Annual Report 2003

Pharmakologisches Institut (PKI)
der Universität Bern

Department of Pharmacology
of the University of Bern

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1. Introduction

1.1. Vorwort

Dies ist der dritte umfassende Jahresbericht des Pharmakologischen Instituts der Universität Bern. Das Pharmakologische Institut hat sich auch im Jahr 2003 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 Pharmakologische Institut 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 2003 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.

Das Jahr 2003 war für die in der Lehre tätigen Mitglieder unseres Instituts vor allem mit der weiteren Umsetzung der Studienreform im 3. Studienjahr Medizin (Problem-based Learning) verknüpft. Insbesondere ging es darum, die Qualität der Lehre weiter zu verbessern. Dies ist auch gelungen, wie Resultate aus internen und externen Befragungen bestätigen. In der Kerngruppe zur Planung und Umsetzung des PBL-Systems arbeitet Prof. Porzig mit, als Pharmakologie-Fachvertreter in den einzelnen Themenblöcken sind die Proff. Honegger, Porzig, Sigel und Simon vertreten. Ausserdem trafen sich die Dozenten des PKI gemeinsam mit Dozenten von Pharmakologischen Instituten anderer Universitäten, um die Lernziele in der Pharmakologie zu aktualisieren und Prüfungsfragen auszuarbeiten. Die Ausbildung der Zahnmedizinstudenten in Pharmakologie erfolgte weiterhin im klassischen Stil über Vorlesungen (verantwortlich: Prof. Stucki). Prof. Honegger nahm neben seiner Lehrtätigkeit an der Medizinischen Fakultät auch umfangreiche Lehrverpflichtungen innerhalb des Pharmaziestudiums an der Universität Bern wahr.

Eine weitere wichtige Aktivität im Rahmen der Lehre stellt unsere Arbeit innerhalb des Programms für die interfakultäre Ausbildung des Forschungsnachwuchses der Universität Bern (PIAF) dar. Prof. Sigel ist Mitglied der PIAF-Kommission. Dazu

kommen zusätzliche Bildungsangebote in Form eines Praktischen Kurses (Prof. Sigel) und einer Summer School (Prof. Simon), die beide weitgehend aus eigenen finanziellen Mitteln bzw. Sponsorengeldern bestritten werden. Die Naturwissenschaftliche Fakultät unterstützten wir bei der Durchführung eines Labor-Kurses (Immunologie II, Kursleiter: PD Dr. Brunner). Im Institut arbeiten gegenwärtig 12 DoktorandInnen (11 PhD, 1 MD), und 3 haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Pharmakologischen Instituts publizierten in 2003 insgesamt 24 Originalarbeiten sowie 9 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ über 180). MitarbeiterInnen des Pharmakologischen Instituts wurden zu insgesamt 46 Vorträgen bzw. Seminaren eingeladen. Frau Dr. Shida Yousefi erhielt den Pfizer-Forschungspreis (gemeinsam mit Prof. Simon). Gegenwärtig werden 5 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. Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Auch im letzten Jahr gelang es, die Infrastruktur des Instituts zu verbessern. Mit Hilfe des Kantons Bern, der Universität Bern und der Medizinischen Fakultät wurden dringend benötigte Forschungsinstrumente angeschafft. Ein grosses Problem ist jedoch die zu geringe finanzielle Unterstützung unseres Instituts im Rahmen des Betriebskredites. Es ist nahezu unmöglich, die Infrastruktur allein aus diesen Mitteln aufrechtzuerhalten. Wir haben deshalb die grosse Hoffnung, dass mit der Unterzeichnung des Leistungsvertrages zwischen der Medizinischen Fakultät und dem PKI eine Besserung eintritt.

Ich danke allen Mitarbeitern und Mitarbeiterinnen für ihren Einsatz, welcher auch im Jahr 2003 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 2004

1.2. Foreword

This is the third 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 2003 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 the 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 2003, we tried to promote communication between scientists and the public. The organization of art exhibitions within our institute is an example for these efforts.

The year 2003 was, at least for the teaching staff of our institute, associated with the further implementation of the new “Problem-based Learning (PBL)”-system for medical students in their third study year. In particular, our goal was to further improve the quality of the whole teaching process. This goal was largely achieved, as demonstrated by the results of several internal and external evaluations. Prof. Porzig is a member of the core group that oversees teaching in the third study year. As specialists for Pharmacology, the professors Honegger, Porzig, Sigel, and Simon contribute to all of the thematic teaching blocks. In addition, we met with colleagues from the other Swiss universities in order to specify the learning objectives and MC questions for the exams in Pharmacology for medical students. The teaching of dentistry students in Pharmacology has retained the classical lecture format. Responsible teacher here is Prof. Stucki. Prof. Honegger was, besides his teaching activities within the Medical Faculty, very much involved in the undergraduate study in Pharmacy at the University of Bern.

Another important teaching activity is required within the graduation program for MD/PhD students of the University of Bern (PIAF). Additional teaching offers, such as a practical course (Prof. Sigel) and a summer school (Prof. Simon), were provided. Importantly, both events were organized using mainly our own financial resources and/or with the help of external sponsors. We also supported the Natural Sciences

Faculty in carrying out a laboratory course (Immunology II, course leader: PD Dr. Brunner). Currently, 11 PhD students and 1 MD student work at the PKI and three students successfully finished their graduate study in 2003.

Moreover, the scientific staff of the Department of Pharmacology published 24 original and 9 review articles in international peer-reviewed journals (the sum of the "impact factors" is greater than 180). Co-workers of the institute were invited to 46 lectures or seminars. Dr. Shida Yousefi received the Pfizer research prize (together with Prof. Simon). Five co-workers are currently supported by grants of the Swiss National Science Foundation. Several prominent researchers visited the institute and presented seminars. The Bern Immunology Club (BIC) attracted, also thanks to the efforts of members of the PKI, both group leaders as well as many young scientists. In summary, research plays an important role at the PKI and is performed at a high level.

The infrastructure could again be improved during the last year. With the help of the Canton Bern, the University of Bern, and the Medical Faculty, the institute was equipped with urgently needed research instruments. However, one major problem remained. The financial support of the institute within the ordinary budget of the Medical Faculty 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.

I thank all co-workers for their hard work that contributed to the success of the PKI in 2003. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, February 2004

2. Staff 2003

Director

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

Deputy Director

Prof. Dr. Hartmut Porzig, MD

Permanent Members

Prof. Dr. Ulrich E. Honegger, PhD
Prof. Dr. Hartmut Porzig, MD
Prof. em. Dr. Harald Reuter, MD
Prof. Dr. Erwin Sigel, PhD
Prof. Dr. Hans-Uwe Simon, MD, PhD
Prof. Dr. Jörg Stucki, PhD

Scientific Staff

Dr. Kurt Baltensperger, PhD
Roland Baur, head technician
Dmytro Berezhnoy, PhD student
Nathalie Boulineau, PhD student* (since February 2003)
Daniela Brütsch, diploma student* (March – July 2003)
Dr. Sibylle Bürgi, PhD
Dr. Sébastien Conus, PhD
Arezoo Daryadel, PhD student*
Gian Marco De Marchis, MD student*
Roberto Hess, MD student*
Karin Kirschner, PhD student (until September 2003)
Ivana Kotevic, PhD student*
Evelyne Kozlowski, technician
Jernej Kristl, M.Sc. student* (April – September 2003)
Sibylla Martinelli, PhD student*
Dr. Frédéric Minier, PhD*
Susanne Probst, technician
PD Dr. Claes Ruedeberg, PhD, consultant*
Inès Schmid, head technician
Ekatherina Vassina, PhD student
Anton Vichalkovski, PhD student*
Dr. Clemens Wagner, PhD
Adrian Wirz, PhD student*
Dr. Shida Yousefi, PhD
Dr. Stephan von Gunten, MD, PhD student*

External University Teachers

PD Dr. Armand Cachelin, MD, PhD*
Prof. Dr. Peter Hoffmann, MD*
Prof. Dr. Francesca Levi-Schaffer, PhD* (Visiting Professor of the University of Bern)
PD Dr. Stefan Mühlebach, PhD*
PD Dr. Peter Späth, PhD*
PD Dr. Uwe Zangemeister-Wittke, PhD*

Guest scientists

Dr. Dagmar Simon*
Dr. Alex Straumann*

External Computer Support

Faton Shala*

Office

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

Workshop

Hans Andres

House Keeping

Maria Di Loreto (until May 2003)
Mariter Vieites (since June 2003)
Esther Weber

*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 06, 2003	Prof. Hartmut Porzig	Antiarrhythmika
Jan 14, 2003	Prof. Hartmut Porzig	Beeinflussung der kontraktilen Herzfunktion durch Pharmaka
Jan 30, 2003	Prof. Hartmut Porzig	Diuretika
March 31, 2003	Prof. Erwin Sigel	Pharmakokinetik (III)
April 09, 2003	Prof. Erwin Sigel	Zucker
April 09, 2003	Prof. Erwin Sigel	Fett
April 09, 2003	Prof. Erwin Sigel	Gicht
April 09, 2003	Prof. Erwin Sigel	Syndrom X, Gewichtskontrolle
April 28, 2003	Prof. Ulrich Honegger	Antiepileptika
April 30, 2003	Prof. Hartmut Porzig	Lokalanaestetika
May 14, 2003	Prof. Ulrich Honegger	M. Parkinson- und Demenz-Therapien
May 14, 2003	Prof. Erwin Sigel	Wachstum / Anabolika
May 21, 2003	Prof. Erwin Sigel	Nebenniere
May 21, 2003	Prof. Erwin Sigel	Schilddrüse / Kropf
June 16, 2003	Prof. Ulrich Honegger	Angriffspunkte von Psychopharmaka
June 18, 2003	Prof. Ulrich Honegger	Neuroleptika und Anxiolytika
June 23, 2003	Prof. Ulrich Honegger	Antidepressiva
June 25, 2003	Prof. Ulrich Honegger	Schmerz und Analgesiologie
June 25, 2003	Prof. Ulrich Honegger	Pharmakokinetik im Alter
June 26, 2003	Prof. Ulrich Honegger	Anästhesie
June 30, 2003	PD Dr. Peter Späth	Arzneimittelentwicklung
July 02, 2003	Prof. Hans-Uwe Simon	Immunmodulation

Oct 21, 2003	Prof. Hans-Uwe Simon	Pharmakodynamik (I)
Oct 27, 2003	Prof. Hartmut Porzig	Pharmakodynamik (II)
Oct 29, 2003	Prof. Ulrich Honegger	Pharmakokinetik (I)
Oct 29, 2003	Prof. Ulrich Honegger	Pharmakokinetik (II)
Oct 29, 2003	Prof. Peter Hoffmann	Einführung in die Toxikologie
Nov 05, 2003	Prof. Hans-Uwe Simon	Entzündungshemmung
Nov 11, 2003	Prof. Hartmut Porzig	Signalübertragung im ANS
Nov 17, 2003	Prof. Ulrich Honegger	Polypharmazie (4. study year)
Nov 24, 2003	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Dec 03, 2003	Prof. Hartmut Porzig	Antithrombotische Therapie und Antikogulantien
Dec 10, 2003	Prof. Hartmut Porzig	Pharmakologie des sympathischen Nervensystems
Dec 10, 2003	Prof. Hartmut Porzig	Wirkprinzipien von Antihypertonika
Dec 17, 2003	Prof. Hartmut Porzig	Vasoaktive und antianginöse Substanzen

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

Date	**Lecturer**	**Title of the lecture**
Jan 06, 2003	Dr. Kurt Baltensperger	Sympathikus
Jan 08, 2003	Dr. Kurt Baltensperger	Kreislaufpräparate (I)
Jan 13, 2003	Dr. Kurt Baltensperger	Kreislaufpräparate (II)
Jan 15, 2003	PD Dr. Armand Cachelin	Starke Analgetika
Jan 20, 2003	Dr. Sibylle Bürgi	Lokalanästhetika
Jan 22, 2003	Dr. Sibylle Bürgi	Insulin, Orale Antidiabetika
Jan 27, 2003	Prof. Erwin Sigel	Anxiolytika, Hypnotika

