Annual Report 2005

Institut für Pharmakologie (PKI)

der Universität Bern

Department of Pharmacology

of the University of Bern

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1. Introduction

1.1. Vorwort

Dies ist der fünfte umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat sich auch im Jahr 2005 bemüht, seine Aufgaben in Lehre und Forschung innerhalb der Medizinischen Fakultät vorbildlich zu erfüllen. Die Pharmakologie besitzt eine Brückenfunktion zwischen biologischer Grundlagen- und klinischer Forschung. Das PKI arbeitet deshalb eng mit den verschiedensten Kliniken des Inselspitals und mit anderen Forschungseinrichtungen der Universität Bern zusammen. Damit wollen wir helfen, die klinische Forschung sowie die Aus-, Weiter- und Fortbildung an der Medizinischen Fakultät zu stärken. Zum anderen sind wir an der Zusammenarbeit mit Firmen interessiert, wie die weiter hinten aufgeführten gegenwärtigen Kontakte der einzelnen Forschungsgruppen zeigen. Auch im Jahr 2005 trugen wir dazu bei, die Kommunikation zwischen Wissenschaftlern und Öffentlichkeit zu fördern. Dazu dienten u.a. die Vernissagen, die viele Gäste in das PKI lockten.

Mit dem Jahr 2005 begannen bedeutende Veränderungen in unserem Institut. Die Herren Prof. Porzig (28.2.2005), Prof. Honegger (30.09.2005) und Prof. Stucki (31.12.2005) traten altershalber zurück. Als Nachfolgerin von Herrn Porzig wurde Frau Prof. Dr. Andrea Huwiler (Start: 1.2.2006) gewählt. Als neue Dozenten nahmen Frau PD Dr. Shida Yousefi und Herr PD Dr. Uwe Zangemeister-Wittke bereits ihre Tätigkeit auf.

Neben unserer regulären Lehrtätigkeit im 3. Studienjahr Medizin sowie bei der Ausbildung der Zahnmediziner sind wir aktiv innerhalb der neu gegründeten interfakultären Graduate School for Cellular and Biomedical Sciences tätig. Die Proff. Simon und Sigel sind Mitglieder von Betreuungskommissionen innerhalb dieses Ausbildungsprogramms für Doktorandinnen und Doktoranden. Dazu kommen zusätzliche Bildungsangebote in Form von Seminaren, praktischen Kursen (Prof. Sigel und Frau PD Dr. Yousefi) und einer Summer School (Prof. Simon). Letztere wird weitgehend aus eigenen finanziellen Mitteln bzw. Sponsorengeldern bestritten. Im Institut arbeiten gegenwärtig 17 DoktorandInnen (12 PhD, 5 MD), und 7 haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2005 insgesamt 36 Originalarbeiten sowie 10 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >200). MitarbeiterInnen des Instituts wurden zu insgesamt 57 Vorträgen bzw. Seminaren eingeladen. PD Dr. Shida Yousefi und Dr. Stephan von Gunten wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 4 Mitarbeiter mit namhaften Beiträgen des Schweizerischen Nationalfonds unterstützt. Zahlreiche Persönlichkeiten besuchten das Institut und hielten Forschungsseminare. Der Berner Immunologie-Club erfreut sich, auch durch die aktive Hilfe aus dem PKI, einer grossen Beliebtheit. Ein von Prof. Simon organisierter Kongress über eosinophile Granulozyten zog über 150 Teilnehmer aus dem In- und Ausland an (für Bilder: http://www.pki.unibe.ch/eos/eos.html). Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Ein grosses Problem ist die zu geringe finanzielle Unterstützung unseres Instituts zur Aufrechterhaltung der Infrastruktur. Wir haben deshalb die grosse Hoffnung, dass es möglichst bald zu einem Leistungsvertrag zwischen der Medizinischen Fakultät und dem PKI kommt und dadurch eine Besserung der Situation eintritt.

Das PKI nimmt auch ausserhalb der Universität seine Verantwortung für die Weiterentwicklung des Fachs Pharmakologie wahr. Wir bemühen uns um enge Kontakte zu anderen universitären Instituten für Pharmakologie vor allem innerhalb der Schweiz und Deutschlands. Innerhalb der Schweizerischen Gesellschaft für Pharmakologie und Toxikologie (SGPT) und der neu gegründeten Schweizerischen Gesellschaft für Experimentelle Pharmakologie (SGEP) wurden von uns zahlreiche Initiativen gestartet, z.B. bei der Organisation von wissenschaftlichen Veranstaltungen. Prof. Simon amtet gegenwärtig sowohl als Präsident der SGPT als auch der SGEP.

Ich danke allen Mitarbeitern und Mitarbeiterinnen für ihren Einsatz, welcher auch im Jahr 2005 zu einer Bilanz beitrug, die internationalen Massstäben gerecht wird. Ebenso danke ich allen Sponsoren und Freunden des Instituts.

Prof. Dr. med. Hans-Uwe Simon
Direktor

Bern, Februar 2006

1.2. Foreword

This is the fifth comprehensive report of the Department of Pharmacology of the University of Bern. Clearly, our department has worked hard to fulfil its tasks in teaching and research within the Medical Faculty in 2005 in high quality. Pharmacology fulfils functions in both basic biological science and clinical research. The Department of Pharmacology wants to succeed in both areas and, therefore, maintains intense contacts with several clinics of the University Hospital (Inselspital) as well as with different research institutes of the University of Bern. This way, we hope to strengthen both research and teaching at the Medical Faculty. On the other hand, we are very much interested in collaborating with the industry on new developments. Current activities are listed in this report. Also in 2005, we tried to promote communication between scientists and the public. The organization of art exhibitions within our institute is an example for these efforts.

In 2005, important changes began in our department. Prof. Porzig (Febr. 28, 2005), Prof. Honegger (Sept. 30, 2005), and Prof. Stucki (Dec. 31, 2005) retired. The successor of Prof. Porzig is Prof. Andrea Huwiler, who will start her work on Febr. 1, 2006. As new principal investigators, we recruited PD Dr. Shida Yousefi and PD Dr. Uwe Zangemeister-Wittke.

Besides the regular teaching within the third study year of medical students and our teaching of dentistry students, we are actively involved within the graduation program for MD/PhD students of the University of Bern. In 2005, the Graduate School for Cellular and Biomedical Sciences was founded by the Medical, Natural Sciences, and Veterinary Medical Faculties, and Prof. Simon and Prof. Sigel are members of tutoring committees within this school. Additional teaching activities outside the medical curriculum, such as seminars, practical courses (Prof. Sigel and PD Dr. Yousefi), and summer school (Prof. Simon) were provided. Importantly, the latter event was financed exclusively by external sponsors. Currently, 12 PhD students and 5 MD students work at the PKI and 7 students successfully finished their graduate study in 2005.

In 2005, the scientific staff of the Department of Pharmacology published 36 original and 10 review articles in international peer-reviewed journals (the sum of the “impact

factors" is more than 200). Co-workers of the institute were invited to 57 lectures or seminars. PD Dr. Shida Yousefi and Dr. Stephan von Gunten received research prizes. Four co-workers are currently supported by grants of the Swiss National Science Foundation. Several prominent researchers visited the institute and presented seminars. An international congress on Eosinophils with more than 150 participants was organized by Prof. Simon (for pictures: http://www.pki.unibe.ch/eos/eos.html). In summary, research plays an important role at the PKI and is performed at a high level.

One major problem is the financial support of the institute within the ordinary budget of the Medical Faculty that is not sufficient to keep the infrastructure in shape and running. We very much hope that the planned contract between the Medical Faculty and the PKI will improve our situation in the near future.

The PKI also takes responsibility to represent pharmacological interests outside of the university. We have close contacts to other institutes of Pharmacology, in particular in Switzerland and Germany. We are actively working within the Swiss Society of Pharmacology and Toxicology (SSPT) and the newly founded Swiss Society of Experimental Pharmacology (SSEP), for instance in the organization of scientific events. Prof. Simon currently serves as the president of both SSPT and SSEP.

I thank all co-workers for their hard work that contributed to the success of the PKI in 2005. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, February 2006

2. Staff 2005

Director

Prof. Dr. Hans-Uwe Simon, MD, PhD

Deputy Director

Prof. Dr. Hartmut Porzig, MD (until February 2005)
Prof. Dr. Andrea Huwiler, PhD (since February 2006)

Permanent Members

Prof. Dr. Ulrich Honegger, PhD (until September 2005)
Prof. Dr. Andrea Huwiler, PhD (since February 2006)
Prof. Dr. Hartmut Porzig, MD (until February 2005)
Prof. em. Dr. Harald Reuter, MD
Prof. Dr. Erwin Sigel, PhD
Prof. Dr. Hans-Uwe Simon, MD, PhD
Prof. Dr. Jörg W. Stucki, PhD (until December 2005)
PD Dr. Shida Yousefi, PhD (since January 2006)
PD Dr. Uwe Zangemeister-Wittke (since November 2005)

Scientific Staff

Nicola Andina, MD, PhD student (since June 2005)
Roland Baur, head technician
Nathalie Boulineau, PhD student*
Dr. Andreina Bruno, PhD (until March 2005)
Dr. Sibylle Bürgi, PhD (until September 2005)
Dr. Sébastien Conus, PhD
Arezoo Daryadel, PhD student*
Niculina Gebhardt, MD student* (until April 2005)
Remo Filippo Grifone, MD student* (until September 2005)
Reto Kaderli, MD student* (until April 2005)
Kuldeep Kaur, PhD student (since June 2005)
Ganna Kostylina, PhD student
Ivana Kotevic, PhD student* (until September 2005)
Evelyne Kozlowski, technician
Esther Lehmann, PhD student (since September 2005)
Sibylla Martinelli, PhD student* (until February 2005)
Susanne Probst, technician
PD Dr. Claes Ruedeberg, PhD, consultant* (until September 2005)
Souzan Salemi, PhD (since September 2005)
Inès Schmid, head technician

Kelly Tan, PhD student*
David Troi, MD student*
PD Dr. Robert Urbanczik, PhD (until December 2005)
Ekatherina Vassina, PhD student (until May 2005)
Anton Vichalkovski, PhD student* (until July 2005)
Dr. Clemens Wagner, PhD (until March 2005)
Adrian Wirz, PhD student* (until June 2005)
Dr. Stephan von Gunten, MD, PhD student
Thomas von Rütte, MD student*
Dr. Algirdas Ziogas, PhD (since November 2005)

External University Teachers

PD Dr. Kurt Baltensperger, PhD
Dr. Sibylle Bürgi, PhD
PD Dr. Armand Cachelin, MD, PhD
Doz. Dr. Irena Mlinaric, PhD (Visiting Professor of the University of Bern)
PD Dr. Peter Späth, PhD
PD Dr. Roger Zühlke, PhD

Guest scientists

Dr. Dagmar Simon, MD*
PD Dr. Alex Straumann, MD*

External Computer Support

Faton Shala*
Dominik Wyss*

Office

Erika Fritsche, head secretary
Peggy Shala, secretary
Franziska Marti*, secretary to Prof. Reuter

Workshop

Hans Andres

House Keeping

Mariter Vieites
Esther Weber (until December 2005)
Isa Conforti (since September 2005)

*at least partially paid from external sources, mostly research grants

3. Teaching Activities
3.1. Lectures

Lectures for medical students

Date	Lecturer	Titel of the lecture
Jan 10, 2005	Prof. Hartmut Porzig	Antiarrhytmika
Jan 17, 2005	Prof. Hartmut Porzig	Beeinflussung der kontraktilen Herzfunktion durch Pharmaka
Jan 31, 2005	Prof. Hartmut Porzig	Diuretika
Feb 09, 2005	Prof. Hartmut Porzig	Grundlagen der Homöopathie (aus der Sicht der Pharmakologen)
April 06, 2005	Prof. Erwin Sigel	Pharmakokinetik III (Arzneimittel-Interaktionen, akt./tox. Metaboliten, Prodrug)
April 06, 2005	Prof. Erwin Sigel	Pharmakokinetik III (Pharmakogenetik, P-Glykoproteine)
April 19, 2005	Prof. Erwin Sigel	together with P. Diem: Zucker
April 19, 2005	Prof. Erwin Sigel	together with P. Diem: Fett
April 19, 2005	Prof. Erwin Sigel	together with P. Diem: Syndrom X, Gicht, Gewichtskontrolle
April 25, 2005	Prof. Ulrich Honegger	Antiepileptika
April 27, 2005	Prof. Hartmut Porzig	Lokalanästhetika
May 11, 2005	Prof. Ulrich Honegger	Therapie von M. Parkinson und Demenzen
May 23, 2005	Prof. Erwin Sigel	together with P. Diem: Nebenniere
May 30, 2005	Prof. Erwin Sigel	together with P. Diem: Schilddrüse
June 02, 2005	Prof. Ulrich Honegger	Anästhesiologie I
June 02, 2005	Prof. Ulrich Honegger	Anästhesiologie II
June 06, 2005	Prof. Ulrich Honegger	Angriffspunkte von Psychopharmaka

