Annual Report 2002

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 zweite umfassende Jahresbericht des Pharmakologischen Instituts der Universität Bern. Die Pharmakologie hat eine Brückenfunktion zwischen biologischer Grundlagen- und klinischer Forschung. Das Pharmakologische Institut ist deshalb sehr an Kontakten zu den Kliniken des Inselspitals und zu anderen Forschungseinrichtungen der Universität Bern interessiert. Damit wollen wir helfen, die klinische Forschung sowie die 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.

Das Jahr 2002 war für die Lehrtätigen unseres Instituts vor allem mit der Umsetzung der Studienreform im 3. Studienjahr Medizin verknüpft. Seit Wintersemester 2001/2002 ist das neue System „Problem-based Learning (PBL)“ im Einsatz. Die Realisierung dieses Projektes war ein voller Erfolg, an dem die Dozenten des Pharmakologischen Instituts stark beteiligt waren. In der Kerngruppe zur Planung und Umsetzung des PBL-Systems ist Herr Prof. Porzig, als Pharmakologie-Fachvertreter in den einzelnen Themenblöcken sind die Herren Proff. Honegger, Porzig, Sigel und Simon vertreten. Ausserdem erarbeiteten die Dozenten des PKI gemeinsam mit Dozenten von Pharmakologischen Instituten anderer Universitäten einen gesamt-schweizerischen Lernzielkatalog für Pharmakologie. Die Ausbildung der Zahnmedizinstudenten in Pharmakologie erfolgte weiterhin im klassischen Stil (verantwortlich: Herr Prof. Stucki). Herr Prof. Honegger agierte als Ortspräsidenten für Pharmazie des BAG und sicherte in dieser Eigenschaft die Möglichkeit des Pharmaziestudiums an der Universität Bern in den unteren 4 Semestern ab.

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. Dazu kommen zusätzliche Bildungsangebote in Form eines Praktischen Kurses (Prof. Sigel) und einer Summer School (Prof. Simon), die beide aus eigenen finanziellen Mitteln bzw. Sponsorengeldern bestritten werden. Im Institut arbeiten gegenwärtig 14 DoktorandInnen.

Die Mitarbeiter und Mitarbeiterinnen des Pharmakologischen Instituts publizierten in 2002 insgesamt 22 Originalarbeiten sowie 11 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ über 90). MitarbeiterInnen des Pharmakologischen Instituts wurden zu insgesamt 35 Vorträgen bzw. Seminaren eingeladen. Frau Dr. Sabine Baumann erhielt den Bürgi-Preis für Ihre Dissertationsschrift (Betreuer: Prof. Sigel). Gegenwärtig werden 4 Mitarbeiter mit namhaften Beiträgen des Schweizerischen Nationalfonds unterstützt. Zahlreiche Persönlichkeiten besuchten das Institut und hielten Forschungsseminare. Der Berner Immunologie-Club wurde gegründet und trifft sich einmal pro Monat im PKI. Ein gemeinsam mit PD Dr. Th. Brunner (Institut für Pathologie) organisierter Apoptose-Kongress zog über 200 Teilnehmer aus dem In- und Ausland an. Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Auch im letzten Jahr gelang es, die Infrastruktur des Instituts wesentlich zu verbessern. Mit Hilfe des Kantons Bern, der Universität Bern und der Medizinischen Fakultät wurde unser Haus innen renoviert sowie dringend benötigte Forschungsinstrumente angeschafft. Damit haben sich die Arbeits- und Lebensbedingungen für die Mitarbeiter und Mitarbeiterinnen des PKI in den letzten zwei Jahren wesentlich verbessert. Unser Dank wurde mit einer Akademischen Feier, an der auch der Rektor und der Dekan der Medizinischen Fakultät anwesend waren, zum Ausdruck gebracht. Die Akademische Rede hielt Herr Professor M. Bickel, ehemaliger Direktor des PKI, der die Geschichte unseres Instituts interessant und übersichtlich zusammenfasste. Ebenso führten wir einen „Tag der offenen Tür“ durch, um die Kommunikation zwischen Wissenschaftlern und Öffentlichkeit zu fördern. Dazu dienen auch regelmässig stattfindende Vernissagen, die viele Gäste in das PKI lockten.

Ich danke allen Mitarbeitern und Mitarbeiterinnen für ihren Einsatz, welcher auch im Jahr 2002 zu einer Bilanz beitrug, die internationalen Massstäben gerecht wird. Ebenso danke ich allen Sponsoren und Freunden des Instituts.

Prof. Dr. med. Hans-Uwe Simon Bern, Februar 2003
Direktor

1.2. Foreword

This is the second comprehensive report of the Department of Pharmacology of the University of Bern. Pharmacology fulfils functions in both basic biological science and clinical research. The Department of Pharmacology wants to succeed in both areas and is therefore very much interested in intense contacts to the clinics of the University Hospital (Inselspital) as well as to the different research institutes of the University of Bern. We hope aim at strengthening 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.

The year 2002 was, at least for the teaching staff of our institute, associated with the practical implementation of the new “Problem-based Learning (PBL)”-system for medical students in their third study year. The actual realisation of this project was a great success, in which the permanent members of the institute contributed in a significant manner. 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 established, together with colleagues from the other Swiss universities, a catalog, which defines the learning objectives in Pharmacology for medical students. The teaching of dental medical students in Pharmacology was performed in the classical style. Responsible teacher here is Prof. Stucki. Prof. Honegger, the local president of the Pharmacy society, coordinated the undergraduate study in Pharmacy at the University of Bern.

Another important teaching activity is demanded 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 own financial resources and/or with the help of sponsors. Currently, 14 PhD and MD graduate students work at the PKI.

In 2002, the scientific staff of the Department of Pharmacology published 22 original and 11 review articles in international peer-reviewed journals (the sum of the “impact factors” is greater than 90). Co-workers of the institute were invited to 35 lectures or seminars. Dr. Sabine Baumann received the Bürgi prize for her outstanding doctoral

thesis (supervisor: Prof. Sigel). Four 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) was founded and meets monthly at the PKI. An international congress on Apoptosis with more than 200 participants was organized together with PD Dr. Th. Brunner (Department of Pathology). In conclusion, research plays an important role at the PKI and is performed at a high level.