Jan 29, 2003	Prof. Ulrich Honegger	Psychopharmaka
Feb 03, 2003	PD Dr. Armand Cachelin	Immunsuppressiva
Feb 05, 2003	Prof. Ulrich Honegger	Magensäurehemmer
Feb 10, 2003	PD Dr. Stefan Mühlebach	Antibiotika (I)
Feb 12, 2003	PD Dr. Stefan Mühlebach	Antibiotika (II)
Feb 17, 2003	PD Dr. Stefan Mühlebach	Antibiotika (III)
Feb 19, 2003	Prof. Jörg Stucki	Repetitorium

Lectures for Pharmacy students

Date	**Lecturer**	**Title of the lecture**
May 09, 2003	Prof. Ulrich Honegger	Einführung in die pharmazeutische Wissenschaften
May 16, 2003	Prof. Ulrich Honegger	Berufsbilder der Pharmazie
May 23, 2003	Prof. Ulrich Honegger	Berufsbild Forschung
June 20, 2003	Prof. Ulrich Honegger	Pharmazie und Gesellschaft: Suchtprävention
June 27, 2003	Prof. Ulrich Honegger	Repetitorium, Evaluation

Lectures for students of the Natural Sciences Faculty

Date	**Lecturer**	**Title of the lecture**
April 23, 2003	Prof. Hans-Uwe Simon	Regulation der Granulozyten-Apoptose
Sept-Dec, 2003	Dr. Clemens Wagner	Uebungen zu Physik I

3.2. Coordination PBL Medical Students, 3. year (2003/2004)

Core group:
Prof. Hartmut Porzig

Representatives of Pharmacology in teaching blocks:
Prof. Ulrich E. Honegger (blocks V and VI)
Prof. Hartmut Porzig (blocks II and III)
Prof. Erwin Sigel (block IV)
Prof. Hans-Uwe Simon (blocks I and VII)

3.3. Tutorials (study year 2003/2004)

Medical students 3. year:
Dr. Sibylle Bürgi
Dr. Sébastien Conus
Dr. Stephan von Gunten
Prof. Ulrich E. Honegger
Prof. Erwin Sigel*
Dr. Shida Yousefi
PD Dr. Uwe Zangemeister-Wittke

*double tutorials

3.4. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan 08, 2003	Prof. Dr. J. Reichen University of Bern	Molecular basis of hyperdynamic circulation in portal hypertension
Jan 16, 2003	Dr. S.G. Plötz University of Munich	Eosinophile Hauterkrankungen
Jan 17, 2003	Dr. D.R. Green La Jolla Institute for Immunology and Allergy, San Diego	One hour in the life and death of a cell
Jan 22, 2003	Prof. Dr. V. Niggli University of Bern	Development of polarity and migration of neutrophils: involvement of Rho/ Rho-kinase and phosphatidylinositol 3-kinase
April 16, 2003	Dr. C. Boesch and Dr. H. Reutimann Unitectra Bern and Zurich	Patenting of University Inventions: Requirements – Procedure – Costs

May 07, 2003	Prof. Dr. T. Seebeck University of Bern	Cyclic AMP signaling in Trypanosoma brucei
May 21, 2003	Prof. Dr. U. A. Meyer Biozentrum Basel	Induction of drug metabolism – the role of nuclear receptors
June 04, 2003	Dr. S. Christen University of Bern	Role of reactive oxygen species in bacterial meningitis
Aug 29, 2003	Dr. M. Uguccioni Institute for Research in Medicine, Bellinzona	Chemokine expression and function in pathology
Aug 29, 2003	Prof. Dr. J. Lotval University of Göteborg	The regulation of traffic of inflammatory cells from bone marrow to airways
Aug 29, 2003	PD Dr. T. Geiser University of Bern	Inflammation and repair in the development of pulmonary fibrosis
Aug 29, 2003	Prof. Dr. A. Frew Univ. of Southampton	Mechanisms of air pollution-induced airways inflammation
Oct 14, 2003	Prof. Dr. F. Levi-Schaffer University of Jerusalem	Mast cells and eosinophils: A cellular chatting!
Oct 29, 2003	Prof. Dr. W. Hofstetter University of Bern	TNF alpha – exclusively a stimulator of bone resorption?
Nov 19, 2003	PD Dr. R. Moser and Dr. B. Schnyder Inst. of Biopharmaceut. Research, Matzingen	Protective dual-functions of proinflammatory cytokines in chronic disorders
Dec 17, 2003	Dr. C. Zuppinger University of Bern	New targeted cancer therapies, new dangers for the heart?

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 09, 2003	Prof. Dr. C. Dahinden	Role of basophils in innate immunity
Feb 06, 2003	Prof. Dr. W. J. Pichler	Molecular mechanisms of drug allergies
March 06, 2003	PD Dr. T. Brunner	Apoptosis regulation in the gut
May 01, 2003	Dr. S. Miescher	Autoimmune Urticaria: To be or not to be
June 05, 2003	PD Dr. B. Moser	T-cell migration control during adaptive immune responses
June 26, 2003	Prof. Dr. A. Ochsenbein	Regulation of the immune response by antigen-dose and –localization
Sept 25, 2003	Dr. S. Yousefi	A new player in the mitochondrial death pathway
Sept 25, 2003	Dr. St. von Gunten	Role of Siglecs in the regulation of apoptosis
Oct 30, 2003	Dr. E. Padovan	Dendritic cells in protective and adverse immune responses
Nov 27, 2003	Prof. L. Nicod	The impact of innate immunity on dendritic cells

3.6. Academic Degrees

Ralf Baumann, Dr. phil.
Thesis: Macrophage migration inhibitory factor (MIF) delays apoptosis in neutrophils by inhibiting the mitochondria-dependent death pathway.
University of Bern, May 2003

Frank Altznauer, Dr. phil.
Thesis: Crucial but cell type-specific components of apoptotic pathways and their deregulation in neutrophilic inflammation.
University of Bern, October 2003

Karin Kirschner, Dr. phil.
Thesis: Erythropoietin promotes resistance to Imatinib.
University of Bern, October 2003

Daniela Brütsch, Dipl. pharm.
Thesis: Wirkungsvergleich von SSRI- und Trizyklika-Antidepressiva auf das Recycling von β-Adrenozeptoren.
ETH Zurich, July 2003

Jernej Kristl, Dipl. pharm.
Thesis: Immunohistological characterization of eosinophils in idiopathic eosinophilic oesophagitis.
University of Ljubljana, September 2003

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Ulrich E. Honegger

Group members: Dr. Sibylle Bürgi, PhD
Adrian Wirz, PhD student
Gian-Marco De Marchis, MD student
Roberto Hess, MD student
Susanne Probst, technician
Daniela Brütsch, Diploma student (March to July 2003)
PD Dr. Claes Ruedeberg, PhD, consultant

Our main interests focus on antidepressant drugs, in particular on the elucidation of their modes of action. For many years we have concentrated on classical, well established tricyclic compounds but have lately expanded our research efforts to the antidepressant activity 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.

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. 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-adrenoceptors 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. I*n 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 β-adrenergic signal pathway. A comparison between hypericum perforatum (St. John's wort) extracts, TCA- and SSRI-antidepressants.

D. Brütsch, S. Bürgi, A.Wirz, 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, R. Hess, 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 or ^{3}H-serotonin 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.

In collaboration with Prof. Hamburger from the Friedrich-Schiller University in Jena, Germany we investigated fractions of an alcoholic St. John's wort extract that are either highly enriched with or depleted of hyperforin for antidepressant effectiveness in our *in vitro*-systems. Hyperforin, a major constituent of St. John's wort is known for

its high potency to induce metabolic enzymes; its antidepressant activity, 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 principle in the extract.

Cellular kinetics of persistent compounds with endocrine effectiveness

S. Probst, S. Mühlebach, U.E. Honegger

(Collaboration with PD Dr. S. Mühlebach, Kantonsspital Aarau and PD Dr. G. Karlaganis, BUWAL, Bern)

Persistent lipophilic compounds are relevant representatives of environmental contaminants. They have entered the biosphere partly unintended from waste deposits, through leakage from closed systems or as residues of incineration due to resistance to high temperature. They show chemical blockage by chloro- or bromo-substitution of metabolically vulnerable positions in the molecule, e.g. of lipophilic aromatic ring systems normally degradable by cytochrome P_{450} enzymes as shown in PCB or DDT derivatives. The global distribution and marked bioaccumulation of such compounds through the food chain is a consequence of their extreme lipophilicity and high level of metabolic resistance leading to persistence in fat deposits eventually in man. There is little knowledge on mechanisms of fat storage and release of such compounds nor is a simple test method available to screen new chemical entities for their potential of bioaccumulation. To study more thoroughly ecotoxicological aspects of such compounds their kinetic behaviour has to be characterised in defined test models such as cell culture systems using well-defined and reproducible conditions. Apart from methodological studies to establish useful screening or test systems with representative cell lines to imitate important uptake and storage organs like fat, brain or skin, such cell culture systems allow to study toxicokinetics of selected model compounds using varying experimental conditions. Specific interactions with defined receptors may be investigated which may have relevance for acute or long-term effects. An ultimate goal will be to establish structure-effect correlations for a better ecotoxicological risk assessment of new chemical compounds developed and released into defined technical application fields. The aim of this study was to define methodological and experimental conditions in single and multiple (sector) cell culture systems (lit) using fibroblasts, adipocytes (differentiated 3T3 cells) and astrocytoma C6 cells. Selected model compounds with different molecular size and degree of halogenization were investigated. From our present results we can conclude that *in vitro*-cell culture systems are useful tools for the pharmacokinetic screening of highly persistent lipophilics. A correct and stable solution of these compounds in the culture media can best be achieved after incorporation into liposomes. The use of different cell types with distinct properties allows to detect differences in cell-specific kinetics and storage of lipophilics. The combination of up to four sectors covered with monolayers of different cell types in one plate represents a simple *in vitro*-system to analyze competitive cellular uptake of persistent lipophilic contaminants. Extents of uptake and accumulation were drug- and cell-specific. Rates of uptake were fast and reached equilibrium within 15 minutes.

Effects of extracts of Valeriana plants on GABA uptake into rat brain slices.

C. Ruedeberg, U.E. Honegger

(Collaboration with Prof. W. Schaffner, Institute of Pharmaceutical Biology, University of Basel, Switzerland)

Valeriana plants of genetically mutated species or extracts prepared by different solvents and individual, isolated constituents were compared for their potency to

modulate radiolabelled GABA uptake into freshly prepared rat brain slices. Specific GABA uptake was characterized in the presence of nonradiolabelled GABA or with selective GABA uptake inhibitors. It was of interest to find that plant extracts inhibited ^{3}H-GABA uptake dose-dependently, while e.g. valerenic acid was without inhibitory effectiveness.

Original publication

S. Bürgi, K. Baltensperger, U. E. Honegger:
Antidepressant-induced switch of β1-adrenoceptor trafficking as a mechanism for drug action.
J. Biol. Chem. 278 (2003), 1044-1052.

Group Prof. Hartmut Porzig

Group members: Dr. Kurt Baltensperger, PhD[1]
Karin Kirschner, PhD student (until September 2003)
Ivana Kotevic, PhD student
Anton Vichalkovski, PhD student

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

The research interests of our group center on mechanisms regulating proliferation and differentiation of human hematopoietic, in particular erythroid progenitor cells. In principle, during blood cell formation there are three major problems that have to be solved: (1) maintain a constant pool of undifferentiated stem cells, (2) regulate proliferation and lineage commitment according to the overall needs of the body, (3) maintain a constant number of terminally differentiated blood cells. To reach these objectives, a host of humoral signals participate in determining the fate of hemato-poietic 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, purine nucleotides and lipids and constitutes the focus of our most recent research projects. The cross-talk between cytokine - and G protein-coupled receptor – linked signal transduction pathways is independently investigated by Dr. K. Baltensperger. Of particular interest in this respect is the development of new strategies for the treatment of malignant diseases, such as BCR-Abl positive leukemias.