June 06, 2005	Prof. Ulrich Honegger	Neuroleptika: Wirkungsmechanismen und Nebenwirkungen
June 08, 2005	Prof. Ulrich Honegger	Anxiolytika
June 08, 2005	Prof. Ulrich Honegger	Antidepressiva
June 15, 2005	Prof. Ulrich Honegger	Pharmakokinetik im Alter
June 22, 2005	Prof. Ulrich Honegger	Schmerztherapie
July 06, 2005	Prof. Hans-Uwe Simon	Immunmodulation
Oct 25, 2005	Prof. Hans-Uwe Simon	Pharmakodynamik 1
Oct 26, 2005	Prof. Hans-Uwe Simon	Pharmakodynamik 2
Oct 31, 2005	Prof. Hans-Uwe Simon	Einführung in die Toxikologie
Nov 09, 2005	Prof. Hans-Uwe Simon	Entzündungshemmung
Nov 15, 2005	Prof. Hartmut Porzig	Das autonome Nervensystem
Nov 30, 2005	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Dec 07, 2005	Prof. Hartmut Porzig	Antithrombotische Therapie II und Antikogulantien
Dec 14, 2005	Prof. Hartmut Porzig	Pharmakologie des sympathischen Nervensystems
Dec 14, 2005	Prof. Hartmut Porzig	Wirkprinzipien der Antihypertonika
Dec 21, 2005	Prof. Hartmut Porzig	Vasoaktive und antianginöse Substanzen

Lectures for dental students (Coordinator: Prof. Dr. J. W. Stucki)

Date	**Lecturer**	**Title of the lecture**
March 30, 2005	Prof. Hartmut Porzig	Allgemeine Pharmakologie: Einführung, Rezeptoren
April 04, 2005	Prof. Hartmut Porzig	Allgemeine Pharmakologie: Dosis-Wirkungskurven
April 06, 2005	Prof. Jörg Stucki	Antagonisten

April 11, 2005	Prof. Jörg Stucki	Absorption, Verteilung
April 13, 2005	Prof. Jörg Stucki	Ausscheidung
April 18, 2005	Prof. Jörg Stucki	Arzneimittelmetabolismus
April 20, 2005	Prof. Jörg Stucki	Gesamtkinetik, Dosierung
April 25, 2005	Prof. Ulrich Honegger	Lokale Präparate
April 27, 2005	PD Dr. Armand Cachelin	Starke Analgetika
May 02, 2005	Prof. Erwin Sigel	Schwache Analgetika I
May 04, 2005	Prof. Erwin Sigel	Schwache Analgetika II
May 09, 2005	Prof. Erwin Sigel	Blutverdünner
May 11, 2005	PD Dr. Armand Cachelin	Immunsuppressiva
May 18, 2005	PD Dr. K. Baltensperger	Sympathikus
May 23, 2005	PD Dr. K. Baltensperger	Kreislaufpräparate I
May 25, 2005	PD Dr. K. Baltensperger	Kreislaufpräparate II
May 30, 2005	Dr. Sibylle Bürgi	Lokalanästhetika
June 01, 2005	Dr. Sibylle Bürgi	Insulin, Orale Antidiabetica
June 06, 2005	Prof. Ulrich Honegger	Psychopharmaka
June 08, 2005	Prof. Erwin Sigel	Anxiolytica
June 13, 2005	Prof. Ulrich Honegger	Magensäurenhemmer
June 15, 2005	Dr. Sibylle Bürgi	Antibiotika I
June 20, 2005	Dr. Sibylle Bürgi	Antibiotika II
June 22, 2005	Prof. Jörg Stucki	Examensvorbereitung

Lectures for Pharmacy students

Date	**Lecturer**	**Title of the lecture**
April 01, 2005	Prof. Ulrich Honegger	Einführungsvorlesung

April 08, 2005	Prof. Ulrich Honegger	Logistik bis zur Apotheke (mit Exkursion)
April 29, 2005	Prof. Ulrich Honegger	Industriepharmazie (mit Exkursion)
June 03, 2005	Prof. Ulrich Honegger	Zukunftsaussichten
June 03, 2005	Prof. Ulrich Honegger	Pharmazeuten in Lehre und Forschung

Lectures for students of the Natural Sciences Faculty

Date	Lecturer	Title of the lecture
April 13, 2005	Prof. Hans-Uwe Simon	Regulation der Granulozyten-Apoptose

3.2. Coordination PBL Medical Students, 3rd year (2005/2006)

Core group:
Prof. Hartmut Porzig, Prof. Andrea Huwiler

Representatives of Pharmacology in teaching blocks:
Prof. Andrea Huwiler (blocks VI and VII)
Prof. Hartmut Porzig (blocks III and IV)
Dr. Stephan von Gunten (block V)
Prof. Hans-Uwe Simon (blocks I, II, and VIII)

3.3. Tutorials (study year 2005/2006)

Medical students 3rd year:
Dr. Sébastien Conus
Dr. Stephan von Gunten
Prof. Hans-Uwe Simon
PD Dr. Shida Yousefi
PD Dr. Uwe Zangemeister-Wittke

3.4. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan 14, 2005	Daniela Wunsch, M.Sc. University of Berlin	Diagnosis of acute-chronic rejection of kidney grafts
March 02, 2005	Dr. Ann Zeuner Dept. Hematol., Oncology & Mol. Medicine, Rome	Regulatory mechanisms in normal and preneoplastic hematopoiesis
June 29, 2005	Dr. Urs Thomet Bsys GmbH, Witterswil	From University to Start-up Company: The HERG Channel as Springboard into Entrepreneurship
July 04, 2005	PD Dr. Michael Huber University of Freiburg (D)	New aspects to an old story: Lipopoly-saccharide (LPS, endotoxin) and Cellular activation
Oct. 19, 2005	Dr. Basil Gerber Dept. of Rheumatology, Immunol. & Allergol., Inselspital, Bern	Molecular characterization of T cell receptor – drug interactions
Oct. 26, 2005	Prof. Dr. M. Hediger University of Bern	Role of the epithelial calcium channel TRPV6 in calcium homeostasis: New lessons from knockout mice
Nov 02, 2005	Dr. Mirjana Urosevic University of Zurich	Targetin Toll-like receptors for cancer treatment: to immunity and beyond
Nov 23, 2005	Prof. Dr. C. Dahinden University of Bern	Novel mediators of allergy

In addition, the scientific staff of the institute meets to discuss ongoing research projects and recently published work each Tuesday at 5 pm.

3.5. Bern Immunology Club

Date	Teacher	Title of the seminar
Jan 26, 2005	PD Dr. Shida Yousefi	Apoptosis signaling by an autophagy gene product
Feb 23, 2005	PD Dr. Robert Rieben	Innate Immunity, the endothelium, Myocardial infarction and the heart-Lung machine
March 09, 2005	Prof. Dr. Frank Seibold Prof. Dr. Christoph Müller	Chronisch-entzündliche Darmer-krankungen
March 30, 2005	PD Dr. Alois Lang	Cystic Fibrosis – Pseudomonas vaccination
April 27, 2005	Prof. Dr. Georg Holländer	Aspects of cellular and molecular Basis of primary immunodeficiencies
May 25–29, 2005	4th Biennial Congress of the International Eosinophil Society	
Aug 13-15, 2005	4th International Summer School	
Sept 28, 2005	Dr. Jens Stein	Intracellular control of lymphocyte Migration
Oct 26, 2005	Prof. Dr. Steven Leib	Pathophysiologic Aspects of Brain Damage in Bacterial Meningitis: New Therapeutic Strategies?
Nov 02, 2005	Proffs. Pichler, Yawalker and Villiger	Sterile neutrophilic inflammations
Nov 30, 2005	Stephan Gadola	On the interaction of T-cell receptors with human CD1d

3.6. Academic Degrees

Shida Yousefi, PD Dr.
Habilitation, University of Bern, November 2005

Remo Filippo Grifone, Dr. med.
Thesis: 3D image analysis of granulocytes: Macrophage migration inhibitory factor, RhoH/TTF and eosinophil extracellular traps.
University of Bern, September 2005

Ivana Kotevic, Dr. phil.
Thesis: Interaction of the $P2Y_2$ Receptor with $G\alpha 16$ and with itself in human cell lines.
University of Bern, March 2005

Sibylla Martinelli, Dr. phil.
Thesis: New molecular and pharmacological aspects of neutrophil functions and apoptosis.
University of Bern, April 2005

Ekatherina Vassina, Dr. phil.
Thesis: Expression and function of cIAP-2, survivin and TRAIL in inflammatory diseases.
University of Bern, May 2005

Anton Vichalkovski, Dr. phil.
Thesis: Interaction of G-protein-coupled receptors with tyrosine kinases during growth and differentiation of human hematopoietic progenitor cells.
University of Bern, March 2005

Stephan von Gunten, Dr. phil.
Thesis: Siglec-9: A new cytokine-sensitive death receptor on neutrophils.
University of Bern, October 2005

Adrian Wirz, Dr. pharm.
Thesis: In vitro study of the mode of action of antidepressants in cell culture models. Comparison of the effects of Hypericum perforatum L. extracts and classical synthetic compounds on the β–adrenergic signal pathway.
University of Basel, May 2005

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Ulrich E. Honegger

Group members: Dr. Sibylle Bürgi, PhD (until September 2005)
Adrian Wirz, PhD (until June 2005)
Susanne Probst, technician
PD Dr. Claes Ruedeberg, PhD, consultant

Interested in antidepressant drugs, we focus on the elucidation of their modes of action. For many years we have concentrated on classical, well established synthetic compounds but have recently expanded our research efforts to the antidepressant activity and properties of plant extracts. Studies are performed in *in vitro*-systems including cultured cells and brain slices of rats. Cell culture models are also used for the investigation of the kinetic behaviour of lipophilic, persistent polyhalogenated compounds. As a research group, known within the Department of Clinical Research of the Medical Faculty (DKF) for its expertise in receptor ligand binding, we have collaborated with different research groups of our university. In particular with the research group of PD Dr. Balsiger, with Prof. Mullis' group, University Children's Hospital, Inselspital, and with the group of Prof. Blum from the Veterinary Faculty and others.

A closer look at the antidepressant-induced mechanisms of β-adrenoceptor down-regulation

S. Bürgi, K. Baltensperger, U. Kämpfer*, J. Schaller*, U. E. Honegger
(Collaboration with the *Department of Chemistry and Biochemistry, University of Bern)

Long-term use of most antidepressants leads to a decrease in the number of functional β1-adrenoceptors in central postsynaptic membranes and in cultured cells. Due to the coincidence this reduction in receptor density is thought to play a critical role in mediating the therapeutic effect of antidepressants. The exact mechanisms for β1-adrenoceptor down-regulation are not completely understood. Recent studies in our laboratory using cultured rat astrocytoma C6 cells have demonstrated that antidepressant-induced reduction of receptor surface expression may be caused by an impairment of β1-adrenoceptor recycling. In chronically antidepressant-treated cells, β1-adreno-ceptors underwent normal agonist-induced internalization, but instead of recycling back to the cell surface, they were retained in intracellular compartments. It has been shown that changes in the phosphorylation pattern of the distal cytoplasmic tail of G-protein coupled receptors can lead to a strong intracellular retention of endocytosed receptors. Metabolic labeling with ^{32}P-orthophosphate followed by SDS-PAGE and phosphor-imager analysis of receptor bands indicated that levels of β1-adrenoceptor phosphorylation were altered by chronic

antidepressant-treatment. We currently analyse drug-induced changes in β1-adrenoceptor phosphorylation using electro-spray ionisation mass spectrometry. The aim of the MS studies is to identify the phosphorylation sites in the carboxy-terminal region of the β1-adrenoceptor and to determine site specific changes in receptor phosphorylation following chronic antidepressant treatment.

Chronic antidepressant-induced changes in recycling of serotonin receptor subtypes

A. Wirz, S. Bürgi, U. E. Honegger

Our studies on antidepressant-induced alterations in the recycling of β1-adrenoceptors have demonstrated that this phenomenon is specific for individual receptors and not a general consequence of altered membrane trafficking. *In vivo*-studies investigating antidepressant effects on the serotonin system have shown that the 5-HT2A receptor subtype is down-regulated following chronic drug treatment, while number and characteristics of the 5-HT1A receptor subtype are not affected by the antidepressant treatment. We transfected COS cells transiently with a 5-HT2A receptor-GFP construct and HEK cells permanently with either the 5-HT2A receptor-GFP construct or with the 5-HT1A receptor. This should allow us to study functionality and trafficking of these receptor subtypes in control and antidepressant exposed cells. The aim will be to distinguish the differences in recycling behavior of these receptor subtypes in response to antidepressants and to correlate it with differences in posttranslational modifications such as receptor phosphorylation or glycosylation.

Antidepressant effects on the b-adrenergic signal pathway. A comparison between hypericum perforatum (St. John's wort) extracts, TCA- and SSRI-antidepressants

A. Wirz, S. Bürgi, U. E. Honegger

β1-adrenoceptor density as well as isoproterenol- and forskolin-stimulated cAMP responses were studied in rat astrocytoma cells chronically exposed to St. John's wort extract, to the tricyclic antidepressant desipramine or to the SSRI antidepressant fluoxetine. It was of interest to see that all treatments were comparably efficient in inducing receptor down-regulation, while the inhibitory effectiveness of the synthetic compounds on cAMP-formation was more pronounced than that of the plant extracts.