The infrastructure has greatly improved in the last year. With the help of the Canton Bern, the University of Bern, and the Medical Faculty, the building was internally renovated as well as equipped with urgently needed research instruments. Thus, working and living conditions have significantly improved within the last two years. We expressed our appreciation for this great help with the organization of an academic celebration (= Akademische Feier), in which also the Rector and the Dean of the Medical Faculty were active participants. The academic speech about the history of our institute was delivered by Prof. M. Bickel, one of the former PKI directors. We also organized a “day of the open door” to promote communication between scientists and people not working in the field. The organization of art exhibitions within our institute is another effort with the same goal.

I thank all co-workers for their hard work that contributed to the success of the PKI in 2002. I also thank all the sponsors and friends of the institute.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, February 2003

2. Staff 2002

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

Frank Altznauer, PhD student (until September 2002)
Dr. Kurt Baltensperger, PhD
Roland Baur, head technician
Ralf Baumann, PhD student (until September 2002)
Dr. Sabine Baumann, PhD* (until June 2002)
Dmytro Berezhnoy, PhD student
Dr. Sibylle Bürgi, PhD
Dr. Sébastien Conus, PhD*
Kristien De Cock, PhD student* (until September 2002)
Gian Marco De Marchis, MD student*
Karin Kirschner, PhD student
Ivana Kotevic, PhD student*
Evelyne Kozlowski, technician
Sibylla Martinelli, PhD student*
Dr. Frédéric Minier, PhD*
Susanne Probst, technician
PD Dr. Claes Ruedeberg, PhD, consultant*
Inès Schmid, head technician
Ekaterina Vassina, PhD student
Anton Vichalkovski, PhD student*
Dr. Clemens Wagner, PhD
Raphael Wirth, MD student*
Adrian Wirz, PhD student*
Karl Wittwer, MD 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*
PD Dr. Stefan Mühlebach, PhD*
PD Dr. Peter Späth, PhD*
PD Dr. Uwe Zangemeister-Wittke, PhD*
PD Dr. Roger D. Zühlke, PhD*

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
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 07, 2002	Prof. Hartmut Porzig	Antiarrhythmika
Jan 31, 2002	Prof. Hartmut Porzig	Wirkungsmechanismen der Diuretika
April 15, 2002	Prof. Erwin Sigel	Aktivierung und Inaktivierung von Xenobiotica (2h)
April 29, 2002	Prof. Ulrich Honegger	Antiepileptika
May 08, 2002	Prof. Hans-Uwe Simon	Immunologische Grundlagen allergischer Reaktionen
June 17, 2002	Prof. Ulrich Honegger	Angriffspunkte und Wirkungsmechanismen von Psychopharmaka
June 27, 2002	Prof. Ulrich Honegger	Der alte Patient: Pharmakologie und Therapie
July 01, 2002	Prof. Hans-Uwe Simon	Immunmodulation
July 04, 2002	PD Dr. Peter Späth	Arzneimittelentwicklung
Oct 22, 2002	Prof. Hans-Uwe Simon	Pharmakodynamik (I)
Oct 31, 2002	Prof. Hartmut Porzig	Pharmakodynamik (II)
Nov 04, 2002	Prof. Ulrich Honegger	Pharmakokinetik (I)
Nov 05, 2002	Prof. Ulrich Honegger	Pharmakokinetik (II)
Nov 14, 2002	Prof. Hans-Uwe Simon	Entzündungshemmung
Nov 28, 2002	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Dec 05, 2002	Prof. Hartmut Porzig	Thromboembolie, Thrombophilie, antithrombotische Therapie (II)
Dec 12, 2002	Prof. Hartmut Porzig	Pharmakologie des sympathischen Nervensystems
Dec 12, 2002	Prof. Hartmut Porzig	Wirkprinzipien von Antihypertonika

Dec 19, 2002	Prof. Hartmut Porzig	Vasoaktive und antianginöse Substanzen

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

Date	**Lecturer**	**Title of the lecture**
Jan 07, 2002	PD Dr. Armand Cachelin	Starke Analgetika
Jan 09, 2002	PD Dr. Roger D. Zühlke	Lokalanästhetika (I)
Jan 14, 2002	PD Dr. Roger D. Zühlke	Lokalanästhetika (II)
Jan 16, 2002	PD Dr. Roger D. Zühlke	Insulin, Orale Antidiabetika
Jan 21, 2002	Prof. Erwin Sigel	Anxiolytika, Hypnotika
Jan 23, 2002	Prof. Ulrich Honegger	Psychopharmaka
Jan 28, 2002	PD Dr. Armand Cachelin	Immunsuppressiva
Jan 30, 2002	Prof. Ulrich Honegger	Antihistaminika
Feb 04, 2002	Prof. Erwin Sigel	Antikoagulantien, Plättchenhemmer
Feb 06, 2002	Prof. Ulrich Honegger	Lokale Präparate
Feb 11, 2002	PD Dr. Stefan Mühlebach	Antibiotika (I)
Feb 13, 2002	PD Dr. Stefan Mühlebach	Antibiotika (II)
Feb 18, 2002	PD Dr. Stefan Mühlebach	Antibiotika (III)
Feb 20, 2002	Prof. Jörg Stucki	Repetitorium
Nov 04, 2002	Prof. Jörg Stucki	Rezeptoren, Signalwege
Nov 06, 2002	Prof. Jörg Stucki	Dosis-Wirkungskurven
Nov 11, 2002	Prof. Jörg Stucki	Antagonisten
Nov 13, 2002	Prof. Jörg Stucki	Barrieren, Absorption, Verteilung
Nov 18, 2002	Prof. Jörg Stucki	Bioavailability, Ausscheidung
Nov 20, 2002	Prof. Jörg Stucki	Arzneimittelmetabolismus
Nov 27, 2002	Prof. Jörg Stucki	Gesamtkinetik, Dosierung

Dec 02, 2002	Prof. Jörg Stucki	Toleranz, Abhängigkeit
Dec 04, 2002	Prof. Jörg Stucki	Chronopharmakologie
Dec 09, 2002	Prof. Jörg Stucki	Ergänzungen, Repetitorium
Dec 11, 2002	Prof. Erwin Sigel	Schwache Analgetika (I)
Dec 16, 2002	Prof. Erwin Sigel	Schwache Analgetika (II)
Dec 18, 2002	Prof. Erwin Sigel	Antikoagulantien, Plättchenhemmer