A second line of ongoing research deals with functional aspects of the sodium/ calcium exchanger protein in cardiac cells and with the expression pattern of its three major subtypes in primary neuronal cell cultures and in brain tissue. This membrane transport system is an important element in maintaining cellular Ca^{2+} homeostasis in excitable cells.

On the basis of his methodological expertise in confocal microscopy, Dr. K. Baltensperger has been asked to cooperate on projects of the Institute of Plant Physiology (group of Prof. Kuhlemeier) and the Clinic of Rheumatology, Clinical Immunology and Allergology (group of Prof. Pichler).

The interaction of G proteins and protein kinase C with BCR/ABL tyrosine kinase-dependent signaling in human leukemia cells

K. Kirschner, K. Baltensperger, H. Porzig

Our studies on BCR-ABL signaling in human leukemia cells have identified an unexpected mechanism of resistance development against the therapeutically used Abl tyrosine kinase inhibitor imatinib (Gleevec). Erythropoietin, a physiological regulator of hematopoiesis, is capable to rescue BCR-ABL positive cells from imatinib-induced apoptosis and sustain cellular growth. Continuous proliferation under the selective pressure of imatinib then leads to the development of resistance and outgrowth of resistant clones at high frequencies. Although these results were obtained in a cell line, our results are of potential clinical relevance, as cytokines apparently can promote resistance development against the tyrosine kinase inhibitor. Further investigations in primary human leukemia cells will be necessary to confirm this hypothesis. A second part of the studies was aimed at establishing a lentiviral transduction system in our laboratory to address the function of specific G protein α-subunits in normal and leukemic cell differentiation. The system allows for the expression of a transgene in combination with a marker for the noninvasive detection of transduced cells, a prerequisite for single cell studies.

See original publication No. 1

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. 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 PKC 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.

'Functional half-life' of the Na^+-Ca^{2+} exchanger in neonatal rat cardiac myocytes revealed by an antisense oligodeoxynucleotide approach

M. Egger, H. Porzig, E. Niggli, B. Schwaller

The Na^+-Ca^{2+} exchanger is essential for the Ca^{2+} homeostasis in many cell types but a specific pharmacological blocker is still lacking. We used an antisense oligodeoxynucleotide (AS-ODN) directed against the rat cardiac Na^+-Ca^{2+} exchanger

(NCX1) to suppress the *de novo* synthesis of the protein. The specificity of this approach was examined in neonatal rat cardiac myocytes and, as a new strategy, in baculovirus-infected Sf9 insect cells transiently expressing NCX1. Suppression of NCX1 synthesis by AS-ODNs was assessed with immunohistochemistry and a quantitative binding assay using the radiolabeled monoclonal antibody R3F1. The reduction of NCX1 activity by AS-ODN treatment was evaluated by recording Na^+-Ca^{2+} exchange currents with the voltage-clamp technique and by examining Ca^{2+} transport via NCX1using laser-scanning confocal imaging of transient Ca^{2+} signals. In cultured neonatal cardiac myocytes the total amount of NCX1 epitopes recognized by the antibody was unaltered after 48 h AS-ODN treatment, while the functionally active fraction of NCX1 in the sarcolemma virtually disappeared. In contrast, in NCX1-baculovirus-infected Sf9 cells devoid of endogenous NCX1, the exposure to AS-ODN resulted in a significant reduction of the synthesis and function of NCX1. Taken together, these results indicate that the NCX1 protein has a short half-life in the plasma membrane of cardiac myocytes, whereas the epitope recognized by the R3F1 antibody remains much longer inside the cells. This leads to significant differences in the "functional half-life" measured with exchange activity compared to the half-life determined by epitope binding.

Brain distribution of the Na^+/Ca^{2+} exchanger-encoding genes NCX1, NCX2, and NCX3 and their related proteins in the central nervous system

(Cooperation with the group of Lucio Annunciato, Dept. of Neurosciences, University Frederico II, Naples, Italy)

In the central nervous system (CNS), the Na^+-Ca^{2+} exchanger plays a fundamental role in controlling the changes in the intracellular concentrations of Na^+ and Ca^{2+} ions. These cations are known to regulate neurotransmitter release, cell migration and differentiation, gene expression, and neurodegenerative processes. In the present study, nonradioactive in situ hybridization and light immunohistochemistry were carried out to map the regional and cellular distribution for both transcripts and proteins encoded by the three known Na^+-Ca^{2+} exchanger genes NCX1, NCX2, and NCX3. NCX1 transcripts were particularly expressed in layers III-V of the motor cortex, in the thalamus, in CA3 and the dentate gyrus of the hippocampus, in several hypothalamic nuclei, and in the cerebellum. NCX2 transcripts were strongly expressed in all hippocampal subregions, in the striatum, and in the paraventricular thalamic nucleus. NCX3 mRNAs were mainly detected in the hippocampus, in the thalamus, in the amygdala, and in the cerebellum. Immunohistochemical analysis revealed that NCX1 protein was mainly expressed in the supragranular layers of the cerebral cortex, in the hippocampus, in the hypothalamus, in the substantia nigra and ventral tegmental area, and in the granular layer of the cerebellum. The NCX2 protein was predominantly expressed in the hippocampus, in the striatum, in the thalamus, and in the hypothalamus. The NCX3 protein was particularly found in the CA3 subregion, and in the oriens, radiatum, and lacunoso-moleculare layers of the hippocampus, in the ventral striatum, and in the cerebellar molecular layer. Collectively, these results suggest that the different Na^+-Ca^{2+} exchanger isoforms appear to be selectively expressed in several CNS regions where they might underlie different functional roles.

See original publication No. 2

G protein-dependent signal transduction and induction of differentiation in hematopoietic cells

I. Kotevic, K. Baltensperger

Hematopoietic cells express a unique heterotrimeric G protein α-subunit, $G_{\alpha 16}$, a member of the $G_{\alpha q}$ family. It is involved in Ca^{2+}-signaling and is capable of inducing cellular differentiation when overexpressed in a leukemia cell line [(Ghose, S., et al., J. Biol. Chem. 274, 12848-12854 (1999)]. Earlier experiments indicated that UTP-stimulated $P2Y_2$ nucleotide receptor ($P2Y_2R$) signaling critically depends on the presence of $G_{\alpha 16}$. In order to demonstrate direct interaction of $G_{\alpha 16}$ with $P2Y_2$Rs, we fused receptor and G protein with the cyan (CFP) and yellow (YFP) variants of green fluorescent protein, respectively, and performed fluorescence energy transfer (FRET) experiments. FRET efficiencies of 10 to 15% were measured in HEK 293 cells cotransfected with both, the $P2Y_2R$-CFP and the $G_{\alpha 16}$-YFP fusions. Efficiencies reached 50 - 75% of those observed with a positive control (a G protein coupled receptor bearing a tandem construct of YFP and CFP at its carboxy-terminus). As expected, no FRET was observed in the absence of $G_{\alpha 16}$-YFP, or with cytosolically expressed YFP, demonstrating specificity of the FRET signal. Single cell Ca^{2+} measurements were performed with fluo-3AM loaded K562 cells, which do not endogenously express either $P2Y_2R$ or $G_{\alpha 16}$. In cells that were transiently transfected with the CFP-tagged $P2Y_2R$ alone, UTP-stimulated Ca^{2+} transients were observed, indicating that $P2Y_2$-CFP is functional and may couple to endogenously expressed G proteins. Co-expression of $G_{\alpha 16}$-CFP and $P2Y_2$-CFP significantly enhanced Ca^{2+}-transients (1.5 - 1.7-fold), demonstrating that fluorescent fusions of $P2Y_2R$ and $G_{\alpha 16}$ are capable to functionally interact. As expected, no UTP-signal was observed in cells that were not transfected, or in cells that were transfected with $G_{\alpha 16}$-CFP alone.Taken together, these results demonstrate a functional and molecular interaction between the $P2Y_2R$ and $G_{\alpha 16}$. Further experiments will address the question whether it is possible to induce differentiation of leukemia cells by activation of $G_{\alpha 16}$ through pharmacological stimulation of the $P2Y_2$-receptor.

Original publications

1. K. Kirschner, K. Baltensperger:
Erythropoietin promotes resistance against the Abl tyrosine kinase inhibitor imatinib (STI571) in K562 human leukemia cells.
Mol. Cancer Res. 1 (2003), 970-980.

2. M. Papa, A. Canitano, F. Boscia, P. Castaldo, S. Sellitti, H. Porzig, M. Taglialatela, L. Annunziato:
Differential expression of the Na^+-Ca^{2+} exchanger transcripts and proteins in rat brain regions.
J. Comp. Neurol. 461 (2003), 31-48.

3. D. Reinhardt, E.-R. Pesce, P. Stieger, T. Mandel, K. Baltensperger, M. Bennett, J. Traas, J. Friml, C. Kuhlemeier:
Regulation of phyllotaxis by polar auxin transport.
Nature 426 (2003), 255-260.

4. S. Bürgi, K. Baltensperger, U. E. Honegger:
Switch of β1-adrenoceptor trafficking as a mechanism for drug action.
J. Biol Chem. 278 (2003), 1044-1052.

Group Prof. Erwin Sigel

Group members: Roland Baur, head technician
Dmytro Berezhnoy, PhD student
Nathalie Boulineau, PhD student (since February)
Dr. Frédéric Minier, PhD

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.

The two functional agonist sites of $GABA_A$ receptors
S.W. Baumann, R. Baur, E. Sigel
Opening of the inherent chloride channel in the $GABA_A$ receptor is achieved through the binding of two agonist molecules, but it has been difficult to obtain information on the contribution of the two individual binding sites. The sites are both located at $\beta(+)/\alpha(-)$ subunit interfaces, suggesting similar properties. One pair of subunits is flanked by γ and β (site 1) and the other by α and γ (site 2), the different environment possibly affecting the binding sites. Here we used concatenated subunits and two point mutations of amino acid residues each in α and β subunits, which are both located in the agonist binding pocket, to investigate the properties of these two sites. The sites were individually mutated and consequences of these mutations on GABA and muscimol induced channel opening and its competitive inhibition by bicuculline were studied. A model predicts that opening occurs also for receptors occupied with a single agonist molecule, but is promoted about 60-fold in those occupied by two agonists, that site 2 has an about three-fold higher affinity for GABA than site 1, whereas muscimol and bicuculline show some preference for site 1 (Fig. 1).
See original publication No. 1

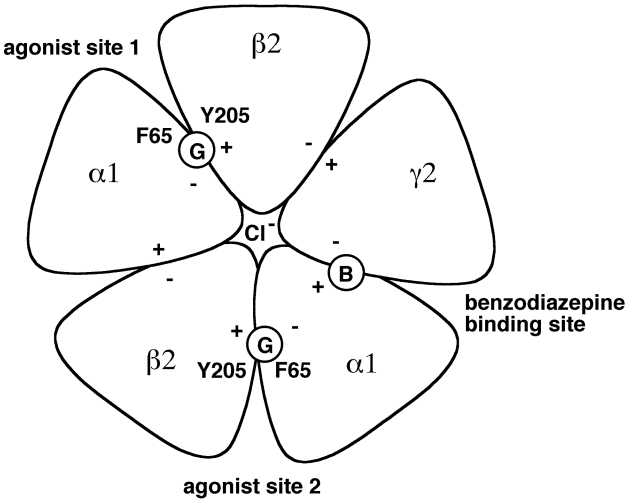

Fig. 1

Defined subunit isoforms of $GABA_A$ receptors

F. Minier and E. Sigel

Similar to the approach outlined above, receptors carrying two α subunit isoforms, α1 and α6 in defined positions were prepared (β2α6γ2/β2α1, β2α1γ2/β2α6, β2α1γ2/β2α1 and β2α6γ2/β2α6). These four receptor types were expressed in Xenopus oocytes and functionally characterized for their activation by GABA and the partial agonist P4S, their inhibition by furosemide and their modulation by diazepam (Table 1). It turns out that this set of functional properties can be used as a diagnostic tool for cerebellar granule cells which express the α6 subunit. This will also open the way for the screening of potentially useful substances at defined $GABA_A$ receptor subtypes. α6 subunits also have been reported to confer a specific subcellular localization. It will be investigated how β2α6γ2/β2α1, β2α1γ2/β2α6, β2α1γ2/β2α1 and β2α6γ2/β2α6 receptors localize after transfection into primary neurons.