Pharmacology of hypericum perforatum (St.John's wort) extracts, and fractions of the plant extract containing different amounts of hyperforin

S. Probst, C. Ruedeberg, U. E. Honegger

St. John's wort extracts are widely and successfully used in the treatment of mild and moderate forms of depression. *In vitro*-test systems are routinely used in our laboratory to investigate antidepressant effectiveness. A model to simulate the acute effects of antidepressant compounds on neurotransmitter reuptake is the use of freshly prepared rat brain slices. The constantly oxygenated slices are incubated with radioactively labelled ^{3}H-norepinephrine, ^{3}H-serotonin and in addition ^{3}H-dopamine in the presence and in the absence of hypericum extract and extract-fractions, varying in their contents of hypericine or hyperforin. 10 μM imipramine is used as a measure for 100% inhibition of uptake. The extracts showed a dose-dependent inhibition of neurotransmitter uptake. Fractions of the whole extract were the more potent the more apolar the contents were. Very similar results were seen when down-regulation of β-adrenoceptors was investigated in extract-exposed astrocytoma cells. The plant

extracts and their fractions showed corresponding efficacies on receptor down-regulation as on neurotransmitter uptake inhibition.
Fractions of the plant extract are either highly enriched with or depleted of hyperforin. Hyperforin, a major constituent of St. John's wort is known for its high potency to induce metabolic enzymes and thus for its interactions with co-administered drugs The antidepressant activity of this constituent, however, is still a matter of controversy. We could demonstrate that hyperforin-free fractions were still effective and that hyperforin is by no mean the only effective antidepressant principle in the extract although the efficacy was higher with increased contents of hyperforin.

The NK1 receptor localizes to the plasma membrane microdomains and its activation is dependent on lipid raft integrity
(Collaboration with Katia Monastyrskaya*, Andrea Hostettler*, Annette Dräger*
from the Institute of Anatomy and * Department of Cell Biology, University of Bern)
Neurokinin 1 receptor (NK1R) is expressed in central and peripheral nervous system as well as in endothelial and smooth muscle cells. It is involved in mediation of pain, inflammation, exocrine secretion and smooth muscle contraction. The group of Prof. Dräger demonstrated that the NK1R is localized in lipid rafts. Cholesterol depletion of NK1R-expressing HEK cells with methyl-b-cyclodextrin (MBCD) abolished receptor signalling. The NK1R raft localization and the NK1 receptor-mediated signalling were rescued by cholesterol replenishment. To rule out the possibility that cholesterol extraction diminished substance P/NK1R-mediated signalling by depleting the pool of NK1R on the cell surface, we performed radioligand binding studies in untreated and cholesterol-depleted NK1R-expressing cells. These binding studies revealed that cholesterol extraction did not affect the expression of NK1R on the cell surface. Our results support their findings that NK1R signalling is dependent on lipid raft integrity.

Short stature caused by a biologically inactive mutant growth hormone (GH-C53S)
(Collaboration with Amélie Besson*, Souzan Salemi*, Johnny Deladoey*, Jean-Marc Vuissoz*, Andrée Eblé*, Martin Bidlingmaier**, Christa Flück*, Primus E. Mullis*
* University Children's Hospital, Pediatric Endocrinology and Metabolism, Inselspital, Bern, ** University's Hospital, Clinical Medicine, Munich)
Short stature can be associated with bio-inactive growth hormone. Prof Mullis and his group have found one homozygous missense mutation, C53S, in the growth hormone molecule of one Serbian patient with growth retardation showing all the clinical characteristics of a bio-inactive growth hormone. Using radioligand binding assays we were able to show that the bio-inactivity of the growth hormone missense variant C53S is due to lower affinity of this mutant for the growth hormone receptor.

Original publications

1. K. Monastyrskaya, A. Hostettler, S. Bürgi, A. Dräger:
The NK1 receptor localises to the plasma membrane microdomains and its activation is dependent on lipid raft integrity.
J. Biol. Chem. (in press).

2. A. Besson, S. Salemi, J. Deladoey, J.–M. Vuissoz, A. Eblé, M. Bidlingmaier, S. Bürgi, U. E. Honegger, C. Flück, P. E. Mullis:
Short stature caused by a biologically inactive mutant growth hormone (GH-C53S).
J. Clin. Endocrinol. Metab. (in press).

3. S. F. Muehlebach, G. Karlaganis, U. E. Honegger:
Kinetic assessment of persistent halogenated xenobiotics in cell culture models. Comparison of mono-and poly-halogenated compounds.
Chemosphere (in press).

Review articles

U. E. Honegger:
Different articles on antidepressants, Hypericum perforatum extract, hypnotics, analgetics and drug interactions were published in the Schweizerische Apotheker-zeitung (SAZ) and Schweizerische Ärztezeitung and other practice-oriented Journals.

Group Prof. Hartmut Porzig

Group members: Ivana Kotevic, as PhD student until 15. 3. 2005,
as PhD until September 2005
Anton Vichalkovski, PhD student until March 2005,
as PhD until July 2005
Niculina Gebhardt, MD student (until April 2005)
Reto Kaderli, MD student (until April 2005)

The research interests of our group center on mechanisms regulating proliferation and differentiation of normal as well as leukemic human hematopoietic progenitor cells. In principle, during physiological blood cell formation there are three major problems that have to be solved: (1) to maintain a constant pool of undifferentiated stem cells, (2) to regulate proliferation and lineage commitment according to the overall needs of the body, (3) to maintain a constant number of terminally differentiated blood cells. To reach these objectives, a host of humoral signals participate in determining the fate of hematopoietic progenitor cells. Best known among these is the cytokine family of peptide growth factors acting via stimulating cellular tyrosine kinases. In recent years it became increasingly clear that the effects of cytokines are modulated by signals that act via G protein-linked receptors. This latter group includes, among others, chemokines, thrombin, purines and lipids and constitutes the focus of several recent research projects.

Leukemic cells find various interesting ways to evade these normal regulatory mechanisms. Therefore, a second line of ongoing research deals with the effects of BCR-Abl activity on G protein-linked cellular Ca^{2+} signaling in leukemic cells. Several model systems allowing to switch between inactive and highly active BCR-Abl are used to dissect the role of this tyrosine kinase in cellular Ca^{2+} handling and growth control.

Modulation of cytokine signaling by thrombin and SDF-1 during growth and differentiation of hematopoietic progenitor cells

A. Vichalkovski, H. Porzig

The effects of two G protein-coupled receptor agonists, the chemokine CXCL12 (SDF-1) and thrombin, on growth and survival have been analyzed in multipotent and erythroid human hematopoietic progenitor cells. While the receptors for the two agonists, CXCR4 and PAR-1, respectively, are expressed in both cell populations, DNA synthesis was enhanced by CXCL12 only in multipotent cells and was inhibited by thrombin only in erythroid cells. We show that CXCL12 on its own promotes cell survival and provides an additive proliferative effect together with cytokines. This effect required the activation of the RhoA-Rho kinase pathway and the stimulation of Ca^{2+}-dependent kinases. The activation of RhoA relied upon a G_i-mediated

stimulation of tyrosine kinases and was blocked both by inhibitors of Src kinases and of Jak kinases. In erythroid, but not in multipotent cells, Epo and the PKC activator PMA stimulated the Src kinase Lyn and enhanced cell growth. Thrombin reduced the stimulating effect of Epo, and tyrosine kinase inhibitors antagonized this effect. Hence, thrombin appeared to block erythroid DNA synthesis by mediating a tyrosine kinase-dependent inhibition of Epo-stimulated PKC subtypes. Detailed analysis of PKC subtype activity under these conditions revealed PKCβ_2 as a specific target for the inhibitory action of Src and Abl tyrosine kinases. We conclude from these data that erythroid commitment of multipotent hematopoietic progenitors is associated with pronounced changes in PKC-tyrosine kinase interactions through establishing a negative feedback loop between PKCβ and tyrosine kinases. These developmental stage-dependent changes may determine which signaling pathways are recruited and whether growth and survival of hematopoietic cells are promoted or inhibited by G protein-coupled receptor agonists. The results of these studies have recently been published (1)

Tyrosine kinase modulation of protein kinase C activity regulates G protein-linked Ca^{2+} signaling in leukemic hematopoietic cells

A. Vichalkovski, Ivana Kotevic, N. Gebhardt, R. Kaderli and H. Porzig

We have used a recombinant mouse pre-B cell line (TonB210.1, expressing Bcr/Abl under the control of an inducible promoter) and several human leukemia cell lines to study the effect of high tyrosine kinase activity on G protein-coupled receptor (GPCR) agonist-stimulated cellular Ca^{2+} release and store-operated Ca^{2+} entry (SOCE). After induction of Bcr/Abl expression, GPCR-linked SOCE increased. The effect was reverted in the presence of the specific Abl inhibitor imatinib (1 μM) and the Src inhibitor PP2 (10 μM). In leukemic cell lines constitutively expressing high tyrosine kinase activity, Ca^{2+} transients were reduced by imatinib and/or PP2. Ca^{2+} transients were enhanced by specific inhibitors of PKC subtypes and this effect was amplified by tyrosine kinase inhibition in Bcr/Abl expressing TonB210.1 and K562 cells. Under all conditions Ca^{2+} transients were blocked or markedly reduced by the PKC activator PMA. In Bcr/Abl expressing (but not in native) TonB210.1 cells, tyrosine kinase inhibitors enhanced PKCα catalytic activity and PKCα co-immunoprecipitated with Bcr/Abl. Unlike native TonB210.1 cells, Bcr/Abl expressing cells showed a high rate of cell death if Ca^{2+} influx was reduced by complexing extracellular Ca^{2+} with BAPTA. Our data suggest that tonic inhibition of PKC represents a mechanism by which high tyrosine kinase activity can enhance cellular Ca^{2+} transients and thus exert profound effects on the proliferation, apoptosis and chemotaxis of leukemic cells. These results have been summarized in a manuscript that is currently under review (after revision) with Cell Calcium (4)

Original Publications

1. Vichalkovski, A., Baltensperger, K., Thomann, D., Porzig, H.:
Two different pathways link G-protein-coupled receptors with tyrosine kinases for the modulation of growth and survival in human erythropoietic progenitor cells
Cell Signal 17 (2005), 447-459.

2. Egger, M., Porzig, H., Niggli, E., Schwaller B.:
Rapid turnover of the ‘functional’ Na+-Ca2+ exchanger in cardiac myocytes revealed by an antisense oligodeoxynucleotide approach
Cell Calcium 37 (2005), 233-243.

3. Kotevic, I. Kirschner, K.M., Porzig, H., Baltensperger, K.:
Constitutive interaction of the P2Y2 receptor with the hematopoietic cell-specific G protein $G_{\alpha 16}$ and evidence for receptor oligomers
Cell Signal 17 (2005), 869-880.

Under review:

4. Vichalkovski A, Kotevic, I., Gebhardt, N., Kaderli, R., Porzig, H.:
Tyrosine kinase modulation of protein kinase C activity regulates G protein-linked Ca^{2+} signaling in leukemic hematopoietic cells
Revised manuscript under review with Cell Calcium

Book Chapters

1. Porzig, H., Engelhardt, S.:
Pharmaka mit Wirkung auf das vegetative Nervensystem
In: Pharmakologie und Toxikologie, Hrsg. C.-J. Estler und H. Schmidt , Schattauer Verlag, 6. Aufl. (in press).

2. Russ, H., Porzig, H.:
Antiparkinsonmittel
In: Pharmakologie und Toxikologie, Hrsg. C.-J. Estler und H. Schmidt , Schattauer Verlag, 6. Aufl. (in press).

3. Porzig, H., Grimminger, F.:
Pharmaka zur Behandlung der arteriellen Hypertonie und des Schocks
In: Pharmakologie und Toxikologie, Hrsg. C.-J. Estler und H. Schmidt , Schattauer Verlag, 6. Aufl. (in press).

4. Allendörfer, J. Kaps, M., Porzig, H.:
Pharmaka zur Behandlung des Schlaganfalls
In: Pharmakologie und Toxikologie, Hrsg. C.-J. Estler und H. Schmidt , Schattauer Verlag, 6. Aufl. (in press).

5. Allendörfer, J. Porzig, H., Kaps, M.:
Pharmaka zur Behandlung der Migräne
In: Pharmakologie und Toxikologie, Hrsg. C.-J. Estler und H. Schmidt , Schattauer Verlag, 6. Aufl. (in press).

Group Prof. Erwin Sigel

Group members: Roland Baur, head technician
Nathalie Boulineau, PhD student
Kuldeep Kaur, PhD student (since June 2005)
Dr. Frédéric Minier, PhD
Kelly Tan, PhD student

The $GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the mammalian nervous system. They are integral membrane proteins consisting of five pseudosymmetrically arranged subunits surrounding a central chloride ion selective channel. Modulation of their function influences our state of vigilance, anxiety and muscle tension. They represent the molecular targets of the frequently used tranquilizers of the benzodiazepine type (Valium®). We are interested in finding novel modulators of the receptor, in the receptor architecture and in the agonist and drug binding sites. For this purpose, we use point mutation and expression of recombinant proteins in HEK-293 cells (transient transfection) and Xenopus oocytes (mRNA microinjection), pharmacological (radioactive ligand binding studies), electro-physiological (2-electrode-voltage clamp, patch-clamp), biochemical, and molecular biology techniques.