Lectures for students of the Natural Sciences Faculty

Date	Lecturer	Title of the lecture
May 08, 2002	Prof. Hans-Uwe Simon	Immunologische Grundlagen allergischer Reaktionen

3.2. Coordination PBL Medical Students, 3. year (2002/2003)

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 2002/2003)

Medical students 3. year:
Dr. Sibylle Bürgi
Prof. Ulrich E. Honegger
Prof. Erwin Sigel*
Prof. Hans-Uwe Simon
Dr. Shida Yousefi*
PD Dr. Uwe Zangemeister-Wittke*

*double tutorials

3.4. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan 16, 2002	Prof. Dr. K. Ammann University of Bern	Von der Hexensalbe zur modernen Kräutertherapie
Jan 23, 2002	Prof. Dr. P. Hoffmann Novartis AG	Arzneimittelentwicklung im 3. Millenium: Gegenwärtige Trends und zukünftige Entwicklungen
Jan 30, 2002	Prof. Dr. B. Meier Firma Zeller AG	Von der „Droge“ zum klinisch geprüften Phytopharmakon
Feb 13, 2002	Dr. K. Berger Büter University of Basel	Von der Wildpflanze zur massgeschneiderten Heilpflanze
Feb 27, 2002	Prof. Dr. R. Brenneisen University of Bern	Vom Hanfkissen zu endogenen Cannabinoiden – Renaissance einer potenten Medizinalpflanze
June 19, 2002	Dr. P. Mäser University of Bern	Genomic and functional analyses of K^+ transporters in plants
June 26, 2002	Prof. Dr. R. Dummer University of Zurich	Malignome der Haut als Modell-erkrankungen für innovative Tumortherapie
Sept 4, 2002	Dr. P. Schwarb Bitplane AG, Zurich	Life Science is Moving
Oct 02, 2002	Prof. Dr. A. Matus Friedrich-Miescher Inst.	Live cell imaging of synaptic plasticity in central nervous system circuits
Oct 23, 2002	Dr. P. Gönczy ISREC	Spindle positioning during asymmetric division of C. elegans embryos
Nov 12, 2002	Prof. G. B. Mills University of Texas	Linking genomics to therapeutics: The phosphatidylinositol 3 kinase pathway as a target in cancer
Nov 20, 2002	Prof. Dr. H. Vogel EPFL	Bioanalytics on the micro- and nanometer scale: Probing the function Of neuroreceptors
Nov 27, 2002	Prof. Dr. S. Gasser University of Geneva	Monitoring chromatin dynamics in yeast: functional chromosome anchorage sites

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. Academic Degrees

Raphael Wirth, Dr. med.
Thesis: „Zellkulturen als Testmodelle für Diagnose und Pathophysiologie, am Beispiel von kultivierten Hautfibroblasten einer Patientin mit Verdacht auf Albright hereditäre Osteodystrophie."
University of Bern, December 2002

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Ulrich E. Honegger

Group members: Dr. Sibylle Bürgi, PhD
Adrian Wirz, PhD student
Raphael Wirth, MD student
Gian-Franco De Marquis, MD student
Susanne Probst, technician
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 pharmacology of plant extracts. Studies are performed in *in vitro*-systems including cultured cells and brain slices of rats. Beside of this main research line we are using fibroblasts cultured from skin biopsies of patients to investigate signal pathways as a diagnostic mean. Cell culture models are also used for the study of COX-inhibitory properties of plant extracts and for the investigation of the kinetic behaviour of lipophilic, persistent polyhalogenated compounds.

A closer look to the antidepressant-induced mechanism of □-adrenoceptor downregulation

S. Bürgi, K. Baltensperger, U.E. Honegger

Long term use of most antidepressants leads to a reduction in the number of functional □□adrenoceptors in the central postsynaptic membranes and in cultured cells. The effect timely coincides with the clinical improvement of depressive symptoms in humans. The exact mechanisms of □□adrenoceptor down-regulation is currently unknown. We have previously shown that chronic exposure of cultured rat astrocytoma cells to antidepressants impair cellular phospholipid (PL) metabolism and specifically change membranous PL-composition. The aim of this study was to investigate whether the drug-induced changes in the membrane properties could influence □□adrenoceptor endocytosis and recycling. An increased rate of receptor endocytosis and/or an inefficient receptor recycling could cause a reduced □□adrenoceptor density on the surface of chronically tricyclic antidepressant-treated astrocytoma cells. To detect drug-induced changes in □□adrenoceptor endocytosis and recycling not only in radioligand binding studies but also by laser scanning confocal microscopy, a □1□adrenoceptor – green fluorescent protein (□1□□R-GFP) fusion construct was stably expressed in astrocytoma cells. Confocal fluorescence microscopy revealed that in antidepressant-treated cells agonist-induced □1□□R-GFP internalization was no longer reversible in contrast to internalized receptors in untreated control cells. Since the recycling of transferrin receptors was not altered in antidepressant treated cells we could conclude that drug-induced changes in □□-adrenoceptor recycling were receptor specific and not a consequence of an

impaired general membrane recycling. A closer look to the □□-adrenoceptor molecule in antidepressant-treated cells revealed changes in the amount of phosphorylation and glycosylation which might interfere with recycling. It is our current and future interest to investigate the role of these molecular changes for recycling and thus down-regulation.
See original publication No. 2.

Chronic antidepressant-induced changes in recycling of serotonin receptor subtypes
A. Wirz, S. Bürgi, U.E. Honegger
From our studies on antidepressant-induced alterations in the recycling of □1□-adrenoceptors we know that this phenomenon is rather receptor-specific than a general one. From *in vivo*-studies with serotonin receptors it has been shown that the 5-HT2 subtype is down-regulated following chronic antidepressant treatment while number and characteristics of the 5-HT1 subtype are not affected by the antidepressant drug treatment. In analogy to the □1□-adrenoceptor – green fluorescent protein fusion construct we transfected COS and HEK cells transiently and astrocytoma cells permanently with 5-HT2 receptors-GFP fusion constructs. In addition fluorescent 5HT1 constructs will be transfected as well. This should allow us to study functionality and trafficking of these receptor types 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 molecular alterations such as phosphorylation or glycosylation.