Table 1

	GABA	Diazepam	Furosemide	P4S
	EC_{50} (μM)	stim (%)	IC_{50} (μM)	E_{max} (%)
γ-β-α1/β-α1	150–200	370	>5000	5
γ-β-α6/β-α6	1	0	30	44
γ-β-α1/β-α6	100	0	30	15
γ-β-α6/β-α1	40	300	30-40	11

Relative positioning of β subunit isoforms in $GABA_A$ receptors

N. Boulineau and E. Sigel

α1β1γ2 receptors have properties different from α1β2γ2 receptors. In contrast to α1β1γ2 receptors, α1β2γ2 receptors respond to the anticonvulsant loreclezole. β2 subunits also confer a specific subcellular location while β1 subunits do not. Concatenated subunits α1β1α1, β1γ2, α1β2α1 and β2γ2 have been prepared. α1β1α1/β2γ2 receptors and α1β2α1/β1γ2 will be expressed in Xenopus oocytes and their pharmacological properties analyzed. Transient transfection into primary

neurons in combination with immunocytolocalization experiments will reveal their subcellular localization. This will show how relative positioning of β1 and β2 subunits in a pentameric $GABA_A$ receptor affects its properties.

Low and high affinity agonist sites of $GABA_A$ receptors

R. Baur, E. Sigel

$GABA_A$ receptors are activated via low affinity binding sites for the agonists GABA or muscimol. Evidence has been provided that the amino acid residue α1F64 located at the β2α1 subunit interface forms part of this binding site. In radioactive ligand binding studies the agonist [^{3}H]muscimol has been found to interact with the receptor via a high affinity binding site. This high affinity site has classically been explained as a conformational variant of the low affinity site. Alternatively, the high affinity binding site has been located to the α1β2 interface and β2Y62 the homologous residue to α1F64, has been proposed to constitute an important part. We investigated the effect of the point mutation α1F64L and the homologous mutation β2Y62L on agonist and antagonist binding and functional properties in wild type and mutated α1β2γ2 $GABA_A$ receptors. While the mutation in the α1 subunit had drastic consequences on all studied properties including desensitization, the mutation in the β2 subunit had little consequence. Our observations argue for the classical view of high and low affinity agonist sites in $GABA_A$ receptors.

See original publication No. 2

Architecture of the benzodiazepine binding site on $GABA_A$ receptors

D. Berezhnoy, 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. We found a covalent interaction of α_1H101C with a reactive group attached to the C-7 position of diazepam. This interaction was studied at the level of ligand binding and at the functional level using electrophysiological methods. Covalent reaction occurs concomitantly with occupancy of the binding pocket. It stabilizes the receptor in its allosterically stimulated conformation. Covalent modification is not observed in wild type receptors or using mutated α_1H101C containing receptors in combination with the reactive ligand pre-reacted with a sulfhydryl group and modification rate is reduced by the binding site ligand Ro15-1788. We present in addition evidence that γ_2A79 is probably located in the access pathway of the ligand to its binding pocket.

See original publication No. 3

Conformational changes in $GABA_A$ receptors

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

The rates of covalent reaction of the two cysteine residues introduced into the 2 α1 subunits at the α(+)/γ(-) and α(+)/β(-) subunit interfaces are both affected by GABA, indicative of a conformational change induced by these ligands distant from their binding sites.

K36 isolated from *Scutellaria baicalensis* acts as a selective anxiolytic

R. Baur, E. Sigel

(Collaboration with Drs. M.S.Y. Huen, K.M. Hui, J.W.C. Leung, J.T.F. Wong and H. Xue, Dept. of Biochemistry, Hong Kong University of Science and Technology, Hong Kong, China)

The monoflavonoid K36, purified from *Scutellaria baicalensis* Georgi inhibited [^{3}H]flunitrazepam binding to the benzodiazepine receptors. In electro-physiological studies, K36 enhanced the GABA-activated current. In *Xenopus* oocytes, half-maximal stimulation of currents elicited by GABA was observed at about 20 nM K36. Maximal stimulation by K36 amounted to about 60 % of that by 0.3 μM diazepam. The enhancement was reversed by co-application of the benzodiazepine antagonist Ro15-1788. K36 is a naturally occurring partial positive allosteric modulator of the $GABA_A$ receptor acting at the benzodiazepine binding site. Behavioral studies demonstrated a selective, short term anxiolytic effect.

See original publication No. 4

An isolated plant compound allosterically stimulates $GABA_A$ receptors independently of the benzodiazepine site

R. Baur, E. Sigel

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

Patenting in evaluation.

Functional characterization of a human mutation in a muscle chloride channel leading to Myotonia Congenita

M.T. Schaerer, E. Sigel

(Collaboration with Drs. L. Chen, D. Lang, J. Fritschi, L. Kappeler and J. Burgunder, Laboratory of Neuromorphology, Departments of Neurology and Clinical Research; and Drs. F. Joncourt and S. Gallati, Laboratory of Molecular Genetics, Children's Hospital; and Prof. Dr. J. Weis, Division of Neuropathology, Institute of Pathology; all University of Bern)

Myotonia congenita is a group of inherited muscular diseases characteristically involving muscle stiffness. ClC-1 is a major voltage dependent chloride ion channel in the skeletal muscle. Exon 17 skipping was identified in a patient at the DNA level. The functional significance of this exon skipping was then investigated by expressing mutagenised CIC-1 in *Xenopus* oocytes. No measurable chloride current could be detected in these oocytes, indicating the expression of a non-functional ClC-1. On the other hand, a normal function could be achieved when both the mutant and wild-type ClC-1 were co-expressed. These data are compatible with the fact that exon 17 skipping leads to a recessive inheritance of the disease.

See original publication No. 5

Zolpidem insensitive mice

E. Sigel

(in collaboration with the groups of Profs. P. Somogyi, W. Sieghart, W. Wisden and E.R. Korpi)

We have shown earlier that the point mutation in the γ2 subunit F77I leads to zolpidem insensitive α1β2γ2 $GABA_A$ receptors that still respond normally to diazepam. Transgenic mice expressing in place of normal γ2 this mutated subunit were shown to be insensitive to zolpidem but not to diazepam. These mice may be

useful to dissect the differential contribution of the γ2 subunit in the brain by restoring normal γ2 subunit expression in selected brain regions.

Original publications

1. S.W. Baumann, R. Baur, E. Sigel:
Individual properties of the two functional agonist sites in $GABA_A$ receptors.
J. Neurosci. 23, 11158-11166.

2. R. Baur, E. Sigel:
On high and low affinity agonist sites in $GABA_A$ receptors.
J. Neurochem. 87, 325-332.

3. D. Berezhnoy, Y. Nyfeler, A. Gonthier, H. Schwob, M. Goeldner, E. Sigel:
Towards a relative orientation of benzodiazepines in their binding pocket on $GABA_A$ receptors.
J. Biol. Chem., in press.

4. M.S.Y. Huen, K.M. Hui, J.W.C. Leung, E. Sigel, R. Baur, J.T.F. Wong, H. Xue:
Naturally occurring 2'hydroxyl-substituted flavonoids as high-affinity benzodiazepine site ligands.
Biochem. Pharmacol. 66, 2397-2407.

5. L. Chen, M.T. Schaerer, D. Lang, F. Joncourt, J. Weis, J. Fritsch, L. Kappeler, S. Gallati, E. Sigel, J.M. Burgunder:
A non-functional chloride channel resulting from Exon 17 skipping in *CLCN1* leads to autosomal recessive myotonia congenita in swiss patients.
Muscle and Nerve, in press.

Review articles

1. F. Minier, E. Sigel:
Ligand-operated membrane channels: GABA.
Encyclopedia of Biological Chemistry, in press.

2. E. Sigel:
The benzodiazepine recognition site on $GABA_A$ receptors.
Medicinal Chemistry Reviews - Online, in press.

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Ekatherina Vassina, PhD student
Dr. Stephan von Gunten, PhD student
Dr. Shida Yousefi, PhD[1]

[1]In addition, independent research work with own Swiss National Science Foundation and Bern Krebsliga 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: Bronchial asthma, 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, some of them were finished and published in 2003. 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 2003.

Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis

S.G. Plötz*, H.-U. Simon*, U. Darsow, D. Simon, E. Vassina, S. Yousefi, R. Hein, T. Smith, H. Behrendt, J. Ring

(Collaboration with the Division of Environmental Dermatology and Allergy GSF/TUM and the Department of Dermatology and Allergy, both Technical University Munich, Germany, as well as with the Department of Dermatology, University of Bern, Switzerland)

The hypereosinophilic syndrome comprises a heterogeneous group of conditions characterized by hypereosinophilia and organ dysfunction caused by eosinophil-mediated tissue damage. The highly variable response to treatment reflects the heterogeneity of the syndrome. Current therapies include corticosteroids, hydroxyurea, interferon-α, and imatinib mesylate. Imatinib can be effective in patients

with the syndrome who have normal or increased serum concentrations of interleukin-5 (IL-5). Recently, patients with hypereosinophilia and fusion of the Fip1-like 1 gene and the gene that encodes platelet-derived growth factor receptor α were found to have a response to imatinib mesylate. Such patients probably have a myeloproliferative disease or a clonal disorder that is largely independent of interleukin-5, a cytokine required for differentiation, activation, and survival of eosinophils. However, in other patients of the syndrome, IL-5 does seem to have a critical role. We observed dramatic clinical improvements of hypereosinophilic syndrome patients with dermatologic manifestations following anti – IL-5 monoclonal antibody treatment. Clinical efficacy was associated with reduced blood and tissue eosinophils, reduced blood IL-5 levels, reduced IL-5 – expressing skin T cells, and reduced numbers of T helper 2 effector memory cells in blood.

See original publication No. 1

*Shared First-Authorship

Natural history of primary eosinophilic esophagitis: A follow-up of 30 adult patients for up to 11.5 years

A. Straumann, H.-P. Spichtin, L. Grize, C. Bitzer, K.A. Bucher, C. Beglinger, H.-U. Simon

(Collaboration with the Department of Gastroenterology, Kantonsspital Olten, Institute of Clinical Pathology, Basel, and Department of Gastroenterology, University Hospital Basel, Switzerland)

Primary eosinophilic esophagitis is a chronic, increasingly recognized, interleukin-5 (IL-5) inflammatory disorder of the esophagus. The leading symptom in adults is uniform attacks of dysphagia, and the established histologic sign is a dense eosinophilic infiltration of the esophageal epithelium. We conducted a prospective case series including 30 adult patients with eosinophilic esophagitis whose diagnosis had been made >1 year before study debut based on typical history, consistent endoscopic abnormalities, and infiltration of the esophageal epithelium with >24 eosinophils/high-power field. After a mean of 7.2 years, patients underwent a comprehensive follow-up examination. All patients survived the study period in good health and stable nutritional state. Dysphagia persisted in 29 patients. Attacks of dysphagia were more frequent in patients with blood eosinophilia or pronounced endoscopic alterations. The eosinophilic infiltration persisted in all symptomatic patients, but cell numbers spontaneously decreased significantly. The inflammatory process evoked fibrosis of the esophageal lamina propria but did not spread to the stomach or duodenum. No case evolved to a hypereosinophilic syndrome. Moreover, no malignant potential has been associated with this disease.