Relative positioning of b subunit isoforms in $GABA_A$ receptors

N. Boulineau, E. Sigel

The major isoforms of $GABA_A$ receptors are thought to be composed of two α, two β and one γ subunit(s). $GABA_A$ receptors containing two β_1 subunits respond differently to the anticonvulsive compound loreclezole and the general anaesthetic etomidate than receptors containing two β_2 subunits. Receptors containing β_2 subunits show a much larger allosteric stimulation by these agents than those containing β_1 subunits. We were interested to know how receptors containing both β_1 and β_2 subunits, in different positions respond to loreclezole and etomidate. To answer this question, subunits were fused at the DNA level to form dimeric and trimeric subunits. Concatenated receptors (α_1-β_1-α_1/γ_2-β_1, α_1-β_2-α_1/γ_2-β_1, α_1-β_1-α_1/γ_2-β_2 and α_1-β_2-α_1/γ_2-β_2) were expressed in Xenopus oocytes and functionally compared in their response to the agonist GABA and to the positive allosteric modulators, loreclezole and etomidate. We have shown that I) in the presence of both β_1 and β_2 subunits in the same pentamer (mixed receptors) direct gating by etomidate is similar to exclusively β_1 containing receptors; II) In mixed receptors, stimulation by etomidate assumed characteristics intermediate to exclusively β_1 or β_2 containing receptors, but the values for the concentrations < 10 µM were always much closer to those observed in α_1-β_1-α_1/γ_2-β_1 receptors; and III) mixed receptors show no positional effects.

See original publication No. 4

Architecture of the benzodiazepine binding site on $GABA_A$ receptors

K. Tan, E. Sigel (Collaboration with Dr. M. Goeldner, University of Strasbourg, France).

Benzodiazepines exert their effects through a specific high affinity binding site on the $GABA_A$ receptor channel, where they act as positive allosteric modulators. To start to elucidate the relative positioning of benzodiazepine binding site ligands in their binding pocket, $GABA_A$ receptor residues thought to reside in the site were individually mutated to cysteine, and combined with benzodiazepine analogs carrying substituents reactive to cysteine. Direct apposition of such reactive partners is expected to lead to an irreversible site-directed reaction. Various modified ligands of the benzodiazepine binding site were found to form covalent bonds with mutated receptors. These will be further characterized. It is anticipated that this work will lead among other things to an understanding of the superposition of positive allosteric modulators and antagonists.

Conformational changes in $GABA_A$ receptors

D. Berezhnoy, E. Sigel (Collaboration with Dr. M. Goeldner, University of Strasbourg, France).

Benzodiazepines allosterically modulate $GABA_A$ receptor function by increasing the apparent affinity of the agonist GABA. We studied conformational changes induced by channel agonists at the benzodiazepine binding site. We used the rate of covalent reaction between a benzodiazepine carrying a cysteine reactive moiety with mutated receptor having a cysteine residue in the benzodiazepine binding pocket, α_1H101C$\beta_2\gamma_2$, as a sensor of its conformation. This reaction rate is sensitive to local conformational changes. Covalent reaction locks the receptor in the conformation stabilized by positive allosteric modulators. By using concatenated subunits, we demonstrated that the covalent reaction occurs either exclusively at the α/γ subunit interface or if it occurs in both α1 subunits, exclusively reaction at the α/γ2 subunit interface can lock the receptor in the conformation stabilized by positive allosteric modulators. We found evidence for an increased rate of reaction of activated receptors, whereas reaction rate with the desensitized state is slowed down. The benzodiazepine antagonist Ro15-1788 efficiently inhibited the covalent reaction in the presence of 100 μM GABA but only partially in its absence or in the presence of 10 μM GABA. It is concluded that Ro15-1788 efficiently protects activated and desensitized states, but not the resting state.

See original publication No. 1

Novel plant substances acting as b subunit isoform selective positive allosteric modulators of $GABA_A$ receptors

R. Baur, E. Sigel

(Collaboration with M. Senn, Drs. U. Séquin and U. Simmen, Dept. of Chemistry and Pharmacy, University of Basel)

Three linear molecules of a polyacetylene structure were isolated from the East African medicinal plant *Cussonia zimmermannii* Harms and shown to allosterically stimulate $GABA_A$ receptors. Stimulation was not abolished by the absence of the γ2 subunit, by the benzodiazepine antagonist Ro15-1788, or the point mutation β_2N265S, that abolishes effects by loreclezole. At a concentration of 30 μM, the substances elicited by themselves only tiny currents. Maximal stimulation at $\alpha_1\beta_2\gamma_2$ amounted to 110 – 450% for the three substances and half maximal stimulation was observed at concentrations of 1 – 2 μM. Stimulation was subunit composition dependent and was for the substance MS-1 $\alpha_1\beta_2\gamma_2 \sim \alpha_1\beta_2 \sim \alpha_3\beta_2\gamma_2 > \alpha_2\beta_2\gamma_2 > \alpha_5\beta_2\gamma_2 \sim$

$\alpha_1\beta_3\gamma_2 \sim \alpha_6\beta_2\gamma_2 > \alpha_1\beta_1\gamma_2$, for MS-2 $\alpha_1\beta_2\gamma_2 \sim \alpha_3\beta_2\gamma_2 \sim \alpha_1\beta_2 > \alpha_2\beta_2\gamma_2 \sim \alpha_6\beta_2\gamma_2 \sim \alpha_5\beta_2\gamma_2 > \alpha_1\beta_1\gamma_2$, and for MS-4 $\alpha_1\beta_2\gamma_2 \sim \alpha_1\beta_2 \sim \alpha_5\beta_2\gamma_2 \sim \alpha_3\beta_2\gamma_2 \sim \alpha_2\beta_2\gamma_2 > \alpha_6\beta_2\gamma_2 \gg \alpha_1\beta_1\gamma_2$. Maximal stimulation by MS-1 at $\alpha_1\beta_2\gamma_2$ was 450%, at $\alpha_1\beta_1\gamma_2$ 80%, and at $\alpha_1\beta_3\gamma_2$ 150%. MS-1 was thus specific for receptors containing the β_2 subunit. The reversal potential was unaffected by 10 µM MS-1, while apparent picrotoxin affinity for current inhibition was increased about three-fold. In summary, these positive allosteric modulators of $GABA_A$ receptors of plant origin have a novel, unusual chemical structure and act at a site independent of that of benzodiazepines and loreclezole.
See original publication No. 3

Benzodiazepines Affect Channel Opening of $GABA_A$ Receptors Induced by Either Agonist Binding Site

R. Baur, E. Sigel

Benzodiazepines allosterically modulate $GABA_A$ receptors by increasing the apparent affinity of the agonist GABA to elicit chloride currents. Such an increase in apparent affinity of channel gating could either be due to an increase in affinity for GABA or due to a facilitation of channel opening. In the first case, conformation of the affected sites would have to be altered. In the second case, the affected sites are not necessarily altered, as diazepam could facilitate conformational changes leading to the open channel. It is controversial as to whether benzodiazepines affect only channel opening induced by occupation of one of the two agonist binding sites, or by both. We used receptors formed by concatenated subunits to selectively destroy one of the two agonist sites by point mutation. Both of the receptors harboring only one active agonist site could be stimulated by diazepam. We therefore present evidence that binding of diazepam can affect channel opening induced by either agonist binding site.
See original publication No. 2

Influence of the point mutation α_1H101R on the assembly of $GABA_A$ receptors

R. Baur, E. Sigel

The point mutation H101R in the α_1 subunit of $GABA_A$ receptors is known to abolish effects by the benzodiazepine diazepam. This mutation and homologous mutations in other α subunits have been used to quantify receptor pentamers containing two different α subunit isoforms, and to study the role of α subunit isoforms in the response of mice to the diazepam. Both types of study assumed implicitly or explicitly that this mutation strongly affects assembly with the γ_2 subunit. We investigated the assembly properties of mutated in comparison to wild type subunits, and demonstrated that α_1H101R has similar assembly properties as wild type α_1.
See original publication No. 5

A drug screening system using $GABA_A$ receptors of defined subunit composition and positioning: Concatenation of five subunits

R. Baur, F. Minier, E. Sigel

A $GABA_A$ receptor is composed of five subunits. We showed that these five subunits can be concatenated to yield a functional receptor. This concatenated receptor α_1–β_2–α_1–γ_2–β_2 has the advantage of a known subunit arrangement. The properties after functional expression in Xenopus oocytes of this concatenated receptor are not significantly different from a receptor formed by individual subunits $\alpha_?$, $\beta_?$ and $\gamma_?$ in respect to apparent affinity for GABA to induce channel opening, inhibition of currents elicited by GABA by bicuculline and picrotoxin and reversal potential of this current.

Slight differences were observed in current desensitization. The extent of current stimulation by diazepam was significantly larger in concatenated receptors, presumably due to absence of receptors formed by $\alpha_?$ and $\beta_?$. Extent of expression amounted to about 40 % of that of non-concatenated receptors in Xenopus oocytes but remained small in HEK-293 cells. The ability to functionally express receptors consisting of five subunits opens the way to drug screening at well-defined $GABA_A$ receptors. The method should also be applicable to other members of the ligand-gated ion channel family, that comprises nicotinic acetylcholine receptors, glycine receptors and $5HT_3$ receptors.

$GABA_A$ receptors in immune cells

N. Boulineau, F. Minier, E. Sigel
(Collaboration with the groups of Prof. H.-U. Simon and Prof. T. Brunner)

The functional role of $GABA_A$ receptors in immune cells is poorly understood. In order to approach this problem we initially attempt to characterize these receptors at the structural level using flow cytometry and confocal microscopy and at the functional level using the patch clamp technique.

Original publications

1. D. Berezhnoy, R. Baur, A. Gonthier, B. Foucaud, M. Goeldner, E. Sigel:
Conformational changes at benzodiazepine binding sites of $GABA_A$ receptors detected with a novel technique
J. Neurochem. 92 (2005), 859-866.

2. R. Baur, E. Sigel:
Benzodiazepines affect channel opening of $GABA_A$ receptors induced by either agonist binding sites.
Mol. Pharmacol. 67 (2005), 1005-1008.

3. R. Baur, M. Senn, U. Simmen, U. Séquin, E. Sigel:
Novel plant substances acting as β subunit selective positive allosteric modulators of $GABA_A$ receptors.
Mol. Pharmacol. 68 (2005), 787-792.

4. N. Boulineau, R. Baur, F. Minier, E. Sigel:
Consequence of the presence of two different β subunit isoforms in a $GABA_A$ receptor
J. Neurochem., Nov 21 (2005); [Epub ahead of print].

5. R. Baur, E. Sigel:
Influence of the point mutation α_1H101R on the assembly of $GABA_A$ receptors
NeuroReport 16 (2005), 1955-1958.

Our work has been discussed in “Perspectives” in Sciences’STKE: D.R. Burt, Sci. STKE pe5 (2005).

Patent

1. Martin Senn, Urs Simmen, Urs Séquin, Reto Brun, Erwin Sigel:
Novel polyacetylene compounds.
British patent No. UK 04 281 64.8
(Universität Basel, Universität Bern, Tropeninstitut)

Review articles

1. E. Sigel, F. Minier:
Educational paper: The Xenopus oocyte: System for the study of functional expression and modulation of proteins
Molecular Nutrition and Food Research 49, 228-34.

2. E. Sigel:
The benzodiazepine recognition site on $GABA_A$ receptors
Medicinal Chemistry Reviews – Online.

Group Prof. Hans-Uwe Simon

Group members: Nicola Andina, PhD student (since June 2005)
Dr. Andreina Bruno, PhD (until March 2005)
Dr. Sébastien Conus, PhD
Arezoo Daryadel, PhD student
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Ganna Kostylina, PhD student
Evelyne Kozlowski, technician
Esther Lehmann, PhD student (since September 2005)
Sibylla Martinelli, PhD student (until February 2005)
Souzan Salemi, PhD (since September 2005)
Inès Schmid, head technician
David Troi, MD student
Ekatherina Vassina, PhD student (until May 2005)
Dr. Stephan von Gunten, MD, PhD
Thomas von Rütte, MD student
PD Dr. Shida Yousefi, PhD[1]

[1]In addition, independent research work with own Swiss National Science Foundation projects.

We are interested in the precise features of chronic inflammatory responses. Several diseases serve as models to study such processes. In particular, we investigate pathogenic mechanisms of the following diseases: Atopic dermatitis, idiopathic eosinophilia, eosinophilic esophagitis, cystic fibrosis, sepsis, rheumatoid arthritis, chronic obstructive pulmonary disease, and cancer. Our research goal is the identification of new drug targets for future therapeutic approaches in these diseases. Besides the pathogenic aspects of our research, we have developed several in vitro and in vivo test systems to determine potential effects of a given drug on the immune system. Moreover, we are involved in several clinical drug studies. Our research requires a network of physician-scientists from many different clinics. Most of the participating groups are located at the Medical Faculty of the University of Bern. Results of these collaborative interactions are seen in the following abstracts, which briefly describe our research activities in 2005.