Pharmacology of St.John's wort (hypericum perforatum) extracts, their fractions and individual constituents
S. Probst, C. Ruedeberg, U.E.Honegger
St. John's wort extracts are widely and successfully used in the treatment of mild and moderate forms of depression. *In vitro*-test systems are routinely used in our laboratory to investigate antidepressant effectiveness. A model to simulate the acute effects of antidepressant compounds on neurotransmitter reuptake is the use of freshly prepared rat brain slices. The constantly oxygenated slices are incubated with radioactively labelled 3H-norepinephrine or 3H-serotonin in the presence and the absence of hypericum extract, extract-fractions and individual compounds of it, such as hypericine or hyperforine. 10 □□ imipramine is used as a measure for 100% inhibition of uptake. The extracts showed a dose-dependent inhibition of neurotransmitter uptake which was equally efficient in the case of serotonin but less efficacious for norepinephrine. It was of interest to see that both purified compounds, suspected to be part of the active principle were without any effect on neurotransmitter uptake. Fractions of the whole extract were the more potent the more apolar the contents were. A very similar result was seen when chronic effects were investigated on down-regulation of □□adrenoceptors of extract-exposed astrocytoma cells. The plant extracts, their fractions and the individual compounds 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 investigate fractions of an alcoholic St. John's extract that are either highly enriched with or depleted of hyperforine in our *in vitro*-systems to test for antidepressant effectiveness. Hyperforine, a major constituent of St. John's wort is

known for its high inducing potency of metabolic enzymes, its antidepressant activity, however, is still a matter of controversy.

Cultured skin fibroblasts of a patient with an Albright syndrome (Albright hereditary osteodystrophy, AHO) as a mean to localise the molecular impairment of the G protein-dependent cAMP formation

R. Wirth, U.E. Honegger

(Collaboration with Prof. Dr. U. Wiesmann, Children Hospital Bern)

AHO patients are characterised by a form of hypoparathyreoidism which involves an impaired formation of cAMP following the stimulation of PTH. Since these patients suffer from multiple symptoms indicating a general defect that influences many physiological functions we assumed a possible fault at the level of the G-protein. Skin fibroblasts were extensively used in our laboratory to investigate β-adrenoceptor-dependent cAMP formation, we studied this signal pathway in cells of an AHO-patient. We compared the cAMP-response in cultured skin fibroblasts of the patient with that of a sex and age-matched healthy person. cAMP-formation following isoprenaline stimulation was drastically reduced in the patient's cells compared to that in the control fibroblasts. The same was true for the prostaglandin-E2 stimulated cAMP-formation. It was, however, of interest to see that adenylyl cyclase activity was more responsive to the direct enzyme stimulation by forskoline. Thus cAMP-formation in cells of AHO patients seems to be affected by a general impairment of the stimulating G-protein.

See M.D.-thesis of R. Wirth, accepted in December 2002 by the University of Bern

Cellular kinetics of persistent compounds with endocrine effectiveness

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

(Collaboration with PD Dr. S. Mühlebach, Kantonsspital Aarau)

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 will be 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 publications

1. R. Styger, U.N. Wiesmann, U.E. Honegger:
Plasmalogen content and □□adrenoceptor signalling in fibroblasts from patients with Zellweger syndrome. Effects of hexadecylglycerol.
Biochim. Biophys. Acta 1585 (2002), 39-43.

2. S. Bürgi, K. Baltensperger, U.E. Honegger:
Antidepressant-induced switch of □$_1$□adrenoceptor trafficking as a mechanism for drug action.
J. Biol. Chem. 278 (2003), 1044-1052.

Review articles

1. U.E. Honegger, C. Reinke:
Johanniskraut – State of the Art.
SAZ 18 (2002), 608-614.

2. U.E. Honegger:
Ayurveda, nur ein momentaner Trend.
Gesundheit Sprechstunde 21 (2002), 35.

Book chapter

1. A. Seidenberg, U.E. Honegger:
Heroin: Ein Opioid mit besonderen Eigenschaften.
In: "Ärztliche Verschreibung von Betäubungsmitteln". Bundesamt für Gesundheit, Schweiz. Verlag Hans Huber, Bern, Göttingen, Toronto, Seattle, 2002, p. 247-260.

Group Prof. Hartmut Porzig

Group members: Dr. Kurt Baltensperger, PhD[1]
Karin Kirschner, PhD student
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

Typically, leukemic cells are resistant towards physiological signals inducing terminal differentiation in hematopoietic cells because they have acquired a mechanism providing autonomous and irreversible stimulation of cell proliferation. One such mechanism is the induction of BCR/ABL tyrosine kinase activity in chronic myelogenous leukemia (CML) generated by a chromosome translocation. This kinase permanently promotes cell division by stimulating key intermediates within the signaling pathway of cytokine growth factors. In the current project, we investigate novel mechanisms allowing BCR/Abl expressing leukemic cells (K562) to aquire resistance against imatinib mesylate (Gleevec), a highly successful specific inhibitor of the BCR/Abl kinase. Currently, this drug is the mainstay of CML therapy. It appears that the development of resistant K562 clones results from a partial reestablishment of erythropoietin sensitivity in the imatinib-treated cells. There is no recovery of sensitivity towards other cytokines. Erythropoietin promotes cell survival and inhibits apoptotic cell death. This prolonged survival of leukemic cells favors the accumulation of imatinib-resistant mutants. Our studies show that endogenous serum erythropoietin levels are sufficient to generate a significant increase in the number of resistant cell clones.