See original publication No. 2

Clinical and immunological effects of low-dose IFN-α treatment in patients with corticosteroid-resistant asthma

H.-U. Simon, H. Seelbach, R. Ehmann, M. Schmitz

(Collaboration with the High-Altitude Clinic Davos-Wolfgang, Davos, Switzerland)

Interferon (IFN)-α is a cytokine that possesses potent anti-viral and immunoregulatory activities. We aimed to assess clinical and immunological effects of low-dose IFN-α in patients with severe corticosteroid-resistant asthma with and without Churg-Strauss syndrome. There is currently no efficient pharmacological treatment available for this group of patients. We studied 10 patients with corticosteroid-resistant asthma, in which 3 x 10^6 IU/d IFN-α were administrated in addition to the prednisone dose given already before introduction of the cytokine

therapy. The prednisone dose was gradually reduced dependent on the clinical situation and used as a clinical readout to evaluate the efficacy of the cytokine therapy. To distinguish between IFN-α - and prednisone - mediated immunological changes, the corticosteroid dose was kept constant for at least 2 weeks upon introduction of the cytokine therapy in 7 patients. The effects of treatment on clinical and immunological parameters were measured at weeks 2-4 and months 5-10 depending on the availability of the patient. IFN-α treatment rapidly improved the clinical situation as assessed by lung function parameters and required prednisone dose. Important immunological changes included: Decreased leukocyte numbers, increased relative numbers of CD4+ T cells, increased differentiation of T helper (Th)1 cells, and increased expression of interleukin (IL)-10 in peripheral blood mononuclear cells (PBMC). Taken together, IFN-α treatment was associated with dramatic improvements in the condition of patients with corticosteroid-resistant asthma with and without Churg-Strauss syndrome. Potential mechanisms of action include the establishment of a correct Th1/Th2 balance and the induction of the anti-inflammatory IL-10 gene.

See original publication No. 3

The interleukin-13 production by peripheral blood T cells from atopic dermatitis patients does not require CD2 costimulation

D. Simon, S. von Gunten, S. Borelli, L.R. Braathen, H.-U. Simon

(Collaboration with the Department of Dermatology, University of Bern, Bern, and the Clinic for Dermatology and Allergy, Davos, Switzerland)

Although allergic mechanisms appear to be important, the pathogenesis of both extrinsic and intrinsic forms of atopic dermatitis (AD) is unknown. We compared the cytokine production of peripheral blood mononuclear cells (PBMC) of extrinsic AD (EAD), intrinsic AD (IAD), and normal control individuals after stimulation with anti-CD3 and/or anti-CD28 monoclonal antibodies (mAb) in the presence or absence of anti-CD2 blocking mAb. Cytokine production was measured by immunoassays in supernatants of 24-h cultures. EAD patients showed decreased capacity to synthesise interferon (IFN)-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) upon anti-CD3 mAb stimulation compared to IAD patients. Both EAD and IAD patients demonstrated increased production of interleukin (IL)-5 and IL-13. As expected, IFN-γ, GM-CSF, and IL-5 levels were reduced in the presence of anti-CD2 blocking mAbs. CD28 co-stimulation restored the release in cultures with anti-CD2 mAbs added, suggesting that CD2 and CD28 have redundant functions in T cell activation and subsequent cytokine production. Strikingly, IL-13 production was not blocked by anti-CD2 mAbs and also not increased by agonistic anti-CD28 mAb, in particular within the EAD patient group. The signalling pathway initiated by the T cell receptor complex leading to increased IL-13 production in AD patients appears to be highly sensitive and is largely independent on CD2 co-stimulatory signals.

See original publication No. 4

Interleukin-2 primes eosinophil degranulation in hypereosinophilia and Wells' syndrome

H.-U. Simon, S. Plötz, D. Simon, U. Seitzer, L.R. Braathen, G. Menz, A. Straumann, R. Dummer, F. Levi-Schaffer

(Collaboration with the Department of Dermatology, Division of Environmental Dermatology and Allergy GSF/FUM, Technical University of Munich, Munich, Germany; Department of Dermatology, University of Bern, Bern, Switzerland; Department of Cell Biology and Immunology, Division of Veterinary Infectiology and

Immunology, Research Center Borstel, Borstel, Germany; High-Altitude Clinic Davos-Wolfgang, Davos, Switzerland; Department of Gastroenterology, Kantonsspital Olten, Olten, Switzerland; Department of Dermatology, University of Zurich, Zurich, Switzerland; Department of Pharmacology, School of Pharmacy, The Hebrew University-Hadassah Medical School, Jerusalem, Israel)
Patients with hypereosinophilia frequently suffer from eosinophil-mediated damages of the heart, lungs, skin, and other organs, while some do not. The reason(s) for this difference is not known. We observed that eosinophils from most patients with hypereosinophilia express the α-chain of the interleukin-2 receptor (CD25) and that interleukin-2 enhances platelet-activating factor - stimulated release of eosinophil cationic protein from CD25 expressing but not CD25 negative eosinophils. Such a "priming" effect has previously been described for eosinophil hematopoietins. These data suggest that patients with increased eosinophil surface CD25 expression are at higher risk of eosinophil degranulation and subsequent tissue damage when interleukin-2 is present at inflammatory sites.
See original publication No. 5

Concurrent presence of agonistic and antagonistic anti-CD95 autoantibodies in intravenous Ig preparations
F. Altznauer, S. von Gunten, P. Späth, H.-U. Simon
(Collaboration with ZLB Bioplasma AG, Bern, Switzerland)
Although there have been several reports suggesting the presence of physiologic anti-CD95 (Fas, APO-1) autoantibodies in human intravenous immunoglobulin (IVIg) preparations, it is still unclear whether and under which conditions these autoantibodies block or stimulate the CD95 receptor. We examined the effects of IVIg on CD95-mediated apoptosis in CD95-sensitive human blood neutrophils in vitro. The presence of anti-CD95 antibodies was determined by competition assays using flow cytometry. Cell death and apoptosis were assessed by ethidium bromide uptake test and annexin V staining, respectively. Pretreatment of neutrophils with IVIg prevented binding of FITC-conjugated anti-CD95 mAb to the cell surface, suggesting that IVIg contain CD95 autoantibodies. Using low concentrations of IVIg (1-10 mg/ml), we observed a dose-dependent inhibition of anti-CD95 monoclonal antibody (CH11) - mediated neutrophil apoptosis. Higher concentrations of IVIg (20-50 mg/ml), however, induced neutrophil death and apoptosis in a dose-dependent manner. This effect was partially blocked by soluble CD95 receptors (recombinant Fc-Fas) but not by an anti-CD95 blocking mAb, which was shown to recognize the CH11 epitope of CD95. In conclusion, both agonistic and antagonistic anti-CD95 antibodies are present in IVIg and the effect on CD95 is dose-dependent. Our findings have potential implications for IVIg treatment, which is intended to target the CD95 receptor.
See original publication No. 6

Calpain-1 regulates Bax and subsequent Smac-dependent caspase-3 activation in neutrophil apoptosis
F. Altznauer, S. Conus, A. Cavalli, G. Folkers, H.-U. Simon
(Collaboration with the Department of Pharmaceutical Sciences, University of Bologna, Bologna, Italy, and the Department of Pharmaceutical Sciences, University of Zurich, Zurich, Switzerland)
In the absence and in the resolution of inflammatory responses, neutrophils rapidly undergo spontaneous apoptosis. Here we report about a new apoptosis pathway in these cells that requires calpain-1 activation and is essential for the enzymatic

activation of the critical effector caspase-3. Decreased levels of calpastatin, a highly specific intrinsic inhibitor of calpain, resulted in activation of calpain-1, but not calpain-2, in neutrophils undergoing apoptosis, a process, which was blocked by a specific calpain-1 inhibitor or by intracellular delivery of a calpastatin peptide. Further support for the importance of the calpastatin-calpain system was obtained by analyzing neutrophils from patients with cystic fibrosis that exhibited delayed apoptosis associated with markedly increased calpastatin and decreased calpain-1 protein levels compared to neutrophils from control individuals. Additional studies were designed to place calpain-1 into the hierarchy of biochemical events leading to neutrophil apoptosis. Pharmacological calpain inhibition during spontaneous and Fas receptor-induced neutrophil apoptosis prevented cleavage of Bax into an 18-kDa fragment unable to interact with Bcl-x_L. Moreover, calpain blocking prevented the mitochondrial release of cytochrome c and Smac, which was indispensable for caspase-3 processing and enzymatic activation, both in the presence and absence of agonistic anti-Fas receptor antibodies. Taken together, calpastatin and calpain-1 represent critical proximal elements in a cascade of pro-apoptotic events leading to Bax, mitochondria, and caspase-3 activation, and their altered expression appears to influence the life span of neutrophils under pathologic conditions.
See original publication No. 7

Macrophage migration inhibitory factor delays apoptosis in neutrophils by inhibiting the mitochondria-dependent death pathway

R. Baumann, C. Casaulta, D. Simon, S. Conus, S. Yousefi, H.-U. Simon
(Collaboration with the Departments of Pediatrics and Dermatology, University of Bern, Switzerland)

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine known to activate macrophages and T cells. In this study, we demonstrate that recombinant MIF delays apoptosis of these cells *in vitro*. MIF action is dose- and time-dependent as well as specific since it was abolished with a neutralizing anti-MIF antibody. MIF, like G-CSF, delayed cleavage of the proapoptotic members of the Bcl-2 family Bid and Bax in neutrophils, suggesting that MIF inhibits apoptosis pathways proximal to mitochondria activation. Indeed, MIF also prevented the release of cytochrome c and Smac from the mitochondria and subsequent activation of the critical effector caspase-3 in these cells. Moreover, we observed increased MIF plasma levels in patients with cystic fibrosis (CF), a heterogeneous recessive genetic disorder associated with bacterial infectious and delayed neutrophil apoptosis. In conclusion, MIF is a survival cytokine for human neutrophils, a finding with pathologic relevance in infectious diseases.
See original publication No. 8

Inflammation-associated cell-cycle-independent block of apoptosis by survivin in terminally differentiated neutrophils

F. Altznauer*, S. Martinelli*, S. Yousefi, C. Thürig, I. Schmid, E. Kozlowski, E.M. Conway, M.H. Schöni, P. Vogt, C. Müller, M.F. Fey, U. Zangemeister-Wittke, H.-U. Simon
(Collaboration with the Departments of Oncology, Pediatrics, and Pathology, University of Bern, the Departments of Medical Oncology and Clinical Pathology, University of Zurich, Switzerland, and the Center for Transgene Technology and Gene Therapy, University of Leuven, Belgium)

Survivin has received great attention due to its expression in many human tumors and its potential as a therapeutic target in cancer. Survivin expression has been

described to be cell-cycle-dependent and restricted to the G_2-M checkpoint, where it inhibits apoptosis in proliferating cells. In agreement with this current view, we found that survivin expression was high in immature neutrophils, which proliferate during differentiation. In contrast to immature cells, mature neutrophils contained only little or no survivin protein. Strikingly, these cells re-expressed survivin upon GM-CSF or G-CSF stimulation *in vitro* and under inflammatory conditions *in vivo*. Moreover, survivin-deficient mature neutrophils were unable to increase their life span following survival factor exposure. Taken together, our findings demonstrate that: (i) Overexpression of survivin occurs in primary, even terminally differentiated cells and is not restricted to proliferating cells; and (ii) Survivin acts as an inhibitor of apoptosis protein (IAP) in a cell-cycle-independent manner. Hence, survivin plays distinct and independent roles in the maintenance of the G_2-M checkpoint and in apoptosis control, and its overexpression is not restricted to proliferating cells. These data provide new insights into the regulation and function of survivin, and have important implications for the pathogenesis, diagnosis, and treatment of inflammatory diseases and cancer.
*Shared First-Authorship

Induction of genes mediating highly efficient interferon signalling during neutrophil differentiation

S. Martinelli*, M. Urosevic*, P.A. Oberholzer, A. Daryadel, C. Baumann, M.F. Fey, R. Dummer, H.-U. Simon, S. Yousefi

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

Interferons (IFNs) are cytokines that possess potent anti-viral and immunoregulatory activities. In contrast, their potential role(s) in anti-bacterial defense and neutrophil activation mechanisms is less well explored. By comparing gene expression patterns between immature and mature human neutrophils, we obtained evidence that intracellular proteases and other anti-bacterial proteins are produced at earlier stages of maturation whereas the genes for receptors and signaling molecules required for the release of these effector molecules are preferentially induced during terminal differentiation. For instance, mature neutrophils strongly expressed genes that increase their responses to type I and type II IFNs. Interestingly, granulocyte/macrophage – colony-stimulating factor (GM-CSF) was identified as a repressor of IFN signaling components and consequently of IFN-responsive genes. Both IFN-α and IFN-γ induced strong tyrosine phosphorylation of STAT1 in mature but not in immature neutrophils. Functional in vitro studies suggested that IFNs act as priming factors on mature neutrophils allowing the release of myeloperoxidase (MPO) upon subsequent stimulation with complement factor 5a (C5a). In contrast, both IFN-α and IFN-γ had only little capacity to prime immature cells in this system. Moreover, both IFNs did not have significant anti-proliferative effects on immature neutrophils. These data contribute to our understanding regarding changes of gene expression during neutrophil differentiation and IFN-mediated anti-bacterial defense mechanisms.
*Shared First-Authorship

Functional expression of CD134 by neutrophils

R. Baumann, S. Yousefi, D. Simon, S. Russmann, C. Müller, H.-U. Simon
(Collaboration with the Departments of Dermatology, Clinical Pharmacology, and Pathology, University of Bern, Switzerland)

CD134 (OX40) is a member of the tumor necrosis factor (TNF) receptor superfamily expressed on activated T-cells. Here, we show that human peripheral blood neutrophils express CD134. Activation of CD134 by soluble CD134 ligand (OX40 ligand/gp34) resulted in delayed caspase-3 activation and consequently in delayed neutrophil apoptosis *in vitro*. Moreover, CD134 ligand, like G-CSF, inhibited cleavage of the pro-apoptotic Bcl-2 family members Bid and Bax in these cells, suggesting that CD134-mediated signals block apoptosis pathways proximal to mitochondria activation. In conclusion, CD134 regulates neutrophil survival, suggesting that this molecule does not only contribute to adaptive but also to innate immune responses.

