novel real-time quantitative PCR test for trisomy 21, Clin Chem 48, 362-3.
Zimmermann, B., Holzgreve, W., Zhong, X. Y., and Hahn, S. (2002b). Inability to clonally expand fetal progenitors from maternal blood, Fetal Diagn Ther 17, 97-100.
Zinkernagel, C., Naef, M. R., Bucher, H. C., Ladewig, D., Gyr, N., and Battegay, M. (2001a). Onset and pattern of substance use in intravenous drug users of an opiate maintenance program, Drug Alcohol Depend 64, 105-9.
Zinkernagel, C., Taffe, P., Rickenbach, M., Amiet, R., Ledergerber, B., Volkart, A. C., Rauchfleisch, U., Kiss, A., Werder, V., Vernazza, P., and Battegay, M. (2001b). Importance of mental health assessment in HIV-infected outpatients, J Acquir Immune Defic Syndr 28, 240-9.
Zivkovic, S. A., Heyman, R., and Pless, M. (2003). Subacute rhombencephalitis optica responsive to intravenous immunoglobulins, Eur J Neurol 10, 83-6.
Zorzato, F., Anderson, A. A., Ohlendieck, K., Froemming, G., Guerrini, R., and Treves, S. (2000). Identification of a novel 45 kDa protein (JP-45) from rabbit sarcoplasmic-reticulum junctional-face membrane, Biochem J 351, 537-43.
Zorzato, F., Yamaguchi, N., Xu, L., Meissner, G., Muller, C. R., Pouliquin, P., Muntoni, F., Sewry, C., Girard, T., and Treves, S. (2003). Clinical and functional effects of a deletion in a COOH-terminal lumenal loop of the skeletal muscle ryanodine receptor, Hum Mol Genet 12, 379-88.
Zuklys, S., Balciunaite, G., Agarwal, A., Fasler-Kan, E., Palmer, E., and Hollander, G. A. (2000). Normal thymic architecture and negative selection are associated with Aire expression, the gene defective in the autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), J Immunol 165, 1976-83.
Zulewski, H., Abraham, E. J., Gerlach, M. J., Daniel, P. B., Moritz, W., Muller, B., Vallejo, M., Thomas, M. K., and Habener, J. F. (2001). Multipotential nestin-positive stem cells isolated from adult pancreatic islets differentiate ex vivo into pancreatic endocrine, exocrine, and hepatic phenotypes, Diabetes 50, 521-33.
Zulewski, H., Muller, B., Exer, P., Miserez, A. R., and Staub, J. J. (1997). Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls, J Clin Endocrinol Metab 82, 771-6.
Zumsteg, U. (2000). [Cystic fibrosis: current therapy. Diabetes], Schweiz Med Wochenschr Suppl 122, 15S-16S.
Zumsteg, U., Frigerio, S., and Hollander, G. A. (2000). Nitric oxide production and Fas surface expression mediate two independent pathways of cytokine-induced murine beta-cell damage, Diabetes 49, 39-47.
Zuniga, A., Michos, O., Spitz, F., Haramis, A. P., Panman, L., Galli, A., Vintersten, K., Klasen, C., Mansfield, W., Kuc, S., Duboule, D., Dono, R., and Zeller, R. (2004). Mouse limb deformity mutations disrupt a global control region within the large regulatory landscape required for Gremlin expression, Genes Dev 18, 1553-64. Epub 2004 Jun 15.
Zuniga, A., Quillet, R., Perrin-Schmitt, F., and Zeller, R. (2002). Mouse Twist is required for fibroblast growth factor-mediated epithelial-mesenchymal signalling and cell survival during limb morphogenesis, Mech Dev 114, 51-9.

Personen Index

Wir danken für die freundliche Unterstützung folgender Firmen:

Ernst & Young Ltd
Fluka AG
Huber & Co. AG Labor- und Spitalbedarf
Kendro Laboratory Products AG
Leica Microsystems (Schweiz) AG
Pharma-Consulting