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

A. Vichalkovski, H. Porzig

While hematopoietic progenitor cells express more than ten different G protein-coupled receptors, the functional role of these receptors in cell development has remained obscure. We focus on signaling mechanisms linked to receptors for SDF-1 and thrombin because both agonists are already known to modulate growth responses in some cell types possibly via pathways including protein kinase C (PKC) and/or the small GTPase Rho. Thrombin has been shown to inhibit erythropoietin (Epo) and stem cell factor (SCF)-dependent cell proliferation, while SDF-1 was reported to enhance hematopoietic cell growth. Based on our previous experience we currenly explore to what extent the cytokines TPO, SCF, IL-3, GM-CSF and Epo affect the function of thrombin and SDF-1 during lineage commitment and differentiation of erythroid and granulocyte/macrophage differentiation. Multipotent hematopoietic progenitors that carry the CD34 antigen and that we isolate from peripheral blood (in cooperation with the Department of Hematology, University of Bern) or from cord blood (in cooperation with the Woman's Hospital, University of Bern) are kept in suspension culture and grow in the presence of different cytokine combinations. In parallel to the described studies in primary cells which are usually in short supply, we are using established hematopoietic cell lines (HEL, MB-02, HL-60) to study specific aspects of SDF-1 mediated signal transduction. ^{14}C-Thymidine incorporation studies in suspension cultures of primary cells after a standardized starvation protocol, suggest that SDF-1 exerts its growth promoting effect exclusively via a G protein of the G_i family and the small GTPase RhoA, but, surprisingly, unlike most cytokines and G protein-coupled receptor ligands, does not seem to target PKC. Early progenitors growing in the presence of stem cell factor(SCF), thrombopoietin (TPO) and interleukin-3 (IL-3) show strong SDF-1 responses while thrombin affects almost exclusively erythropoietin-dependent terminally differentiating cell populations in spite of the fact that functional thrombin and CXCR4 receptors seem to be present in multipotential as well as in erythroid cells. The growth-

promoting effect of SDF is largely, but not completely additive to the growth stimulating effect of cytokines (SCF, IL-3, GM-CSF). Nevertheless, first experiments with pharmacological inhibitors suggest that intracellular signal transduction pathways differ depending on whether or not SDF-1 stimulation occurs in the presence or absence of a co-stimulating cytokine.

Immunohistochemical analysis of sodium/calcium exchanger expression in rat hippocampus cultures

H. Porzig

(Collaboration with K.D. Philipson, UCLA, Los Angeles, CA)

Na^+/Ca^{2+} exchange activity is known to be expressed throughout the brain in both glial and neuronal tissue. mRNA of all three major subtypes of the mammalian Na^+/Ca^{2+} exchanger protein (NCX1, NCX2, NCX3) has been detected in most brain areas, albeit at varying densities. However, for lack of subtype specific labels, the cellular expression pattern of this transport protein has remained largely unknown. We have used three subtype-specific antibodies, two monoclonal and one polyclonal, to identify the cellular distribution of the exchanger subtypes in rat hippocampus cell cultures. Surprisingly, we found little overlap for the expression of this membrane protein in different cell types. NCX1 labeled almost exclusively the membranes of neuronal cells and their associated dendritic network. It was found in nearly all neuronal cells of the population growing in culture. NCX2 was predominantly localized in various types of glia cells. Only occasionally it was detected in membranes of neuronal cell bodies but never in the dendritic network. In addition to labeling membranes, the NCX2 antibody strongly cross-reacted with an unidentified glial fibrillar protein. NCX3 expression appeared very low in hippocampus cultures and was restricted to a small subpopulation of neuronal cells. It was never detected in glia cells. Our results provide novel information on the cell-specific expression of the three Na^+/Ca^{2+} exchanger subtypes (NCX1, NCX2 and NCX3) in mammalian brain. These data may reflect functional differences among the subtypes that are not obvious from studies in recombinant cell lines and hence, may help to understand the functional role of specific glia-associated Ca^{2+} transport systems.

See original publications Nr. 2 and 3.

Remodeling of the Na^+-Ca^{2+} exchange activity in rat cardiac myocytes after infarction

A.M. Gomez, B. Schwaller, H. Porzig, G. Vassort, E. Niggli, M. Egger

(Collaboration with E. Niggli, Dept. of Physiology, University of Bern, and B. Schwaller, Dept. Histology and General Embryology, University of Fribourg)

Hypertrophied and failing cardiac myocytes show prolonged $[Ca^{2+}]_i$ transients. While it is widely accepted that the sarcoplasmic reticulum (SR) Ca^{2+} pump function is decreased in hypertrophied myocytes, the possible involvement of the Na^+-Ca^{2+} exchange (NCX) in the $[Ca^{2+}]_i$ transient lengthening remains uncertain. The cardiac NCX is one important mechanism for Ca^{2+} extrusion and cell relaxation, together with the SR Ca^{2+} pump. We analyzed the NCX function in rat ventricular myocytes 5-6 months after experimental myocardial infarction, produced by left coronary artery ligation in rats. Caged Ca^{2+} was dialyzed into the cytoplasm via a patch-clamp pipette and released by flash photolysis to activate NCX and measure the associated current (I_{NaCa}), while $[Ca^{2+}]_i$ changes were simultaneously recorded with a confocal microscope. Cells from post-myocardial infarction (PMI) rats had a 2.2 fold larger membrane surface and a more marked (about 2.75 fold) myocyte volume increase compared to sham-operated animals (SO). I_{NaCa} density activated by $[Ca^{2+}]_i$ jumps of

comparable amplitudes was significantly higher in myocytes from PMI rats (263.9%). This increase was also reflected at the level of total NCX protein expression, where values were higher (180±11% of control) in PMI myocytes. Surprisingly, although the I_{NaCa} in PMI cells was larger, the Ca^{2+} transport rate was maintained. Interestingly, PMI and SO myocytes presented virtually identical NCX Ca^{2+} transport rates per cell volume. We conclude that the increase in NCX density may constitute an adaptive response rather than a causal change, intended to maintain the required Ca^{2+} extrusion from a larger volume, to allow for adequate relaxation.
See original publication Nr. 1.