Reduced dermal infiltration of cytokine-producing inflammatory cells in atopic dermatitis following short-term topical tacrolimus 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 studies, topical immunomodulators have been shown to be effective in the treatment of atopic dermatitis (AD). As calcineurin inhibitors, they target signaling pathways that control gene expression, in particular the expression of cytokines. We examined the cellular infiltrate of skin lesions of ten AD patients and characterized the cytokine pattern expressed by the infiltrating cells before and after short-term topical therapy with tacrolimus 1% ointment. Skin biopsies were examined for histological alterations (HE staining), composition of the inflammatory infiltrate (immunofluorescence) and cytokine expression (ELISA, immunofluorescence) one and three weeks after initiation of tacrolismus therapy. Systemic immunological effects were assessed by analyzing peripheral blood leukocytes (immunofluorescence) as well as in vitro stimulated pan-T cell cytokine production and proliferation (ELISA, lymphocyte proliferation test). All patients showed a significant improvement of their skin lesions associated with a marked regression of spongiosis, acanthosis, and of the density of the inflammatory infiltrate in the dermis. The latter was due to reduced infiltration of T cells, B cells, and eosinophils. In contrast, the numbers of mast cells did not change. Moreover, the expression of the T helper (Th) 2 cytokines interleukin (IL)-5, IL-10, and IL-13 in CD4+ T cells was reduced after therapy. Interestingly, tacrolimus therapy was also associated with a reduction of CD8+ T cells expressing the Th1 cytokine interferon-γ. Furthermore, the numbers of epidermal CD1a+ dendritic cells increased following treatment. In the peripheral blood, a decrease of granulocytes (eosinophils and neutrophils), but no changes in the distribution of lymphocyte subpopulations were noticed. In conclusion, topical tacrolimus treatment has anti-inflammatory effects on AD skin as indicated by reduced infiltration of cytokine expressing inflammatory cells. No evidence for drug-induced systemic immunosuppression was obtained.

Original publications

1. S.G. Plötz*, H.-U. Simon*, U. Darsow, D. Simon, E. Vassina, S. Yousefi, R. Hein, T. Smith, H. Behrendt, J. Ring:
Use of an anti-interleukin-5 antibody in the hypereosinophilic syndrome with eosinophilic dermatitis.
N. Engl. J. Med. 349 (2003), 2334-2339.
*Shared First-Authorship

2. A. Straumann, H.-P. Spichtin, L. Grize, K.A. Bucher, C. Beglinger, H.-U. Simon:
Natural history of primary eosinophilic esophagitis: A follow-up of 30 adult patients for up to 11.5 years.
Gastroenterology 125 (2003), 1660-1669.

3. H.-U. Simon, H. Seelbach, R. Ehmann, M. Schmitz:
Clinical and immunological effects of low-dose IFN-α treatment in patients with corticosteroid-resistant asthma.
Allergy 58 (2003), 1250-1255.

4. D. Simon, S. von Gunten, S. Borelli, L.R. Braathen, H.-U. Simon:
The interleukin-13 production by peripheral blood T cells from atopic dermatitis patients does not require CD2 costimulation.
Int. Arch. Allergy Immunol. 132 (2003), 148-155.

5. H.-U. Simon, S. Plötz, D. Simon, U. Seitzer, L.R. Braathen, G. Menz, A. Straumann, R. Dummer, F. Levi-Schaffer: Interleukin-2 primes eosinophil degranulation in hypereosinophilia and Wells' syndrome.
Eur. J. Immunol. 33 (2003), 834-839.

6. F. Altznauer, S. von Gunten, P. Späth, H.-U. Simon:
Concurrent presence of agonistic and antagonistic anti-CD95 autoantibodies in intravenous Ig preparations.
J. Allergy Clin. Immunol. 112 (2003), 1185-1190.

7. F. Altznauer, S. Conus, A. Cavalli, G. Folkers, H.-U. Simon:
Calpain-1 regulates Bax and subsequent Smac-dependent caspase-3 activation in neutrophil apoptosis.
J. Biol. Chem. 279 (2004), 5947-5957.

8. R. Baumann, C. Casaulta, D. Simon, S. Conus, S. Yousefi, H.-U. Simon:
Macrophage migration inhibitory factor delays apoptosis in neutrophils by inhibiting the mitochondria-dependent death pathway.
Faseb J. 17 (2003), 2221-2230.

9. S. Russmann, H.U. Iselin, D. Meier, A. Zimmermann, H.-U. Simon, P. Caduff, J. Reichen:
Acute hepatitis associated with montelukast.
J. Hepatol. 38 (2003), 694-695.

10. A. Straumann, L. Rossi, H.-U. Simon, P. Heer, H.-P. Spichtin, C. Beglinger:
Fragility of the esophageal mucosa: A pathognomonic endoscopic sign of primary eosinophilic esophagitis?
Gastrointestinal Endoscopy 57 (2003), 407-412.

11. Z.G. Friedlender, H.-U. Simon, M. Shalit:
Metastatic carcinoma presenting with concomitant eosinophilia and thromboembolism.
Am. J. Med. Sci. 326 (2003), 98-101.

12. S. Yousefi, X.-Z. Ma, R. Singla, Y.-C. Zhou, D. Sakac, M. Bali, Y. Liu, B.M. Dahai, D.R. Branch: HIV-1 infection is facilitated in T cells by decreasing p56lck protein tyrosine kinase activity.
Clin. Exp. Immunol. 133 (2003), 78-90.

13. D. Simon, C. Boudny, H. Nievergelt, H.-U. Simon, L.R. Braathen:
Tacrolimus ointment is effective in Pityriasis lichenoides.
Br. J. Dermatol. (2004), in press.

Review articles

1. S. Yousefi, H.-U. Simon:
SHP-1: A regulator of neutrophil apoptosis.
Sem. Immunol. 15 (2003), 195-199.

2. H.-U. Simon:
Neutrophil apoptosis pathways and their modifications in inflammation.
Immunol. Rev. 193 (2003), 101-110.

3. S. Yousefi, S. Conus, H.-U. Simon:
Cross-talk between death and survival pathways.
Cell Death Differ. 10 (2003), 861-863.

4. H.-U. Simon, P. Späth:
IVIG – mechanisms of action.
Allergy 58 (2003), 543-552.

5. H.-U. Simon:
Targeting apoptosis in the control of inflammation.
Eur. Respir. J. 22, suppl. 44 (2003), 20s-21s.

6. A. Straumann, H.-U. Simon:
The physiological and pathological roles of eosinophils in the gastrointestinal tract.
Allergy 59 (2004), 15-25.

7. D. Simon, L.R. Braathen, H.-U. Simon:
Eosinophils and atopic dermatitis.
Allergy 59 (2004), in press.

Book chapters

1. H.-U. Simon, H. Reuter, M. H. Bickel:
Zur Geschichte des Pharmakologischen Instituts der Universität Bern. In: Geschichte der pharmakologischen, klinisch-pharmakologischen und toxikologischen Institute im deutschsprachigen Raum (Ed. A. Philippou); Editio Cantor Verlag, 2003, in press.

2. H.-U. Simon, U. Zangemeister-Wittke:
Apoptosis: Regulation and clinical implications. In: Encyclopedic Reference of Genomics and Proteomics (Eds. D. Ganten, K. Ruckpaul); Springer-Verlag, Heidelberg, 2003, in press.

Patent

F. Altznauer, U. Zangemeister-Wittke, H.-U. Simon, together with researchers of EiRx Therapeutics Limited, Cork, Ireland:
Survivin in the detection and modulation of apoptosis in terminally differentiated cells of the myeloid lineage (neutrophils, eosinophils, macrophages).
World-wide: WO 03/091384

Group Prof. Jörg Stucki

Group member: Dr. Clemens Wagner, PhD[1]

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

Since the seminal papers by Barabasi and Strogatz the analysis of biological networks has made large progress. The small world phenomenon was first discovered in an acquaintance network (Milgram in 1967). Steven Strogatz formalized small world networks in mathematical terms. Starting with a nearest neighbor coupled system, rewiring the connections between the nodes with increasing probability converts the network into a random coupled system. Networks can be characterized by two parameters: the mean path length (L) and the clustering coefficient (C). The former represents a global property of the system whereas the latter describes a local property. During the conversion from a nearest neighbor coupled to a random coupled network, L drops quickly due to the introduction of short cuts to the net. However, because only a few short cuts are introduced the local property C does not change markedly. Networks with such a characteristic are called small world networks. Consider a person in a social network who knows all neighbors but has also a relative in Australia. The person is then connected to people on the fifth continent only over a few links. This type of networks was also observed in systems, which are as different as power-grid networks and neural networks (C. elegans).

Barabasi and coworkers discovered a further type of network. In general, the number of links per node shows a distribution around a mean value, which often can be represented by a Gaussian distribution. This mean value is called the scale of the network. Therefore, the probability to find a node with links larger than this mean value decays exponentially. Barabasi now achieved to construct scale free networks by using 2 major construction rules. First, networks expand continuously and second, during the growth process new nodes are preferentially connected to nodes, which are already highly connected. Networks constructed in such a way reveal a power-law distribution of vertex connectivities. The important property of scale-free networks is that a few nodes become highly connected and can be identified as hubs. Hence, these networks are rather robust against random attacks, however, if the targets of an attack are the hubs the system easily breaks down. Our goal is to explore the properties of these networks when the nodes are furnished with chaotic oscillators.

The ability of the system to synchronize depends on the coupling strength and on the density of connections. In the visual system it is thought that synchronization of neurons is part of the recognition process. Therefore, the latency of synchronization is a major ingredient for fast object recognition. Thus, a further branch of our research is to study the speed of information transfer in these networks.

Properties of fractally coupled networks

C. Wagner, R. Stoop

(Collaboration with the Institute of Neuroinformatics, ETHZ, Zürich, Switzerland)

In fractally coupled networks the probability that two sites of a lattice are connected decays with the distance to the power of a α. The exponent α of the power-law controls the number of connections and the average radius of connectivity. There are two extremal cases, for $\alpha = \infty$ the network is nearest neighbor coupled whereas for $\alpha = 0$ the system is globally coupled. We have analyzed this network in terms of the mean path length and the clustering coefficient. While decreasing the exponent from ∞ to 0 the number of connections rises from 1 to N, the system size. Due to the power-law behavior of the connectivity distribution the probability of generating short cuts is not vanishing already in the case of a few links per node. Therefore, the mean path length decreases fast with increasing number of connections and after 5 connections it follows the mean path length of a random coupled network. In contrast, the clustering coefficient first follows the curve for the n^{th} nearest neighbor coupled network and rises. Hence, in the case of a few links per node the connections preferentially point to the neighbors. In this parameter region the fractally coupled network resembles a small world network, which is characterized by a low mean path length and a high clustering coefficient. When the number of connections is further increased the clustering coefficient drops to the low level of a random coupled network. In summary: fractally coupled networks form a small world network at low connection density whereas they approach the properties of a random coupled network for a high density of connections.