Apoptotic pathways are inhibited by leptin receptor activation in neutrophils
A. Bruno, S. Conus, I. Schmid, H.-U. Simon
Leptin regulates food intake as well as metabolic, endocrine, and immune functions. It exerts proliferative and anti-apoptotic activities in a variety of cell types, including T cells. Leptin also stimulates macrophages and neutrophils, and its production is increased during inflammation. In this study, we demonstrate that human neutrophils express leptin surface receptors under in vitro and in vivo conditions and that leptin delays apoptosis of mature neutrophils in vitro. The anti-apoptotic effects of leptin

were concentration-dependent and blocked by an anti-leptin receptor monoclonal antibody. The efficacy of leptin to block neutrophil apoptosis was similar to granulocyte colony-stimulating factor. Using pharmacological inhibitors, we obtained evidence that leptin initiates a signaling cascade involving phosphatidylinositol-3-OH kinase and mitogen activated protein kinase – dependent pathways in neutrophils. Moreover, leptin delayed the cleavage of Bid and Bax, the mitochondrial release of cytochrome *c* and Smac, as well as the activation of both caspase-8 and caspase-3 in these cells. Taken together, leptin is a survival cytokine for human neutrophils, a finding with potential pathologic relevance in inflammatory diseases.
See original publication No. 1

Siglec-9 transduces apoptotic and non-apoptotic death signals into neutrophils depending on the pro-inflammatory cytokine environment

S. von Gunten, S. Yousefi, M. Seitz, S. M. Jakob, T. Schaffner, R. Seger, J. Takala, P. M. Villiger, H.-U. Simon
(Collaboration with the Departments of Rheumatology/Clinical Immunology/ Allergology, Intensive Care Medicine, and Pathology, University of Bern, as well as with University Children's Hospital, Zurich, Switzerland)

We report about new apoptotic and non-apoptotic death pathways in neutrophils that are initiated via the surface molecule sialic acid binding immunoglobulin-like lectin (Siglec)-9. In normal neutrophils, Siglec-9 activation induced apoptosis. Inflammatory neutrophils obtained from blood of patients suffering from acute septic shock or from joint fluids of rheumatoid arthritis patients demonstrated increased Siglec-9- but normal Fas receptor-mediated cytotoxic effects when compared with normal blood neutrophils. The increased Siglec-9-mediated death was mimicked *in vitro* by short-term pre-incubation of normal neutrophils with pro-inflammatory cytokines, such as granulocyte/macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-α, and IFN-γ, and was demonstrated to be caspase-independent. Experiments using scavengers of reactive oxygen species (ROS) and neutrophils unable to generate ROS indicated that the Siglec-9-mediated caspase-independent neutrophil death in the presence of GM-CSF depends on ROS. Interestingly, this form of neutrophil death was characterized by cytoplasmic vacuolization and several other non-apoptotic morphological features, which were also seen in neutrophils present in joint fluids from rheumatoid arthritis patients. Taken together, these data suggest that apoptotic (caspase-dependent) and non-apoptotic (ROS-dependent) death pathways are initiated in neutrophils *via* Siglec-9. The new insights have important implications for the pathogenesis, diagnosis, and treatment of inflammatory diseases such as sepsis and rheumatoid arthritis.
See original publication No. 2

Cytokine expression in healthy and inflamed mucosa: probing the role of eosinophils in the digestive tract

A. Straumann, J. Kristl, S. Conus, E. Vassina, H.-P. Spichtin, C. Beglinger, H.-U. Simon
(Collaboration with the Department of Gastroenterology, Kantonsspital Olten, Olten, Institute of Clinical Pathology, Basel, and the Department of Gastroenterology, University of Basel, Basel, Switzerland)

In eosinophilic esophagitis, the esophagus is infiltrated with activated eosinophils, often causing tissue damage. Since the intestine of these patients is unaffected, we hypothesized that in this disease different tissue-dwelling eosinophilic populations may co-exist: activated eosinophils infiltrating the esophagus and resting eosinophils

residing in unaffected intestine. Using immunofluorescence and immunoassays, we investigated the expression of CD25 and the T_H2 cytokines IL-4, IL-5, IL-10, and IL-13 in esophageal, intestinal and blood eosinophils in controls and eosinophilic esophagitis patients. In controls, a small but significant proportion of intestinal, but no blood, eosinophils expressed CD25 and IL-13. On the other hand, eosinophils infiltrating the inflamed esophageal mucosa of eosinophilic esophagitis patients demonstrated strong evidence for activation, since the majority expressed CD25, IL-4, and IL-13. Moreover, IL-13 positive intestinal eosinophils were increased in patients compared to the normal intestinal mucosa. Taken together, there are distinct cytokine expression patterns among eosinophils under non-inflammatory and inflammatory conditions.

See original publication No. 3

Leptin is an eosinophil survival factor

S. Conus, A. Bruno, H.-U. Simon

Leptin regulates food intake as well as metabolic, endocrine, and immune functions. It exerts proliferative and anti-apoptotic activities in a variety of cell types, including T cells. Leptin also stimulates macrophages and neutrophils, and its production is increased during inflammation. To examine the expression of leptin receptors on eosinophils and the effect of recombinant leptin on pro-apoptotic pathways in these cells. The presence of leptin receptor was examined by reverse transcriptase – polymerase chain reaction and immunofluorescence analysis in freshly isolated blood eosinophils and in tissue eosinophils. The effect of recombinant leptin on apoptotic pathways in eosinophils was studied by flow cytometric, immunoblotting and immunofluorescence techniques. Human eosinophils express leptin surface receptors under *in vitro* and *in vivo* conditions and leptin delays apoptosis of mature eosinophils *in vitro*. The anti-apoptotic effects of leptin were concentration-dependent and blocked by an anti-leptin receptor monoclonal antibody. The efficacy of leptin to block eosinophil apoptosis was similar to granulocyte/macrophage colony-stimulating factor. Leptin delayed the cleavage of Bax as well as the mitochondrial release of cytochrome *c* and Smac, suggesting that it blocks pro-apoptotic pathways proximal to mitochondria in eosinophils. Using pharmacological inhibitors, we obtained evidence that leptin initiates a signaling cascade involving phosphatidylinositol-3-OH kinase and mitogen activated protein kinase – dependent pathways in eosinophils. In conclusion, leptin is a survival cytokine for human eosinophils, a finding with potential pathologic relevance in allergic and parasitic diseases.

See original publication No. 4

Inflammatory cell numbers and cytokine expression in atopic dermatitis after topical pimecrolimus treatment

D. Simon, E. Vassina, S. Yousefi, L. R. Braathen, H.-U. Simon

(Collaboration with the Department of Dermatology, University of Bern, Switzerland)

In several clinical trials the topical application of pimecrolimus was shown to be effective in the treatment of atopic dermatitis (AD). By targeting calcineurin-dependent signaling pathways, pimecrolimus controls cytokine gene expression. The purpose of this study was to investigate the effect of pimecrolimus on the inflammatory infiltrate and cytokine expression pattern in atopic dermatitis upon topical therapy. From ten patients with acute AD, skin biopsies as well as immunophenotype and cytokine production of peripheral blood mononuclear cells (PBMC) were examined before and three weeks after therapy. The clinical improvement was associated with a marked regression of histopathological features.

In particular, the density of the inflammatory infiltrate mostly containing lymphocytes and eosinophils declined. By double immunofluorescent staining, a reduced expression of the T helper (Th) 2 cytokines interleukin (IL)-5, IL-10, and IL-13 in both CD4+ and CD8+ T cells was demonstrated after therapy. Pimecrolimus therapy was also associated with a reduced expression of the Th1 cytokine interferon (IFN)-γ. Interestingly, the numbers of epidermal CD1a+ dendritic cells increased following treatment. In the peripheral blood, a decrease of lymphocytes and eosinophils was noticed, but the distribution of lymphocyte subpopulations and their capacity of cytokine production did not change. In conclusion, topical pimecrolimus exhibits anti-inflammatory effects in AD by reducing the inflammatory cell infiltrate and cytokine expression in the dermis.
See original publication No. 5

Increased expression and a potential anti-inflammatory role of TRAIL in atopic dermatitis

E. Vassina, M. Leverkus, L. R. Braathen, H.-U. Simon, D. Simon
(Collaboration with the Department of Dermatology, University of Bern, Switzerland, and the Department of Dermatology, University of Magdeburg, Germany)

TRAIL, the tumor necrosis factor-related apoptosis-inducing ligand induces apoptosis of many transformed but also of non-transformed cells. In addition, TRAIL receptor activation has been reported to activate non-apoptotic signaling pathways. Here, we report an increased expression of TRAIL in peripheral blood T cells and monocytes from patients with atopic dermatitis compared to control individuals. High TRAIL expression was also observed in skin-infiltrating T cells of atopic dermatitis patients. Topical tacrolimus treatment reduced the total number of T cells in the skin, but the relative proportion of TRAIL positive cells within both CD4+ and CD8+ cell populations did not change. TRAIL was demonstrated to induce the expression of interleukin-1 receptor antagonist in keratinocytes in a caspase-independent manner in vitro. Moreover, increased expression of interleukin-1 receptor antagonist was observed in keratinocytes of atopic dermatitis lesional skin. These data suggest that TRAIL expressing inflammatory skin cells may contribute to the epidermal activation of the interleukin-1 receptor antagonist gene in atopic dermatitis.
See original publication No. 6

CINCA syndrome: a defect in peripheral tolerance mechanisms?

T. Bihl, E. Vassina, M. K. Boettger, R. Goldbach-Mansky, M. Seitz, P. M. Villiger, H.-U. Simon
(Collaboration with the Departments of Rheumatology/Clinical Immunology/ Allergology, University of Bern, Switzerland, and National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, MD, USA)

Chronic infantile neurological cutaneous and articular (CINCA) syndrome is a severe chronic inflammatory disease, in which the pathogenesis is unknown. We examined the capacity of CINCA peripheral blood mononuclear cells (PBMC), which carried the T348M mutated form of cryopyrin, to release cytokines upon primary stimulation of monocytes (LPS) and lymphocytes (PHA), respectively. In contrast to normal PBMC and independent from the inflammatory activity of the patient, T348M cryopyrin expressing PBMC did not generate significant amounts of interleukin (IL)-10 upon LPS stimulation, but produced normal levels of this cytokine upon PHA stimulation. The data reported here provide evidence for a defective tolerance mechanism towards microbial antigens in a so-called autoinflammatory disease.
See original publication No. 7

Eosinophils form extracellular traps in bacterial and parasitic infectious diseases

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Eosinophils are considered as proinflammatory effector cells, which may be helpful in the defense against bacteria and parasites. Here, we demonstrate that activated eosinophils release granule and nuclear proteins, which form extracellular fibers. Similar structures have previously been described following activation of neutrophils and called neutrophil extracellular traps (NETs). We further show that eosinophil extracellular traps (EETs) bind and kill bacteria. EETs were identified in vivo in the course of bacterial and parasitic infections, respectively. Thus, eosinophils contribute to innate immune responses in tissues by inhibition of pathogen spreading and, subsequently, by pathogen killing.

Anticancer drugs target survivin via a PI3K-dependent but Akt-independent signaling pathway in immature neutrophils

S. Martinelli, G. Kostylina, V. Niggli, C. Baumann, M. F. Fey, S. Yousefi, H.-U. Simon
(Collaboration with the Departments of Pathology and Medical Oncology, University of Bern, Switzerland)

Myelosuppression is the most common unwanted side effect associated with the administration of anticancer drugs and infections remain a common cause of death in chemotherapy treated patients. Several mechanisms of the cytotoxicity of these drugs have been proposed and may synergistically operate in a given cell. Survivin expression has been associated with cancer, but recent reports suggest that this molecule is also expressed in several immature and mature hematopoietic cells. Here we demonstrate that specific survivin depletion increases caspase-3 activity and that survivin overexpression blocks anticancer drug - induced death in immature human neutrophils. Moreover, treatment of these cells with anticancer drugs reduced endogenous survivin levels causing apoptosis. The anticancer drugs did not directly target survivin, instead they blocked the activity of phosphatidylinositol-3-OH kinase (PI3K), which regulated survivin expression and apoptosis in immature neutrophils. Strikingly, and in contrast to other cells, this pathway did not involve the serine/threonine kinases Akt or the mammalian target of rapamycin (mTOR). These data suggest that drugs, which block either Akt or mTOR, may preferentially induce apoptosis of cancer cells since they exhibit no cytotoxicity for immature neutrophils.

Cytokine-inducible survivin and IAP-2 expression contributes to delayed eosinophil apoptosis in the hypereosinophilic syndrome

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The exact molecular mechanisms leading to the clinical picture of hypereosinophilic syndrome (HES) are unknown. Here, we show that cultured eosinophils purified from blood of HES patients exhibit delayed spontaneous death and relative resistance towards ceramide- but not CD95-mediated death. The subsequent investigation of members of the inhibitor of apoptosis (IAP) family revealed that HES but not normal eosinophils expressed high levels of cellular (c)IAP-2 and survivin. X-linked IAP (XIAP) was usually present in both HES and normal eosinophils. The eosinophil hematopoietins IL-3, IL-5, and granulocyte/macrophage colony-stimulating factor

(GM-CSF) increased the expression of cIAP-2, survivin, and XIAP in normal eosinophils in vitro. In the blood of HES patients, we observed increased concentrations of IL-3 and/or IL-5, suggesting that these cytokines are, at least partially, responsible for the elevated levels of cIAP-2 and survivin in the eosinophils of these patients. Utilizing a cell-free system in which caspase-3 was activated in eosinophil cytosolic extracts by addition of cytochrome *c*, immunodepletion of cIAP-2, survivin, and XIAP, respectively, resulted in accelerated caspase activation. These data suggest that some members of the IAP family including survivin are regulated by survival cytokines and inhibit the caspase cascade in HES eosinophils. The cytokine-dependent mechanism of delayed eosinophil apoptosis described here may also apply to other eosinophilic diseases.