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

A. Canitano, P. Castaldo, S. Sellitti, A. Amoroso, H. Porzig, M. Taglialatela, M. Papa, L. Annunciato
(Collaboration with the Dept. of Neurosciences, University Frederico II, Naples, Italy)

Differential tissue expression of the genes encoding for the Na^+/Ca^{2+} exchanger isoforms NCX1, NCX2 and NCX3 is studied in rat brain using isoform-specific riboprobes and antibodies. The isoforms were detected using *in situ* hybridization (ISH), immunohistochemistry (IHC), confocal laser microscopy and immunogold electron microscopy. In the cerebral cortex ISH and IHC showed that NCX1 and NCX2 expression levels are generally higher than the one of NCX3. In the hippocampus the granular cell layer of the dentate gyrus and the pyramidal cells of CA1-CA4 subfields show high expression levels of the 3 transcripts and proteins. Within the hypothalamus, high expression levels of NCX1 and NCX2 are found in the ventromedial nucleus. In this region, the group 1 metabotropic glutamate receptor stimulation is coupled to the activation of NCX current.. NCX2 transcripts are selectively expressed in the hypothalamic tuberomammillary nucleus. The cerebellum shows the largest density of NCX1, NCX2 and NCX3 positive cells. Confocal microscopy shows that NCX3 does not co-localize with the presynaptic marker synaptophysin suggesting that this isoform is not prominently involved in neurotransmitter release reactions.

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

I. Kotevic, K. Baltensperger

Our studies focus on the role of G_{16}, a G protein exclusively expressed in hematopoietic cells. When expressed as a constitutively active mutant, this G protein appears to provide a strong differentiating signal, as demonstrated earlier in the leukemia cell line, MB-02. In the past year we have invested considerable effort into the examination of one of the potential candidate G protein coupled receptors coupling to G_{16}. Stable MB-02 cell lines were established that express a fusion of the P_{2Y2} purinoceptor and green fluorescent protein (GFP) to aid further experiments to define G_{16} signaling. Functional analysis of UTP-induced intracellular Ca^{2+}-changes showed that the P_{2Y2} receptor-GFP fusion was compatible with biological function of the receptor. Localization of the receptor was assessed by confocal microscopy. Stacks of images were subjected to quantitative image analysis for the 3-D representation of the receptor-GFP fusion. We showed that more than 95% of the fusion protein indeed localized to the plasma membrane as expected for a G protein coupled receptor. We planned to use the P_{2Y2} receptor-GFP fusion together with a fusion protein between G_{16} and DsRed2 to measure Förster resonance energy transfer (FRET) between the two fluorophores as a stringent indicator for molecular

interaction. These experiments, however, had to be redesigned, because the red fluorescent protein caused aggregation of G_{16}. The new approach involved cyan and yellow variants of GFP, which should behave identical as GFP, since they differ from the latter in few amino acids, only. The cyan and yellow fluorescent protein variants of the P_{2Y2} receptor and G_{16} were constructed and verified for proper expression by Western blot. A new experimental protocol was developed, and the confocal microscope was adapted accordingly, to allow for the monitoring of the new fluorophores. Characterization of these new constructs showed proper localization of transiently expressed fusion proteins in a leukemia cell line. We also demonstrated that the selective photobleaching of the acceptor fluorophore was possible, a prerequisite for FRET measurements. FRET measurements along with classical methods such as co-immunoprecipitation should allow for the identification of direct molecular interaction partners of G_{16} in leukemia cell lines.

Original publications

1. A.M. Gomez, B. Schwaller, H. Porzig. G. Vassort, E. Niggli, M. Egger:
Increased exchange current but normal Ca^{2+} transport via Na^{+}-Ca^{2+} exchange during cardiac hypertrophy after myocardial infarction.
Circ. Res. 91 (2002), 323-330.

2. T. Thurneysen, D. Nicoll, K.D. Philipson, H. Porzig:
Sodium/calcium exchanger subtypes NCX1, NCX2 and NCX3 show cell-specific expression in rat hippocampus cultures. (Cover picture for this issue was taken from our work)
Mol. Brain Res. 107 (2002), 367-375.

3. T. Thurneysen, D. Nicoll, K.D. Philipson, H. Porzig:
Immunohistological detection of the sodium/calcium exchanger in rat hippocampus cultures using subtype-specific antibodies.
Ann. NY Acad. Sci. 976 (2002), 367-375.

4. S. Bürgi, K. Baltensperger, U.E. Honegger:
Antidepressant-induced switch of β_1-adrenoceptor trafficking as a mechanism for drug action.
J. Biol. Chem. 278 (2003), 1044-1052.

5. S. Schmid, P.C. Kuechler, M. Britschgi, U.C. Steiner, N. Yawalkar, A. Limat, K. Baltensperger, L. Braathen, W.J. Pichler:
Acute generalized exanthematous pustulosis: Role of cytotoxic T cells in pustule formation.
Am. J. Pathol. 161 (2002), 2079-2086.

Group Prof. Erwin Sigel

Group members: Roland Baur, head technician
Dr. Sabine Baumann, PhD (until June 2002)
Dmytro Berezhnoy, PhD student
Kristien De Cock, PhD student (until September 2002)
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. Subtle 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). Our projects are mainly concerned with the major adult isoform of the receptor □1□2□2. We are interested in finding novel natural and chemically synthesized modulators of the receptor, in the receptor architecture, and in the mode of its channel gating. 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), electrophysiological (2-electrode-voltage clamp, patch-clamp), biochemical, and molecular biology techniques. In addition, we look for human mutations affecting $GABA_A$ receptors.

The two functional agonist sites of $GABA_A$ receptors
S.W. Baumann, R. Baur, E. Sigel
The major isoform of the $GABA_A$ receptor is composed of 2□, 2□ and 1□ subunit. These five subunits surround the ion pore in an unknown arrangement. We have fused subunits at the DNA level to form dimeric and trimeric subunits. Functional expression in the Xenopus oocyte of exclusively the correct combination of a dimer and a trimer mimicked the electrophysiological properties of the wild type receptor. Using these techniques we have identified □□□□ as the correct arrangement. The establishment of the receptor architecture and of linked subunits allows to introduce point mutations in □ and □ subunits for the first time in a defined position. The consequence of point mutations affecting the binding of agonists is presently investigated by comparing □2□1□2/□2□1, with those carrying a point mutation located in a defined location (□2□1F64L□2/□2□1 and □2□1□2/□2□1F64L). Whereas the agonist GABA does not differentiate between the two binding sites, the competitive antagonist bicuculline has a three-fold higher affinity to the site on the □ subunit flanked by two □ subunits than the one flanked by a □ and a □subunit.

Presently, we are investigating the effect of the mutations on additional agonists and antagonists. We also study effects of mutation of additional contact points for the agonist.
See original publication No. 5.