Limiter control of chaos

C. Wagner, R. Stoop

(Collaboration with the Institute of Neuroinformatics, ETHZ, Zürich, Switzerland)

The attractor of a chaotic system consists of an infinite number of unstable periodic orbits (UPO). The aim of chaos control methods is to stabilize the system of one of these UPO's. We have recently developed an approach, which controls the system on an orbit using simple limiters. In order to apply the method to a real system we selected the stick-slip motion, which can get chaotic in a certain range of parameters. Stick-slip motion is related to a broad range of phenomena from playing the violin to geophysics and earthquake faults. In the model we used, a body is dragged over a rough surface. A spring is attached at one side to the body and the open end of the spring is pulled with velocity v. It has been shown that this system can be controlled via time delay feedback loop on the force F, which determines the pressure between the body and the surface. We show that this feedback loop can be replaced by a limiter in a selected distance from the open end of the spring. This greatly simplifies the algorithm and might have applications to friction in nanoscale liquid films.

Time series analysis of transcranial magnetic stimulation data

A. Conforto, A. Kälin, C. Wagner
(Collaboration with the Department of Neurology; Inselspital, Bern, Switzerland)

Transcranial magnetic stimulation (TMS) is a noninvasive technique to investigate the signaling pathway from the brain to the peripheral muscles. In 6 healthy subjects part of the motor cortex was stimulated by a magnetic field every 5s and the response in the peripheral muscle was recorded. Discrete time series were obtained by measuring the maximal response amplitude of each stimulation. Due to the large variation of these amplitudes and the non Gaussian distribution, it is unclear whether these data are correlated or not. We first detected a trend in the data, which was eliminated by constructing a time series of amplitude differences or by a Kalman-Filter. As was recognized by the portmanteau test, the amplitudes in the time series of the residues (original data minus trend) were not independent. Therefore we fitted a moving average model (MA(1)) to the data. The analysis revealed that the residues are indeed correlated with a factor of approximately – 0.7. Where these negative correlations come from has to be determined in further experiments.

Elementary modes of chemical reaction networks

C. Wagner, R. Urbanczik, J. Stucki

Chemical reaction networks can be represented as graphs where the chemical compounds form the nodes of the network. The reactions are symbolized as links between the nodes. In metabolic networks these graphs have inputs and outputs in order to produce compounds for cell growth or to maintain cell function. Furthermore, metabolic networks are assumed to be in the steady state so that no accumulation of chemicals in the network occurs. In complex networks redundant pathways can produce the same output from different inputs. The identification of redundant routes in networks can be done by a very elegant method, the elementary mode analysis. It dissects the system into redundant-free sub-networks, the elementary modes. If one of the reactions of an elementary mode is inhibited the entire elementary mode gets deleted. Hence, if all elementary modes containing a given output are eliminated the network does not produce that output anymore. Considering a metabolic network of a parasite, this property can be used to identify a reaction, which eliminates all elementary modes for a selected output. If the output of the network is crucial for survival of the microorganism it gets killed. As an example we studied glycolysis in the bloodstream form of Trypanosoma brucei. It takes place in an organelle called glycosome. Glycose is used as input to the network and Pyruvate and Glycerol are exported. Thereby the network produces ATP. This network is well studied in literature and many inhibitors were developed. However, only a few inhibitors tested are able to abolish Glycolysis. With the elementary mode analysis most of the experimental results could be easily predicted. These encouraging results motivated us to start analyzing further networks. At present, we are investigating the fatty acid synthesis in the apicoplast of Plasmodium falciparum, the parasite, which causes malaria. The apicoplast has the advantage that it is plant derived. Many enzymes of the network are different from those in the human host and are therefore good targets for drug applications.

Original publications

1. R. Stoop, C. Wagner:
Scaling properties of simple limiter control.
Phys. Rev. Lett. 90 (2003), 154101-1 – 154101-4.

2. C. Wagner:
Nullspace approach to determine the elementary modes of chemical reaction systems.
J. Phys. Chem. B (2004), in press.

Book chapter

R. Stoop, M. Christen, J.-J. v.d.Vyver, A. Kern, C. Wagner:
“Properties of the control of noisy, stable and chaotic dynamics“.
Proceedings of the 11'th Workshop on the Nonlinear Dynamics of Electronic Systems 259-262, R. Stoop (Eds.), Studenten-Druckerei Universität Zürich, ISBN 3-03708-004-3, 2003.

4.2. Congress Invitations

Prof. Ulrich E. Honegger

12. European Congress on Obesity, Helsinki (Finland), May 29 – June 01, 2003;
Weight gain – a burden in psychopharmacology.

European Conference on Epilepsy, Lisbon (Portugal), October 12-16, 2003;
Roundtable Antiepileptics: Interactions.

Congress of Obesity of the AU-, D- and CH-Societies on Obesity, Salzburg (Austria)
October 16 – 19, 2003;
Pharmaka-induzierte Obesitas.

Prof. Hans-Uwe Simon

5th Course: Allergy and Immunology Update (AIU), Postgraduate course for allergologists/clinical immunologists with FMH-title and title candidates,Gstaad (CH), January 17 – 19, 2003;
Antihistamines: Antiinflammatory efficacy?

Expert Conference on the Use of IVIG, Bern (CH), February 14 – 15, 2003;
Modulation of apoptosis (controversial and corresponding in vitro results).

59th Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI), Denver (USA), March 7 – 12, 2003;
Introduction: Role of eosinophils in the gastrointestinal tract.

35th Annual Meeting of the Union Schweizerischer Gesellschaften für Experimentelle Biologie (USGEB), Davos (CH), March 19 – 21, 2003;
Calpain-1 regulates Bax and subsequent Smac-dependent caspase-3 activation in neutrophil apoptosis.

ERS Lung Science Conference, Taormina (I), March 28 – 30, 2003;
Targeting apoptosis in the control of allergic inflammation.

Swiss Society of Internal Medicine, Basel (CH), May 21 – 23, 2003;
Apoptose und Entzündung.

DFG, University of Rome, Cell Death Differ. – Workshop on “Programmed Cell Death”, Loveno di Menaggio (I), May 26 – 28, 2003;
Novel extracellular and intracellular key players of neutrophil apoptosis.

XXII. Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Plenary session 2, Paris (F), June 07 – 11, 2003;
Why do allergic diseases persist?

Workshop on the Development of Diagnostic Criteria and Research Tools for the Study of Idiopathic Hypereosinophilic Syndromes, Aspen (USA), June 24 – 25, 2003;
The lymphocytic form of the hypereosinophilic syndrome.

3rd International Eosinophil Symposium, Aspen (USA), June 26 – 29, 2003;
New pathogenic and therapeutic insights into eosinophilic diseases.

Annual Meeting, Swiss Society for Rheumatology, Bern (CH), August 28 – 29, 2003;
Apoptose und Entzündung.

International Symposium: Chronic inflammatory responses of the lung, Bern (CH), August 29, 2003;
Molecular mechanisms of inflammatory cell accumulation.

11th Euroconference on Apoptosis, Ghent (B), October 25 – 28, 2003;
Inflammation-associated cell cycle-independent block of apoptosis by survivin in terminally differentiated neutrophils.

EU Co-ordination and Strategy (COST) Action 844 MC meeting: Apoptosis and programmed cell death, Ghent (B), October 28 – 29, 2003;
Apoptosis of neutrophils.

Retreat, Institut für Allgemeine Pharmakologie und Toxikologie, Pharmazentrum Frankfurt der Uniklinik Frankfurt am Main, Rauischholzhausen (D), October, 29 - 31, 2003;
Survivin: A new anti-inflammatory drug target.

European Academy of Allergology and Clinical Immunology (EAACI) – Section E.N.T.-meeting & Interest Group: Infections & Allergy, Ghent (B), November, 15 – 18, 2003;
Anti – IL-5 and related treatment strategies.

Dr. Clemens Wagner

Complexity 2003, Aix-en-Provence, France, May 6 – 8, 2003;
The small world of fractal coupling.

Seminar at CIIT, Centers for Health Research, Department of Systems Biology, Chapel Hill, North Carolina, USA, October 20, 2003;
Analysis of biological networks.

Dr. Shida Yousefi

DFG, University of Rome, Cell Death Differ. – Workshop on “Programmed Cell Death”, Loveno di Menaggio (I), May 26 – 28, 2003;
From autophagy to apoptosis regulation: APG-5 and its role in apoptosis.

III-Bern 2nd International Summer School; Wilderswil (CH), Aug. 29 – Sept. 01, 2003;
ASP – a new player in apoptotic pathways.

Sibylla Martinelli

DFG, University of Rome, Cell Death Differ. – Workshop on “Programmed Cell Death”, Loveno di Menaggio (I), May 26 – 28, 2003;

Antiapoptosis mediated by the PI3K pathway in immature neutrophils.

4.3. Seminar Invitations

Dr. Kurt Baltensperger

Dept. Pharmacology, SUNY at Stony Brook, NY; Feb 28, 2003; guest of Dr. C. C. Malbon
Protein couples receptor localization: Insights from live cell imaging and image analysis.

Inst. für Infektionskrankheiten, University of Bern; April 4, 2003; guest of Dr. Yoeng-Delphine Bifrare and Dr. Stephan Christen
G-protein coupled receptor localization.

Dr. Sébastien Conus

Dept. of Medical Onkologie, University of Zurich, Colloquium in Applied Cancer Research; Dec. 10, 2003; guest of Dr. U. Zangemeister-Witke
Role of lysosomes in neutrophil apoptosis.

Prof. Ulrich E. Honegger

Symposium: Kombinationstherapien mit Psychopharmaka, Zürich, Jan 30, 2003;
1.5 Milliarden Jahre Cytochrom P450. Vom Einzeller zum Menschen.

Psychiatrie-Symposium, Bern, May 05, 2003;
Neuroleptika und QT_c-Verlängerung.

Phytopharmaka Tag, Bern, May 08, 2003;
Hypericum-extracts and depression.

AGFAM Fortbildungskurse Zürich, Sept 25, 2003, Nov 06, 2003, Nov 20, 2003 and Dec 04,2003;
Psychopharmaka und Rezeptvalildierung.

Neurologists continuation weekend, Sils-Maria (CH); Oct 03-05, 2003;
Neuro-Pharmacology.

Karin Kirschner

Hämatologisches Zentrallabor, Universität Bern; April 03, 2003; guest of Prof. Tobler
Erythropoietin promotes resistance to imatinib.

Prof. Hans-Uwe Simon

Institut für Sozial- und Präventivmedizin, University of Basel, Basel (CH); Jan. 14, 2003; guest of Dr. Birgit Kühn-Dibbert

Immunological principles in allergic diseases.
American Academy of Allergy Asthma & Immunology, 59th Annual Meeting, Denver (USA); March 10, 2003
Effector functions of eosinophils in allergic inflammation.

Institute of Internal Medicine and Pneumology, University of Palermo, Palermo (I); March 31, 2003; guest of Prof. A.M. Vignola
Regulation of neutrophil apoptosis and clinical implications.

Institute of Respiratory Pathophysiology, Italian National Research Council, Palermo (I); April 01, 2003; guest of Prof. A.M. Vignola
Neutrophil apoptosis: Roles of phosphatases, proteases and cytokines.

Department of Internal Medicine, Divisions of Hematology and Clinical Immunology/Allergology, University of Lausanne, Lausanne (CH); May 01, 2003; guest of PD Dr. F. Spertini and Dr. Tibor Kovacsovics
Immunological findings in hypereosinophilic patients.

Institute of Anatomy, University of Bern, Bern (CH); May 14, 2003; guest of Prof. P. Gehr
Novel extracellular and intracellular key players of neutrophil apoptosis.