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Group Prof. Jörg W. Stucki

Group members: Dr. Clemens Wagner, PhD[1] (until March 2005)
PD Dr. Robert Urbanczik, PhD

[1]In addition, independent research work with own Swiss National Science Foundationprojects.

Prof. Dr. Jörg W. Stucki

Mathematical modeling of the regulation of caspase-3 activation and degradation

J.W. Stucki & H.-U. Simon

Caspases are thought to be important players in the execution process of apoptosis. Inhibitors of apoptosis (IAPs) are able to block caspases and therefore apoptosis. The fact that a subgroup of the IAP family inhibits active caspases implies that not each caspase activation necessarily leads to apoptosis. In such a scenario, however, processed and enzymatically active caspases should somehow be removed. Indeed, IAP-caspase-complexes covalently bind ubiquitin, resulting in degradation by the 26S proteosome. Following release from mitochondria, second mitochondrial activator of caspases (Smac) inactivates IAPs. Moreover, although pro-apoptotic factors such as irradiation or anti-cancer drugs may release Smac from mitochondria in tumor cells, high cytoplasmic survivin levels might be able to neutralize it and, consequently, IAPs would further be able to prevent caspase activation. Here, we propose a simple mathematical model, describing the molecular interactions between survivin, Smac, IAPs, and caspase-3, including the requirements for both induction and prevention of apoptosis, respectively. In addition, we predict a novel mechanism of caspase-3 degradation that might be particularly relevant in long-living cells.

See original publication No. 1

Entropy production of the Willamowski-Rössler oscillator

J.W. Stucki & R. Urbanczik

Some properties of the Willamowski-Rössler model were studies by numerical simulations. From the original equation a minimal version was derived which alsoexhibited the characteristic properties of the original model. This minimal model suggests that the Willamowski-Rössler model contains the Volterra-Lotka model as acore component. Akin to the original model, the minimal model has two steady states, a saddle point responsible for chaos and a fixed point which dictates its dynamicbehaviour. The chaotic attractor is located close to the surface of the basin of attraction of the saddle node. Surprisingly, it was found that the mean values of thevariables corresponded to the steady states during oscillations even under chaos. This allowed comparing the entropy production of the Willamowski-Rössler oscillatorwith the entropy production of the steady states. It was found that oscillations always lowered the entropy production of the system. Since under these circumstances lessenergy is dissipated to produce the same output, the oscillating system is more efficient than the non-oscillatory one.

See original publication No. 2

Pyruvate metabolism in rat liver mitochondria: what is optimized at steady state?

J.W. Stucki & R. Urbanczik

A representative model of mitochondrial pyruvate metabolism was decomposed into all its extremal independent currents and compared to experimental data obtained from liver mitochondria incubated with pyruvate as a substrate but in the absence of added ADP. Assuming no regulation of enzymatic activities, the free flow prediction for the output of the model shows large discrepancies with the experimental data. To study the objective of the incubated mitochondria, we calculate the conversion cone of the model, which describes the possible input/output behaviour of the network. We demonstrate consistency of the experimental data with the model since all measured data are within this cone. Since they are even close to the boundary of the cone, we deduce that pyruvate is converted very efficiently (93 %) to produce the measured extramitochondrial metabolites**.** We find that the main function of the incubated mitochondria is the production of malate and citrate, supporting the anaplerotic pathways in the cytosol, notably gluconeogenesis and fatty acid synthesis. Finally, we demonstrate that the major flows through the enzymatic steps of the mitochondrial pyruvate metabolism can be reliably predicted based on the stoichiometric model plus the measured extramitochondrial products. A major advantage of this method is that neither kinetic simulations nor radioactive tracers are needed.

See original publication No. 3

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Dr. Robert Urbanczik

An improved algorithm for stoichiometric network analysis: theory and applications

R. Urbanczik and C. Wagner

Genome scale analysis of the metabolic network of a microorganism is a major challenge in bioinformatics. The combinatorial explosion, which occurs during the construction of elementary fluxes (non-redundant pathways) requires sophisticated and efficient algorithms to tackle the problem.

Mathematically, the calculation of elementary fluxes amounts to characterizing the space of solutions to a mixed system of linear equalities, given by the stoichiometry matrix, and linear inequalities, arising from the irreversibility of some or all of the reactions in the network. Previous approaches to this problem have iteratively solved for the equalities while satisfying the inequalities throughout the process. In an extension of previous work, here we consider the complementary approach and derive an algorithm which satisfies the inequalities one by one while staying in the space of solution of the equality constraints. Benchmarks on different subnetworks of the central carbon metabolism of *Escherichia coli* show that this new approach yields a significant reduction in the execution time of the calculation. This reduction arises since the odds that an intermediate elementary flux already fulfills an additional inequality are larger than when having to satisfy an additional equality constraint.
See original publication No. 1

Functional stoichiometric analysis of metabolic networks
R. Urbanczik and C. Wagner
An important tool in Systems Biology is the stoichiometric modeling of metabolic networks, where the stationary states of the network are described by a high-dimensional polyhedral cone, the so-called flux cone. Exhaustive descriptions of the metabolism can be obtained by computing the elementary vectors of this cone but, owing to a combinatorial explosion of the number of elementary vectors, this approach becomes computationally intractable for genome scale networks.
Hence, we propose to instead focus on the conversion cone, a projection of the flux cone, which describes the interaction of the metabolism with its external chemical environment. We present a direct method for calculating the elementary vectors of this cone and, by studying the metabolism of *Saccharomyces cerevisiae*, we demonstrate that such an analysis is computationally feasible even for genome scale networks.
See original publication No. 2

The Geometry of the Flux Cone of a Metabolic Network
C. Wagner and R. Urbanczik
The analysis of metabolic networks has become a major topic in biotechnology in recent years. Applications range from the enhanced production of selected outputs to the prediction of genotype-phenotype relationships. The concepts used are based on the assumption of a pseudo steady state of the network, so that for each metabolite inputs and outputs are balanced. The stoichiometric network analysis expands the steady state into a combination of non-redundant sub-networks with positive coefficients called extremal currents. Based on the unidirectional representation of the system these sub-networks form a convex cone in the flux-space. A modification of this approach allowing for reversible reactions led to the definition of elementary modes. Extreme pathways are obtained with the same method but splitting up internal reactions into forward and backward rates. In this study we explore the relationship between these concepts. Due to the combinatorial explosion of the number of elementary modes in large networks, we promote a further set of metabolic routes, which we call the minimal generating set. It is the smallest subset of elementary modes required to describe all steady states of the system. For large-scale networks the size of this set is of several magnitudes smaller than that of elementary modes and of extreme pathways.
See original publication No. 3

SNA - a toolbox for the stoichiometric analysis of metabolic networks

R. Urbanczik

Despite recent algorithmic and conceptual progress, the stoichiometric network analysis of large metabolic models remains a computationally challenging problem.

SNA is a interactive, high performance toolbox for analysing the possible steady state behaviour of metabolic networks by computing the generating and elementary vectors of their flux and conversions cones. It also supports analysing the steady states by linear programming. The toolbox is implemented mainly in Mathematica and returns numerically exact results. It is available under an open source license from: *http://bioinformatics.org/project/?group_id=546*.

Thanks to its performance and modular design, SNA is demonstrably useful in analysing genome scale metabolic networks. Further, the integration into Mathematica provides a very flexible environment for the subsequent analysis and interpretation of the results.

See original publication No. 4

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Our research is focused on translational aspects in molecular oncology. A major goal is to investigate anti-apoptosis as a mechanism of cancer drug resistance, and to identify survival pathways and their regulators for targeted intervention. To facilitate cancer cell apoptosis, we have developed second and third generation antisense oligonucleotides and siRNA molecules targeting apoptosis inhibitors of the Bcl-2 and IAP family.

In small cell lung cancer (SCLC) cells we found that Akt/PKB is activated during chemotherapy and mediates anti-apoptosis by regulating the function of the IAP survivin and the BH3 only protein Bad. Another intriguing phenomenon of SCLC cells are proximal defects in death receptor signaling, due to the lack of caspase-8 and various rerceptor subtypes as a consequence of aberrant promoter methylation. We found that these cells not only were resistant to TRAIL-induced apoptosis and even showed enhanced proliferation through activation of the MAPK-ERK1/2 pathway.

In our tumor targeting program we have developed tumor-selective drug delivery systems based on recombinant antibodies and synthetic protein ligands directed against tumor-associated antigens. An Ep-CAM-specific single-chain immunotoxin is currently in phase II oncology trials and other developments for targeted cancer therapy such as immunoliposomes, nanoparticles and new toxin formulations are under investigation.

DeltaNp73 antisense activates PUMA and induces apoptosis in neuroblastoma cells

A.P. Simões-Wüst, B. Sigrist, L. Belyanskaya, S. Donaldson, R. Stahel, U. Zangemeister-Wittke

The TP73 gene codes for various different protein isoforms. They include proteins expressed under the control of the P1 promoter that contain a transactivation domain

and are similar in function to p53 (TAp73 isoforms), as well as proteins regulated by the P2 promoter that lack this domain and function as dominant negative inhibitors of TAp73 and p53 (ΔNp73 isoforms). Whereas TAp73 functions as a tumor suppressor with pro-apoptotic function, ΔNp73 is likely to prevent the induction of apoptosis in tumor cells and to participate in oncogenesis. Here we used a loss-of-function strategy to assess the role of ΔNp73 in SH-SY5Y neuroblastoma cells. An antisense oligonucleotide designed to target ΔNp73 mRNA, but not TAp73, was used to effectively downregulate this transcript. DeltaNp73 downregulation was accompanied by increased levels of the pro-apoptotic BH3 family member PUMA on the mRNA and protein level, and by conformational activation of BAX which translocated to mitochondria. These ΔNp73 antisense-mediated alterations led to the induction of apoptosis as detected by decreased cell viability, the occurrence of cells with fragmented DNA and increased caspase-3 activity in cell lysates. Our results demonstrate the cytoprotective role of ΔNp73 in neuroblastoma and suggest its use as target for molecular intervention therapy.

See original publication No. 1

Apoptosis regulation and drug resistance in malignant pleural mesothelioma

U. Zangemeister-Wittke, S. Hopkins-Donaldson

Malignant pleural mesothelioma (MPM) is a disease with poor prognosis and intrinsic drug resistance. Taking into account a latency period of 20-50 years and a decline in workplace exposure to asbestos in Europe since the 1970s, it has been estimated that the number of men dying from MPM in Europe will double each year until a peak is reached in 2020. Although numerous single-agent and combination treatments have been examined, no effective standard treatment with chemotherapy alone has emerged so far. We investigated p53 activity in MPM cell lines in response to cisplatin treatment and determined the role of Survivin in MPM cell death induction. Our results demonstrated a negative correlation between p53 induction and drug-induced cell death. The cell lines ZL5 and ZL34 were more sensitive to cisplatin compared to SPC212 cells, and p53 activation could be readily measured after 48 h cisplatin incubation. In contrast, no p53 activity was measured for cisplatin resistant SPC212 cells and DNA sequencing demonstrated a p53 missense mutation in these cells. Moreover, we observed that resistant SPC212 cells maintained high levels of Survivin, c-IAP-2 and XIAP expression during cisplatin treatment. On the other hand, in sensitive ZL5 cells survivin expression decreased in the presence of cisplatin. All MPM cell lines tested were negative for both p14ARF and p16 expression, suggesting that they contain deletions in the 9p21 locus. Despite the absence of the positive regulator p14ARF, p53 activity could be induced in response to cisplatin in both ZL5 and ZL34 cells. In addition to the downregulation of Survivin, increase in the positively regulated p53 targets p21 and BAX were also measured in these cells upon cisplatin treatment, suggesting p53 to be fully functional. Thus, the question as to whether p53 is fully functional in MPM is still open and deserves further investigation.

See original publication No. 2

DNA damage triggers the Akt survival pathway in small cell lung cancer cells and attenuates apoptosis by survivin upregulation

L. Belyanskaya, S. Hopkins-Donaldson, S. Kurtz, A.P. Simões-Wüst, S. Yousefi, H.-U. Simon, R. Stahel, U. Zangemeister-Wittke

The inhibitor of apoptosis protein (IAP) survivin is overexpressed in many tumors but is absent in most normal adult tissues. Here we report high levels of survivin

expression in small cell lung cancer (SCLC), and describe the role of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway in survivin upregulation. Moreover, the cytoprotective function of survivin in response to the anti-cancer agent cisplatin (CDDP) was investigated. Negative modulation of PI3K/Akt using pharmacological inhibitors or dominant negative Akt (DN-Akt) decreased Akt kinase activity and resulted in decreased survivin expression and phosphorylation on Thr34, whereas transfection of constitutively active Akt (CA-Akt) increased survivin expression and phosphorylation. Interestingly, we found that treatment of SCLC cells with CDDP further increased survivin expression in a cell cycle independent manner by activation of Akt. CA-Akt or lentiviral survivin also inhibited apoptosis induced by CDDP, whereas DN-Akt or survivin-specific RNA interference sensitized cells to CDDP. Taken together, we identified survivin as an anti-apoptotic protein in SCLC cells that is regulated by Akt, and demonstrate that treatment with the DNA damaging agent CDDP activates the PI3K/Akt/survivin pathway that in part protects cells from drug-induced apoptosis.
See original publication No. 3

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2. V. Wacheck, U. Zangemeister-Wittke:
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Growth and survival factors in malignant pleural mesothelioma (MPM). Malignant Pleural Mesothelioma. Oxford University Press., in press.