Defined subunit isoforms of $GABA_A$ receptors
F. Minier, S.W. Baumann, E. Sigel
Similar to the approach outlined above, receptors carrying two γ subunit isoforms, γ1 and γ6 in defined positions were prepared and will be functionally compared (α2β2γ2/α2β2γ1 and α2β2γ2/α2β2γ6). This will open the way for the screening of potentially useful substances at defined $GABA_A$ receptor subtypes. Furthermore, it will contribute to our understanding of altered or deleted subunit isoforms in transgenic animals.

Relationship between 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 γ1F64 located at the γ2β1 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 β1γ2 interface and the homologous residue to γ1F64, γ2Y62 has been proposed to constitute an important part. We investigated the effect of the point mutation γ1F64L and the homologous mutation γ2Y62L on agonist and antagonist binding and functional properties in wild type and mutated α1β2γ2 $GABA_A$ receptors. While the mutation in the γ1 subunit had drastic consequences on all studied properties including desensitization, the mutation in the γ2 subunit had little consequence. Our observations argue for the classical view of high and low affinity agonist sites in $GABA_A$ receptors.

Architecture of the benzodiazepine binding site on $GABA_A$ receptors
D. Berezhnoy, E. Sigel (Collaboration with Dr. M. Goeldner, University of Strasbourg, France).
The $GABA_A$ receptor is the molecular target of the frequently used tranquilizers of the benzodiazepine type. We want to identify parts of ligands of the benzodiazepine binding sites in contact with specific amino acid residues in the binding pocket. For this purpose, we are looking for a covalent interaction between cysteine reactive ligands of the benzodiazepine binding pocket and appropriate cysteine point mutants of the receptor. This should give information on the structure of the benzodiazepine binding pocket. Initial results indicate interaction of γ1H101 with the C-atom carrying the chloride atom in diazepam. The project will be extended to a comparison of different allosteric modulators of the receptor in order to get information on their relative position and overlapping, and also to different isoforms of the $GABA_A$ receptor.

Application of FRET for the study of conformational changes in the $GABA_A$ receptor

F. Minier, E. Sigel

$GABA_A$ receptor subunits will be each N-terminally and C-terminally modified with either the yellow or the cyan derivative of the enhanced green fluorescent protein (GFP). Two neighboring subunits, each labeled with a different color will be complemented with an appropriate subunits to give a functional receptor expressed in HEK-293 cells. FRET (fluorescent resonance energy transfer) is responsive for distance and relative orientation changes of the two fluorescent entities. It will be used to see whether the relative conformation of two neighboring subunits is affected by agonists, competitive antagonists or benzodiazepines.

The relative amount of cRNA coding for □2 subunits affects stimulation by benzodiazepines in $GABA_A$ receptors expressed in *Xenopus* oocytes

R. Baur, E. Sigel

(Collaboration with Drs. A.J. Boileau, L.M. Sharkey and C. Czajkowski, University of Wisconsin, Madison, USA)

Very variable values for the extent of stimulation by benzodiazepines of recombinant $GABA_A$ receptors expressed in Xenopus oocytes have been reported. We have found, that by increasing the ratio of genetic information coding for the □2 subunit relative to the □1 and □2 subunits, current stimulation can be made larger, more reproducible and is stabilized over expression time.

See original publication No. 2.

Wogonin isolated from *Scutellaria baicalensis Georgi* acts as a selective anxiolytic

R. Baur, E. Sigel

(Collaboration with Drs. K.M. Hui and H. Xue, Dept. of Biochemistry, Hong Kong University of Science and Technology, Hong Kong, China)

The monoflavonoid wogonin, purified from *Scutellaria baicalensis* Georgi inhibited [^{3}H]flunitrazepam binding to the benzodiazepine receptors (BDZ-Rs). In electrophysiological studies, wogonin enhanced the GABA-activated current. In *Xenopus* oocytes, half-maximal stimulation of currents elicited by GABA was observed at about 3 □M wogonin. Maximal stimulation by wogonin amounted to about 37 % of that by 0.3 □M diazepam. The enhancement was partially reversed by the co-application of the BDZ-R antagonist Ro15-1788. We conclude that wogonin is a naturally occurring partial positive allosteric modulator of the $GABA_A$ receptor acting at the BDZ binding.

See original publication No. 3.

Functional charcterization of human mutations in a muscle chloride channel leading to Myotonia Congenita

M.T. Schaerer, E. Sigel

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

Myotonia congenita is a group of inherited muscular diseases characteristically involving muscle stiffness. The chloride channel, ClC-1 which is encoded by the gene *CLCN1*, is a major voltage dependent ion channel in the skeletal muscle. In this

study, exon 17 skipping was identified at the DNA level. This was confirmed by RT-PCR amplification. The functional significance of this exon skipping was then investigated by expressing mutagenised *CLCN1* with exon 17 deletion 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.

Novel positive allosteric modulators of the $GABA_A$ receptor

U. Thomet, R. Baur, E. Sigel

(Collaboration with Drs. R. Razet, A. El Hadri, P. Poitier and R.H. Dodd, Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, Gif-sur-Yvette Cedex, France; and Drs. R. Furtmüller, F. Jursky and W. Sieghart, Brain Research Institute, University of Vienna, Austria)

Novel compounds were synthesized that act in electrophysiological experiments as positive allosteric modulators of recombinant $GABA_A$ receptors. It was shown that most of them do not interact with the benzodiazepine binding site. Most interestingly, some of them were shown to act in a $GABA_A$ receptor isoform specific way. Both families were patented. A large pharmaceutical company has signed an option to license the patents and is presently carrying out in vivo tests.

See original publication No. 1.