VABILO NA ZNANSTVENI SEMINAR, Faculty of Pharmacy, University of Ljubljana, Slovenia; Sept. 12, 2003; guest of Prof. J. Kristl and PD Dr. I. Mlinaric
New key players controlling neutrophil apoptosis.

Dept. of Internal Medicine, Service d'immunologie et d'allergologie, University Hospital Geneva, Geneva (CH); Oct. 31, 2003; guest of Prof. J.-M. Dayer
Neutrophil apoptosis: The identification of new key players.

European Academy of Allergology and Clinical Immunology (EAACI) – Section E.N.T. – meeting & Interest Group: Infections & Allergy; Nov. 17, 2003
Meet the Professor III: IL-5, IL-5 receptors and anti – IL-5 treatment.

Prof. Erwin Sigel

Dept. of Organic Chemistry, University of Basel; Oct. 15, 2003;
Novel isolated plant compounds acting at $GABA_A$ receptors.

Dr. Stephan von Gunten

Bern Immunology Club, University of Bern, Sept. 25, 2003
Role of Siglecs in the regulation of apoptosis.

Dr. Shida Yousefi

Dept. of Medical Onkologie, University of Zurich, Colloquium in Applied Cancer Research; July 02, 2003; guest of Dr. U. Zangemeister-Witke
From autophagy to apoptosis regulation: APG-5 and its role in apoptosis.

Bern Immunology Club, University of Bern, Sept. 25, 2003

A new player in the mitochondrial death pathway.

4.4. Organization of Meetings and Courses

Dr. Kurt Baltensperger

Several introductions to LSM410 laser scanning microscope.

Several introductions to deconvolution and image analysis software.

Introduction to colocalisation software.

Prof. Harald Reuter

The International Human Rights Network of Academies and Scholarly Societies: Science in the service of human rights and international law, Monte Verità, Ascona, May 21-23, 2003

Prof. Erwin Sigel

4th Practical Course: “Functional Analysis of Living Cells”, Feb 24 – Feb 28, 2003

Prof. Hans-Uwe Simon

International Workshop on Programmed Cell Death and Apoptosis (together with E. Candi, D. Delia, K. Schultze-Ostoff, H. Walzak); Villa Vigoni, Loveno di Menaggio (I), May 26-28, 2003

Scientific symposium: Chronic inflammatory responses of the lung, Bern (CH), Aug 29, 2003

2nd III-Bern International Summer School; Wilderswil (CH), Aug 29 – Sept 01, 2003

Bern Immunology Club (together with the other founder members); Dept. of Pharmacology, University of Bern, one meeting in each month of 2003

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon

59th Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI); Session: “Eosinophil-associated gastrointestinal disorders”; Denver (USA), March 7–12, 2003.

15. Mainzer Allergie-Workshop, Deutsche Gesellschaft für Allergologie und Klinische Immunologie; Sitzung “Keratinozyten und Granulozyten”; Mainz (D), March 14-15, 2003.

Annual Meeting of the Swiss Society of Allergology and Immunology (SSAI); Session: “Allergology and Pneumology: United Airways”; St. Gallen (CH), March 27-28, 2003.

Deutsche Forschungsgemeinschaft, University of Rome, Cell Death Differ. – Workshop on “Programmed Cell Death”; Session: “Death pathways”; Loveno di Menaggio (I), May, 26-28, 2003.

XXII. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Main Symposium 19: “Novel Aspects of Immune Regulation”; Paris (F), June 07-11, 2003.

XXII. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Oral Abstract Session 12: “Inflammatory Cells”; Paris (F), June 07-11, 2003.

XXII. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Main Symposium 15: “Immunological Basis for Novel Treatments in Allergy”; Paris (F), June 07-11, 2003.

11th Euroconference on Apoptosis; Session 4: “Survival signalling and cell death control”; Ghent (B), Oct. 25-28, 2003.

European Academy of Allergology and Clinical Immunology (EAACI) – Section E.N.T. – meeting & Interest Group: Infections & Allergy; Plenary Session 4: “Remodelling: Does it exist in the nose?”; Ghent (B), Nov. 15-18, 2003.

4.6. Referee Work for Peer-Reviewed Journals

Prof. Ulrich E. Honegger

Biochemical Pharmacology
Life Sciences
Swiss Medical Weekly

Prof. Hartmut Porzig

J Neurochem
J Neurophysiol
Mol Pharmacol
N-S Arch Pharmacol
Pharmacol Ther

Prof. Erwin Sigel

Biochim Biophys Acta
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
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
Cytokine
DMW
Environm Toxicol
Eur J Immunol
Eur Respir J
Exp Dermatol
Hematologica
Int Arch Allergy Immunol
Int J Cancer
Int J Hyg Environ Health
J Allergy Clin Immunol
J Biochem Biophys Meth
J Clin Invest
J Hepatol
J Immunol
J Invest Dermatol
J Leukocyte Biol
J Pharm Pharmacol
Life Science
Oncogene
Proc Natl Acad Sci USA
Respiration
Swiss Med Wkly
Z ärztl Fortbild Qual.sich (ZaeFQ)

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

Prof. Hans-Uwe Simon

Swiss National Science Foundation (SNF)
Deutsche Forschungsgemeinschaft (DFG)
The Netherlands Organization for Scientific Research (NWO)
Medizinische Fakultät der Universität Tübingen, *fortüne*-Programm
Jubiläumsfonds Österreichische Nationalbank/OeNB, Wien
Landesstiftung Baden-Württemberg, Stuttgart
Philip Morris External Research Program, Linthicum Heights, Maryland, USA
The Wellcome Trust, London, UK
Medical Research Council (MRC)

Prof. Hartmut Porzig

Site visit evaluation of Pharmacology/Pharmacy at the University of Tartu/Estonia for the Estonian Research and Development Council, Talinn

4.8. Awards

Prof. Hans-Uwe Simon

Pfizer-Forschungspreis 2003

Dr. Shida Yousefi

Pfizer-Forschungspreis 2003

5. Administrative, Advisory, and Honorary Posts

Dr. Kurt Baltensperger

Operator of the Confocal Microscopy Facility of the Dept. of Clinical Research (located at the PKI) until August 31, 2003

Operator of the Image Analysis Facility of the Dept. of Clinical Research (located at the PKI) until August 31, 2003

Information Technology Coordinator at the PKI

Roland Baur

Coordinator for radioactive work at the PKI

Prof. Ulrich E. Honegger

Verantwortlicher für das Pharmaziestudium an der Universität Bern

Ortspräsident Pharmazie des BAG, Prüfungssitz 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

Chairman of OSC Examinations during 3rd year medical curriculum

Member of the working group: “Interfakultäre Graduate School” and Curriculum “Medizinische Biologie”

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

Member of the Külz-Preis Committee of the German Socienty for Experimental and Clinical Pharmacology and Toxicology

Prof. Harald Reuter

Member of the Advisory Board of the “Biocenter“, University of Basel

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“

Prof. Erwin Sigel

Biosafety Coordinator for the PKI

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)

Prof. Hans-Uwe Simon

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

Treasurer, European Cell Death Society (ECDO), since 2000

Member of the management committee, European Commission Research Area: structural aspects, COST action 844 “Apoptosis and programmed cell death: molecular mechanisms and applications in Biotechnology and Agriculture”, since 2000

Member of the Executive Committee of the European Academy of Allergology and Clinical Immunology (EAACI), until June 2003

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), since 2002

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

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

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

Dr. Clemens Wagner

Webmaster of the PKI

Dr. Shida Yousefi

Operator of the Confocal Microscopy Facility of the Dept. of Clinical Research (located at the PKI) since Sept 01, 2003

Operator of the Image Analysis Facility of the Dept. of Clinical Research (located at the PKI) since Sept 01, 2003

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 no charge. 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 a total of 31 different users with 13 different affiliations. It was in operation for approximately 550 hours. The facility for confocal microscopy and image analysis was operated by Dr. K. Baltensperger until August 31, 2003. Dr. S. Yousefi has fulfilled the function of the coordinator of this facility since September 01, 2003. Under the supervision of the coordinator, a whole team of qualified individuals provides training for new users, as well as technical and scientific support. The operator's time spent for the facility amounted to over 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

Evelyne and Gregor Kozlowski, Switzerland
Bern, May 08, 2003

Dr. Lorenzo Zala, Switzerland
Bern, Oct. 16, 2003

8. Sponsors

8.1. Research Grants

Dr. Kurt Baltensperger

Swiss National Science Foundation (grant No. 31-059124.99)
Schweizerische Krebsliga (together with H. Porzig, grant No. SKL 778-2-1999)
Novartis Stiftung für Biologisch-Medizinische Forschung

Prof. Ulrich E. Honegger

GlaxoSmithKline
Zeller Medical AG, Romanshorn (CH)

Prof. Hartmut Porzig

Schweizerische Krebsliga (together with K. Baltensperger, grants No. SKL 778-2-1999, OCS-01404-08-2003)
Sandoz Foundation, Basel (CH)
Stiftung zur Förderung der wissenschaftlichen Forschung an der Universität Bern
Jubiläumsstiftung der Schweizerischen Mobiliar Genossenschaft

Prof. Erwin Sigel

Swiss National Science Foundation (grant No. 31-64789.01)
Contribution by EVOTECOAI
Desirée and Niels Yde Stiftung

Prof. Hans-Uwe Simon

Swiss National Science Foundation (grant No. 31-58916.99)
OPO-Foundation, Zurich (CH)
Bernische Krebsliga (together with S. Yousefi)
Sassella-Foundation, Zurich (CH) (together with U. Zangemeister-Wittke)
Bonizzi-Theler-Foundation, Luzern (CH) (together with S. von Gunten)
Kurt- und Senta-Herrmann-Foundation, Vaduz (FL) (together with S. von Gunten)

Dr. Stephan von Gunten

Bonizzi-Theler-Foundation, Luzern (CH) (together with H.-U. Simon)
Kurt- und Senta-Herrmann-Foundation, Vaduz (FL) (together with H.-U. Simon)

Dr. Clemens Wager

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

Dr. Shida Yousefi

Swiss National Science Foundation (grant No. 31-068449.02)
Bernische Krebsliga (together with H.-U. Simon)

8.2. Meetings

Alexis Corporation, Lausen
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

Allergomed, Therwil
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

AstraZeneca AG, Zug
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

Becton Dickinson Biosciences, Allschwil
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

BioConcept AG, Allschwil
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

European Academy of Allergology and Clinical Immunology (EAACI)
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

Essex Chemie AG, Luzern
International Symposium: Chronic inflammatory responses of the lung, Bern, August 29, 2003

Labforce AG, Nunningen
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

Lucerna Chem AG, Luzern
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

Max und Elsa Beer-Brawand-Fonds, University of Bern
International Symposium: Chronic inflammatory responses of the lung, Bern, August 29, 2003

Miltenyi Biotec GmbH, Bergisch-Gladbach (D)
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

Union of the Swiss Societies of Experimental Biology (USGEB)
III-Bern 2nd International Summer School, Bern, August 29 – September 01, 2003

8.3. Travel Support

USGEB
Support of Karin Kirschner, ISEH Meeting Paris, July 2003
Support of Anton Vichalkovski, FASEB Workshop Spetsai, Greece, August 2003

German Society of Pharmacology and Toxicology (DGPT)
Support of Karin Kirschner, Spring meeting of the DGPT

COST: EU action 844 - Switzerland
Support of Dr. Shida Yousefi, ECDO meeting in Ghent, October 2003
Support of Sibylla Martinelli, ECDO meeting in Ghent, October 2003

8.4. Other Support

Bürgi fund
Seminar series of the institute

Roche Pharma (Schweiz) AG, Reinach (CH)
Printing costs for the first announcement of the 4. Biennial Congress of the International Eosinophil Society (Bern, May 26-29, 2005).
http://www.cx.unibe.ch/pki/Eos2005

ZLB Bioplasma AG, Bern (CH)
Reprints costs for the following publications: Allergy 58 (2003), 543-552, and J. Allergy Clin. Immunol. 112 (2003), 1185-1190.