New patent applications/PCT

1. U. Zangemeister-Wittke, C. Di Paolo: Methods for treating cancer using an improved immunotoxin. January 30, 2005. PCT in progress.

4.2. Congress Invitations

Dr. Andreina Bruno

37th Annual Meeting of the Union Schweizerischer Gesellschaften für Experimentelle Biologie (USGEB), Zurich (CH), February 17-19, 2005;
Leptin delays neutrophil apoptosis.

Dr. Sebastien Conus

Joint SSAI/SSPT-Annual Meeting, Bern (CH), March 3-4, 2005;
Role of lysosomal proteases in neutrophil apoptosis.

Prof. Ulrich E. Honegger

Zürcher Psychiatrietag, Lake side Zürich (CH); January 27, 2005;

Optimierung der anxiolytischen Therapie. Anxiolytische und hypnotische Substanzen, von der Gegenwart in die Zukunft.

pharma05, Interlaken (CH); April 15-17, 2005;
Symposium chairman, Interaktionen. Arena-Roundtable.

International Conference on Epilepsy, Workshops on basic research, roundtable, Paris (F); August 27 - September 1, 2005;
Modes of action of antiepileptics.

National Conference of the Brasilian Society of Psychiatry, Belo Horizonte (Brasil); October 12-15, 2005;
Extract of Hypericum (St. John's wort). Mode of action, in vitro studies.

7th Continuation weekend for neurologists, Saanenmöser (CH);
October 21-23, 2005;
Modes of action of centrally acting drugs.

Dr. Ivana Kotevic

4th Focused Meeting – Cell Signaling, British Pharmacological Society, Leicester (UK); April 11-12, 2005;
Constitutive interaction between $P2Y_2$ purinoceptor and the hematopoietic cell-specific G protein $G_{\alpha 16}$ and evidence for receptor oligomerisation.

Prof. Harald Reuter

Tschira-Symposiumder Academia Europaea, Heidelberg (D).

Biennual Meeting of the „International Human Rights Network of Academies and Scholarly Societies", Royal Society, London.

World Science Forum-Budapest, Hungarian Academy of Sciences.

Prof. Erwin Sigel

ISN-ESN (International Society of Neuroscience - European Society of Neuroscience) Meeting, Innsbruck; August 21-26, 2005;
Impact of subunit positioning on $GABA_A$ receptor function

Prof. Hans-Uwe Simon

Expert meeting on „Apoptosis“, Schloss Reisensburg, Science Center, University of Ulm, Ulm (D), January 27-28, 2005;
Siglecs – a new family of death receptors?

7th Course: Allergy and Immunology Update (AIU), Grindelwald (CH), January 28-30, 2005;
Hypereosinophilic syndrome.

Joint SSAI/SSPT-Annual Meeting, Bern (CH), March 3-4, 2005;
Apoptosis pathways in granulocytes: regulation by inflammatory mediators and drugs.

61st Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI), San Antonio (USA), March 18-22, 2005;
Role of Siglecs in cell death regulation: Siglec-9 and neutrophils.

4th Biennial Congress of the International Eosinophil Society (IES), Bern (CH), May 25-29, 2005;
Expression and function of IAPs in eosinophils.

Workshop on Apoptosis “Understanding the death pathways on the road to the clinic”, Loveno di Menaggio (I), May 27-30, 2005;
Regulation of apoptosis by an autophagy gene product.

XXIV. Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Munich (D), June 26 - July 1, 2005;
HES pathophysiology.

Fourth Tuscany Retreat on “Cancer: from birth to death”, Sarteano-Siena (I), August 21-27, 2005;
Death and survival pathways in neutrophils and eosinophils.

13th Euroconference on Apoptosis, Budapest (H), October 1-4, 2005;
An apoptosis gene product as a molecular switch between autophagy and apoptosis.

Pasteur Institute: “Apoptosis, caspases and inflammation”, Paris (F), Nov. 11, 2005;
Regulation of granulocyte apoptosis in inflammation.

PD Dr. Shida Yousefi

3rd Swiss Zeiss-LSM user meeting, Zurich (CH), May 2005;
Detection of neutrophil extracellular traps by confocal microscopy.

European Academy of Allergology and Clinical Immunology (EAACI) Summer Course, Prague (Czech Republic), Sept. 2005;
Role of eosinophils in allergy.

Clinical Dermatology Colloquium, University of Zurich, Zurich (CH), Dec. 7, 2005;
An autophagy gene product as a molecular switch between autophagy and apoptosis.

Workshop of the Microscopy Imaging Center (MIC), University of Bern, Bern (CH), Dec. 14, 2005;
Analyzing cellular events by laser scanning confocal microscopy.

PD Dr. Uwe Zangemeister-Wittke

Annual meeting of the Swiss Society of Experimental Biology, Zürich (CH), February 17, 2005;
Key note lecture on antibodies in cancer therapy.

95th Annual Meeting of the American Association for Cancer Research (AACR). Anaheim, CA (USA), April 18, 2005;
Novel Ep-CAM specific liposomal drug delivery systems for targeted therapy of solid tumors.

4th Tuscany Retreat on Cancer: from Birth to Death, novel insights into the mechanisms of tumor development and death. Palazzo di Piero, Sarteano (Italy), August 28, 2005;
Key note lecture on Apoptosis regulation in small cell lung cancer.

Directors meeting of the Oligonucleotide Therapeutics Society (OTS), New York, NY (USA), September 9, 2005.

4.3. Seminar Invitations

Dr. Andreina Bruno

Dept. of Medical Oncology, University of Zurich, Colloquium in Applied Cancer Research; January 19, 2005; guest of PD Dr. U. Zangemeister-Wittke:
Leptin inhibits neutrophil apoptosis.

Prof. Ulrich E. Honegger

Gesundheits- und Ferienmesse, Bern (CH), January 13, 2005;
Thromboseprophylaxe bei längeren Reisen.

Fortbildung des Kantonal Bernischen Apothekerverbandes, Bern and Biel (CH); January 19 and 20, 2005;
Pharmakotherapie im Alter.

Schweizerische Gesellschaft für Jugendpsychiatrie, Symposium Antihyperaktiva, Bern (CH); April 21, 2005;
Pharmakologie der Hyperaktiva.

Hochschule für Wirtschaft und Verwaltung, Bern (CH); May 18, 2005;
Wirtschaftsethik im Spannungsfeld zwischen Aktionären und Hippokrates. Das Spagat der pharmazeutischen Industrie.

Groupe de réfléxion der Schweizerischen Spitalapotheker, Murten (CH);
September 19, 2005;
Die Entwicklung moderner Neuroleptika, Eine Geschichte des Fortschritts und der Überraschungen.

Komitee Forschung Naturmedizin (KFN), München (D); September 28, 2005;
Johanniskraut: Dem Wirkungsmechanismus auf der Spur.

AGFAM Fortbildungskurs Bern (CH); October 20, 2005;
Psychopharmaka und Rezeptvalidierung.

Zivilgericht, Gerichtskreis Bern-Laupen, Amtshaus Bern (CH); November 9, 2005;
Psychopharmaka, Wirkungsmechanismen und Auswirkungen.

Universitätsspital Zürich USZ, Fortbildung, Zürich (CH); November 11, 2005;
Bipolare affektive Störungen. Neue Therapie-Konzepte nach dem Lithium-"Zeitalter".

Dr. Ivana Kotevic

International Brain Research Organization (IBRO) meeting, Belgrad University (Serbia and Montenegro); September 17-24, 2005;
Fluorescence Resonance Energy Transfer (FRET).

Prof. Hartmut Porzig

Abschiedsvorlesung, Dept. of Pharmacology, Bern (CH), April 17, 2005;
Ein Spaziergang durch 35 Jahre Pharmakologie.
(mit einer Laudatio von Prof. em. Dr. Harald Reuter)

Prof. Erwin Sigel

Paul Scherrer Institut, Villingen; January 11, 2005; guest of Dr. Xiaodan Li:
Use of subunit concatenation for the study of the functional architecture of $GABA_A$ receptors.

Johannes Gutenberg-Universität Mainz, Dept. of Psychiatry, Laboratory of Molecular Biology, Mainz; January 18, 2005; guest of Dr. H. Lüddens and Dr. I. Böhme:
Use of subunit concatenation for the study of the functional architecture of $GABA_A$ receptors.

Otto-von-Guericke Universität Magdeburg, Graduiertenkolleg “Biologische Grundlagen von Erkrankungen des Nervensystems”; March 23, 2005; guest of Dr. G. Reiser:
Use of subunit concatenation for the study of the functional architecture of $GABA_A$ receptors.

Novartis, Bern; June 2, 2005; guest of Dr. W. Hoffmann and Dr. G. Holder:
2h advanced education: The $GABA_A$ receptor isoforms as a potential therapeutic target.

University of Zürich, Dept. of Pharmacology; June 28, 2005; guest of Prof. Dr. U. Rudolph:
Impact of subunit positioning on $GABA_A$ receptor function.

University of Bern, Dept. of Biochemistry and Molecular Biology; September 22; guest of Prof. M. Hediger:
Use of subunit concatenation for the study of the functional architecture of $GABA_A$ receptors.

Prof. Hans-Uwe Simon

Dept. of Asthma Allergy & Respir. Science, King’s College, London (UK); February 24, 2005; guest of Prof. Dr. Tak Lee:
New eosinophil functions in inflammation.

Dept. of Pharmacology, University of Lausanne, Lausanne (CH); March 10, 2005; guest of Prof. Dr. Susanna Cotecchia:
Siglecs and IAPs in granulocyte death regulation.

American Academy of Allergy Asthma & Immunology, 61st Annual Meeting, San Antonio (USA); March 22, 2005;
Apoptosis and inflammation.

Dept. of Genetics and Pathology, University of Uppsala, Uppsala (S); April 1, 2005; guest of Prof. Dr. Gunnar Nilsson:
Apoptosis: Basic principles and clinical implications.

Dept. of Biochemical Pharmacology, University of Konstanz, Konstanz (D); July 22, 2005; guest of Prof. Dr. Albrecht Wendel:
Survivin - a key regulator of apoptosis in granulocytes.

Dr. Robert Urbanczik

Dept. of Mathematics and Computing Science, University Groningen, Feb. 14, 2005: Describing metabolic networks by conversion cones.

Institute for Theoretical Physics and Astrophysics, University Wuerzburg, Nov. 17, 2005: Functional stoichiometric analysis of metabolic networks.

PD Dr. Uwe Zangemeister-Wittke

Regina Elena Cancer Institute, Rome (Italy); October 28, 2005; Seminars in Oncology:
Inducible drug resistance in small cell lung carcinoma by Akt and survivin activation.

Merck Research Laboratories, Boston, MA (USA); September 12, 2005; guest of Prof. Dr. Pradip Majumder:
Induction of anti-apoptosis in small cell lung cancer by chemotherapy and TRAIL.

4.4. Organization of Meetings and Courses

Prof. Erwin Sigel

6th Practical Course: "Functional Analysis of Living Cells", March 7 – March 11, 2005

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology (SSPT): Current concepts with antibodies; USGEB meeting; Zurich (CH), Febr. 17, 2005

Joint SSAI/SSPT-Annual Meeting (Swiss Society of Pharmacology and Toxicology sessions); Bern (CH), March 3-4, 2005

4th Meeting of the International Eosinophil Society; Bern (CH), May 25-29, 2005

4th III-Bern International Summer School; Weissenstein (CH), August 13-15, 2005

Bern Immunology Club (together with the other founder members); Dept. of Pharmacology, University of Bern, one meeting in each month of 2005

PD Dr. Shida Yousefi

DKF, PKI, PIAF - Course in immunofluorescent staining, confocal microscopy, and image analysis. Bern (CH), Oct 19-21, 2005

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon

Symposium der Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie; Session: „Herz und Kreislauf"; Bern (CH), January 27, 2005.

USGEB-Symposium: "Current concepts: Treatment with antibodies": Zurich (CH), February 17, 2005.

Joint SSAI/SSPT-Annual Meeting; Session: “Antiinflammatory and chemotherapy”; Bern (CH), March 3-4, 2005.

4th Biennial Congress of the International Eosinophil Society; Session: “Cutting edge abstracts submitted by young investigators”; Bern (CH), May 25-29, 2005.

4th Biennial Congress of the International Eosinophil Society; Session: “Eosinophils in the regulation of Th2 immune responses”; Bern (CH), May 25-29, 2005.

Workshop on Apoptosis “Understanding the death pathways on the road to the clinic”; Session: “Therapeutic targeting of apoptotic molecules”; Loveno di Menaggio (I), May 27-30, 2005.

XXIV. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Workshop 19: “Eosinophilic inflammation: How to deal with it?”; Munich (D), June 26 - July 1, 2005.

13th Euroconference on Apoptosis; Session: “NF-κB signalling”; Budapest (H), 1-4, 2005.

Pasteur Institute: “Apoptosis, caspases and inflammation”; Session 1; Paris (F), November 4, 2005.

4.6. Referee Work for Peer-Reviewed Journals

Prof. Ulrich E. Honegger

Life Sciences
Swiss Medical Weekly
Planta Medica

Prof. Hartmut Porzig

N-S Arch Pharmacol
Am J Physiol: Cell Physiol

Prof. Erwin Sigel

Biochim Biophys Acta
Bioorganic and Medicinal Chemistry Letters
BioTechniques
Brain Res
Cell+Tissue Research
Eur J Neurosci
FEBS Lett
J Biol Chem
J Membrane Biol
J Neurochem
J Neurosci
J Pharmacol Exp Ther
J Physiol (London)
Mol Pharmacol
Neurochem Int
Neuropharmacology
Pflügers Arch
Planta Medica
Proc. Roy Soc B
Trends Pharmacol Sci (TIPS)

Prof. Hans-Uwe Simon

Allergy
Am J Pathol
Am J Physiol - Cell Physiol
Apoptosis
Biochem Pharmacol
Blood
Cell Death Differ
Clin Exp Allergy
Clin Exp Immunol
Critical Rev Oncol/Hematol
DMW
Environm Toxicol
Eur J Immunol
Expert Rev Clin Immunol
Exp Dermatol
FEBS letters
Hepatology
Human Immunol
Leukemia Res
Int Arch Allergy Immunol
Int J Hyg Environ Health
J Allergy Clin Immunol
J Exp Med
J Mol Med
J Immunol
J Invest Dermatol
J Leukocyte Biol
J Pharm Pharmacol
Nature Chem Biol
Oncogene
Pathobiology
Proc Natl Acad Sci USA
Planta Medica
Swiss Med Wkly
Thorax

Dr. Robert Urbanczik

Physical Review Letters
Physical Review E

PD Dr. Shida Yousefi

Cancer Detection and Prevention

PD Dr. Uwe Zangemeister-Wittke

Clin Cancer Res
Oncogene
Int J Cancer
Cell Death Differ
Oligonucleotides
J Invest Dermatol
Lung Cancer
J Biol Chem
Breast Cancer Res

4.7. Referee Work for Grant Bodies

Prof. Erwin Sigel

Swiss National Science Foundation (SNF)
The Wellcome Trust, London, UK
Medical Research Council (MRC)
Austrian Foundation for the Advancement of Science
Deutsche Forschungsgemeinschaft (DFG)
Schweizerische Stiftung für Alkoholforschung
Fonds zur Förderung der wissenschaftlichen Forschung (FWF), Austria

Prof. Hans-Uwe Simon

Swiss National Science Foundation (SNF)
Deutsche Forschungsgemeinschaft (DFG)
Medizinische Fakultät der Universität Tübingen, *fortüne*-Programm
Landesstiftung Baden-Württemberg, Stuttgart
Science Foundation Irland (SFI)
The Wellcome Trust, London, UK
Medical Research Council (MRC)
Interdisziplinäres Zentrum für Klinische Forschung, Univ. Tübingen

PD Dr. Uwe Zangemeister-Wittke

Swiss Cancer Lague (Oncosuisse)
Cancer League of the Kanton Zürich
Medical Research Council (MRC) London
Deutsche Krebshilfe, Austrian Fonds for the Promotion of Science and Research
Italian Association for Cancer Research (AIRC)
Jubiläumsfonds of the National Bank of Austria

4.8. Awards

Dr. Stephan von Gunten

Novartis Poster Prize
(Swiss Society of Pharmacology and Toxicology, March 2005)

PD Dr. Shida Yousefi

4th Biennial Congress of the International Eosinophil Society
Award for an excellent abstract and presentation (May 2005)

5. Administrative, Advisory, and Honorary Posts

Roland Baur

Coordinator for radioactive work at the PKI

Prof. Ulrich E. Honegger

Verantwortlicher für das Pharmaziestudium an der Universität Bern

Präsident der Kommission für Fakultätsexamen in Pharmazie der Medizinischen Fakultät der Universität Bern

Mitglied der Subkommission Pharmazie des Leitenden Ausschusses des BAG. Verantwortlich für die Universitäten Bern und Fribourg

Mitglied der Arzneimittelkommission des Schweizerischen Apothekerverbandes

Wissenschaftlicher Beirat des Apothekervereins des Kantons Bern

Member of the GlaxoSmithKline Advisory Board for Epilepsy

Member of the GlaxoSmithKline Advisory Board for Biopolar Disorders

Member of the Zeller Medical Advisory Board

Prof. Hartmut Porzig

Member of the steering committee for the curriculum reform of 3rd year medical studies

Member of the Editorial Board of Naunyn-Schmiedebergs Archives of Pharmacology

Prof. Harald Reuter

Elected Member of the International Council of Israeli-Palestinian Science Organization (IPSO)

Chairman of the "Committee on Human Rights" of the Council of Swiss Academies

Member of the "International Human Rights Network of Academies and Scholarly Societies"

President of the "Schweizerische Stiftung für medizinisch-biologische Stipendien" (Swiss foundation for medical-biological stipends)

Obmann (chairman) and Senator for the "Section Physiology and Pharmacology/Toxicology" of the "Deutsche Akademie der Naturforscher Leopoldina"

Member of the Scientific Advisory Board of the Friedrich-Miescher-Institute (Basel)

Member of the Scientific Advisory Board of the Venetian Institute of Molecular Medicine (Padova)

Prof. Erwin Sigel

Biosafety Coordinator for the PKI (until December 2005)

Information Technology Coordinator at the PKI (until December 2005)

Member of the committee supervising the "Programm für die Interfakultäre Ausbildung des Forschungsnachwuchses der Universität Bern (PIAF) (Interfaculty Doctorate and PhD of the Medical Faculty)

Member of the committee supervising the division "Cell Biology" of the Bern "Graduate School for Cellular and Biomedical Sciences".

Prof. Hans-Uwe Simon

Director of the curriculum “Pharmacology” within the program for interfaculty education of graduate students at the University of Bern, 2000-2007

Treasurer, European Cell Death Society (ECDO), 2000-2005

Member of the Ethics Committee, European Academy of Allergology and Clinical Immunology (EAACI), 2003-2005

Member of the Board of the Immunology Section of the European Academy of Allergology and Clinical Immunology (EAACI), since June 2003

Fellow of the American Academy of Allergy, Asthma and Immunology (AAAAI)

Member of the Annual Meeting Planning Committee (Workshops) of the American Academy of Allergy, Asthma and Immunology (AAAAI), 2002-2005

Member of the Immunomodulation Committee (Workshops) of the American Academy of Allergy, Asthma and Immunology (AAAAI), 2004-2006

Member of the Board, Swiss Academy for Medical Ethics

Member of the Central Committee of the Union of the Swiss Societies for Experimental Biology (USGEB/USSBE), since 2001

Member of the Council of the Swiss Society of Pharmacology and Toxicology (SSPT), since 2002

President of the Swiss Society of Pharmacology and Toxicology (SSPT), since 2004

Member of the Scientific Advisory Board, Society in Science: The Branco Weiss Fellowship, since 2003

Member of the Executive Committee, International Eosinophil Society (IES), since 2003

Representative of the Medical Faculty within the Foundation for the Promotion of Scientific Research at the University of Bern, since Nov. 2004

Member of the Scientific Advisory Board “Pharmacology” of Pfizer AG, Switzerland, since 2005

Member of the Advisory Board of GlaxoSmithKline “Commercialization of Mepolizumab for the treatment of hypereosinophilic syndrome (HES), 2005-2006

Consultant, GlaxoSmithKline, “Biomarkers for monitoring the efficacy of Mepolizumab for the treatment of eosinophilic esophagitis (EE), 2005-2006

Member of the Task Force “Centre of Pharmacology of the University of Basel”, 2005

President of the Swiss Society of Experimental Pharmacology (SSEP), 2005-2009

Member of the Supervision commission “Medical Biology” within the Graduate School for Cellular and Biomedical Sciences of the University of Bern, since 2005

Vice-President, European Cell Death Society (ECDO), 2005 - 2007

Associate Editor, Allergy

Section Editor, Apoptosis

Member of the Editorial Board, International Archives of Allergy and Immunology

Member of the Scientific Board, Allergologie

Member of the Editorial Board, Clinical and Experimental Allergy

Member of the Editorial Board, Int. Journal of Hygiene and Environmental Health

Member of the Advisory Board, Allergo-Journal

Member of the Advisory Editorial Board, Planta Medica

Member of the Editorial Board, Cell Death and Differentiation

Member of the Editorial Board, Journal Allergy Clinical Immunology

Dr. Robert Urbanczik

Webmaster of the PKI (until December)

PD Dr. Shida Yousefi

Operator of the Confocal Microscopy Facility of the Dept. of Clinical Research (located at the PKI)

Operator of the Image Analysis Facility of the Dept. of Clinical Research (located at the PKI)

Coordinator for PC work at the PKI

PD Dr. Uwe Zangemeister-Wittke

Member of the Project Group of the Cancer Network Zürich (CNZ)

Chairman of the Swiss Institute of Applied Cancer Research (SIAK) network Laboratory-Based Cancer Research

Member of the Editorial Board of the journal Oligonucleotides

Consultant for Defined Health Inc., NJ, USA

Member of the Council of Healthcare Advisors at the Gerson Lehrman Group, NY, USA

Biosafety Coordinator PKI (since December 2005)

Information Technology Coordinator at the PKI (since December 2005)

6. Services

6.1. Confocal Microscopy

The facility hosts a Zeiss laser scanning microscope (LSM410), which may be used by members of the Medical Faculty at a small charge (CHF 10 per h). As a major expansion of the facility a workstation for quantitative image analysis and 3-D representation of microscopic data was purchased in 2002. During the past year the confocal microscope has been used by 19 different research groups. Together with the Image analysis station, it was in operation for approximately 400 hours. The facility for confocal microscopy and image analysis was operated by PD Dr. S. Yousefi. Under the supervision of the coordinator, a whole team of qualified individuals provided training for new users, as well as technical and scientific support. In 2005, the operator and her team spent for the facility approximately 500 hours.

6.2. Flow Cytometry

A service is provided for analyzing potential pathogenic mechanisms of eosinophilic disorders, sepsis, and other inflammatory diseases. Monitoring of patients under immunomodulatory therapy is also included. The costs are currently covered by research grants of the coordinator (Prof. H.-U. Simon), who can also be consulted for scientific support. Usage of the flow cytometer by non-members of the institute within collaborative projects is also possible.

7. Public Work

7.1. Art Exhibitions

Jean-Pierre Meroz, Biel, Switzerland
Vernissage: April 07, 2005

Ingeborg Maeder, Bern, Switzerland
Vernissage: Nov. 17, 2005

8. Sponsors

8.1. Research Grants

Prof. Ulrich E. Honegger

GlaxoSmithKline
Zeller Medical AG, Romanshorn (CH)

Prof. Hartmut Porzig

Schweizerische Krebsliga (together with K. Baltensperger, grant OCS-01404-08-2003)
Bonizzi-Theler Foundation

Prof. Erwin Sigel

Swiss National Science Foundation (grant No. 3100A0-105372)

Prof. Hans-Uwe Simon

Swiss National Science Foundation (grant No. 310000-107526)
OPO-Foundation, Zurich (CH)
Stanley Thomas Johnson Foundation, Bern (CH)
Stiftung zur Krebsbekämpfung, Zurich (CH)
Bernische Krebsliga
Stiftung zur Förderung der wissenschaftlichen Forschung an der Universität Bern

Dr. Clemens Wager

Swiss National Science Foundation (grant No. 3100A0-102269/1) (until March 2005)

PD Dr. Shida Yousefi

Swiss National Science Foundation (grant No. 31-068449.02)

PD Dr. Uwe Zangemeister-Wittke

Swiss National Science Foundation (grant No. 3100AO-103726)
Krebsliga Zürich
Legat der Krebskommission Zürich (interdisciplinary research networking)
Sassella-Stiftung of the Zürcher Kantonalbank

8.2. Meetings

4th Biennial Congress of the International Eosinophil Society, Bern, May 26-29, 2005, and Eos-Pre-Meeting, Bern, May 24-25, 2005
Max and Elsa Beer-Fonds
Essex AG, Luzern
Pfizer AG, Zürich
Fujisawa AG, Wallisellen
Novartis AG, Basel
Astra Zeneca AG, Zug
European Allergy Network GA2LEN
National Institute of Allergy and Infectious Diseases (NIAID), USA
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), USA
National Institues of Healt (NIH), USA
American Partnership for Eosinophil Disorders (APFED), USA
GlaxoSmithKline, USA
Merck and Company, Inc., USA
Novartis Pharmaceuticals Corp., USA
Pfizer, Inc., USA
Millenium Pharmaceuticals, Inc., USA
GlaxoSmithKline Inc., Canada
AstraZeneca Inc., Canada
Merck Sharp & Dohme-Chibret, Glattbrugg (Congress bags)

4th III-International Summer School, Weissenstein (CH), August 13-15, 2005

Alexis Corporation, Lausen
Allergomed, Therwil
AstraZeneca AG, Zug
Becton Dickinson Biosciences, Allschwil
GlaxoSmithKline AG, Münchenbuchsee
Lucerna Chem AG, Luzern
Novartis Pharma (Schweiz) AG, Bern
PIAF, Universität Bern, Bern
Union of the Swiss Societies of Experimental Biology (USGEB)
ZLB Bioplasma AG, Bern

8.3. Travel Support

Swiss Society of Pharmacology and Toxicology (SSPT)
Support of PD Dr. Shida Yousefi
Support of Dr. Sebastien Conus

World University Society (WUS) – Austrian Committee
Support of Dr. Ivana Kotevic

8.4. Other Support

Bürgi fund Seminar series of the institute