A point mutation in the □3 subunit of the human $GABA_A$ receptor might be linked to inherited sleep problems

A. Buhr, R. Baur, E. Sigel

(Collaboration with Drs. M.T. Bianchi, D.J. Hinkle and R.L. Macdonald, Departments of Neurology, Molecular Physiology and Biophysics and Pharmacology, Vanderbilt University School of Medicine, Nashville, USA; Drs. P. Courtet, V. Pignay and J.P. Boulenger, Services Universitaires de Psychiatrie, CHU Montpellier, INSERM, Montpellier, France; and Prof. Dr. S. Gallati, Dept. of Pediatrics, Inselspital, University of Bern)

In a patient with chronic insomnia, a point mutation was found in the gene of the □3 subunit. This mutation results in the substitution of the amino acid residue arginine for histidine in position 192 (□3R192H). Functional analysis of human □1□3(R192H)□2S $GABA_A$ receptors revealed a slower rate of desensitization compared to □1□3□2S $GABA_A$ receptors. Additionally, current deactivation (a major determinant of IPSC duration) was faster in the mutated receptors. This raises the possibility of decreased GABAergic inhibition contributing to insomnia, as some members of the family of the blood donor also have sleep disorders. The mutation □3R192H might therefore be linked to this condition.

See original publication No. 4.

Original publications

1. A. El Hadri, A. Abouabdellah, U. Thomet, R. Baur, R. Furtmüller, E. Sigel, W. Sieghart, R.H. Dodd:
N-Substituted 4-Amino-3,3-dipropyl-2(3*H*)furanones: New positive allosteric modulators of the $GABA_A$ receptor sharing electrophysiological properties with the anticonvulsant loreclezole
J. Med. Chem. 45 (2002), 2824-2831.

2. A.J. Boileau, R. Baur, L.M. Sharkey, E. Sigel, C. Czajkowski:
The relative amount of cRNA coding for γ2 subunits affects stimulation by benzodiazepines in $GABA_A$ receptors expressed in *Xenopus* oocytes.
Neuropharmacology 43 (2002), 695.

3. K.M Hui, M.S.Y. Huen, H.Y. Wang, H. Zheng, E. Sigel, R. Baur, H. Ren, Z.W. Li, J. T.-F. Wong, H. Xue:
Anxiolyic effect of wogonin, a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi.
Biochem. Pharmacol. 64 (2002), 1415-1424.

4. A. Buhr, M.T. Bianchi, R. Baur, P. Courtet, V. Pignay, J.P. Boulenger, S. Gallati, D.J. Hinkle, R.L. Macdonald, E. Sigel:
Functional characterization of the new human $GABA_A$ receptor mutation γ3(R192H).
Hum. Genet. 111 (2002), 154-160.

5. S.W. Baumann, R. Baur, E. Sigel:
Forced subunit assembly in α1β2γ2 $GABA_A$ receptors: Insight into the absolute arrangement.
J. Biol. Chem. 277 (2002), 46020-46025.

Review articles

1. E. Sigel:
Mapping of the benzodiazepine recognition site on $GABA_A$ receptors
Curr. Trends in Med. Chem. 2 (2002), 833-839.

2. F. Minier, E. Sigel:
Ligand-Operated Membrane Channels: GABA
Encyclopedia of Biological Chemistry, in press.

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Inès Schmid, head technician
Ekaterina Vassina, PhD student
Karl Wittwer, MD 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, idiopathic eosinophilic esophagitis, cystic fibrosis, rheumatoid arthritis, chronic obstructive pulmonary disease, and cytokine-producing cancers. 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. 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 2002.

Death receptors bind SHP-1 and block cytokine-induced anti-apoptotic signaling in neutrophils

I. Daigle, S. Yousefi, M. Colonna, D.R. Green, H.-U. Simon
(Collaboration with the Swiss Institute of Allergy and Asthma Research, University of Zurich, Davos, Switzerland, Basel Institute for Immunology, Basel, Switzerland, and the La Jolla Institute for Allergy and Immunology, San Diego, USA)

Death domain-containing receptors of the tumor necrosis factor (TNF)/ nerve growth factor (NGF) family can induce apoptosis upon activation in many cellular systems. Here, we provide evidence for a tyrosine-based inhibition motif present within the death domain of these receptors. Src homology (SH) 2 - containing tyrosine or inositol phosphatases, SHP-1, SHP-2, and SHIP, can bind in a caspase-independent manner to this motif, suggesting that inhibitory signals might be delivered following cross-linking of death receptors. Indeed, stimulation of death receptors is associated with the disruption of antiapoptosis pathways initiated by survival factors. For instance, Fas, TNF, or TRAIL receptor stimulation abrogates granulocyte/

macrophage colony-stimulating factor (GM-CSF)-, granulocyte colony-stimulating factor (G-CSF)-, and interferon (IFN)-□-mediated antiapoptosis in neutrophils. In these cells, activation of the tyrosine kinase Lyn is prevented, most likely via association with activated SHP-1. Thus, we demonstrate molecular and functional evidence for negative signaling by death receptors.
See original publication No. 1.

Eosinophils express functional interleukin-13 in eosinophilic inflammatory diseases
P. Schmid-Grendelmeier, F. Altznauer, B. Fischer, C. Bitzer, A. Straumann, G. Menz, K. Blaser, B. Wüthrich, H.-U. Simon
(Collaboration with the Allergy Unit, Dept. of Dermatology, University of Zurich, Zurich; High-Altitude Clinic Davos-Wolfgang, Davos, and Dept. of Gastroenterology, Kantonsspital Olten, Olten, Switzerland)
Interleukin (IL)-13 is an immunoregulatory and effector cytokine in allergic diseases such as bronchial asthma. A variety of immune and non-immune cells are known as IL-13 producers. In this study, we investigated whether and under which conditions human eosinophils generate IL-13. Freshly isolated highly purified peripheral blood eosinophils from patients with several eosinophilic inflammatory diseases and from normal control individuals were investigated. We observed that blood eosinophils from patients suffering from bronchial asthma, atopic dermatitis, parasitic infections, hypereosinophilic syndrome, and idiopathic eosinophilic esophagitis expressed IL-13 as assessed by enzyme-linked immunosorbent assay (ELISA), ELISpot-assay, flow cytometry, and immunocytochemistry. By using nasal polyp tissues and immunohistochemistry, we demonstrated IL-13 expression in eosinophils under in vivo conditions. In contrast, blood eosinophils from normal control individuals as well as blood neutrophils from both eosinophilic and control patients did not produce detectable IL-13 levels. However, when blood eosinophils from normal control individuals were stimulated with granulocyte-macrophage colony-stimulating factor (GM-CSF) or IL-5 in vitro, they generated IL-13 mRNA and protein, suggesting that IL-13 expression by eosinophils observed under inflammatory conditions is also a cytokine driven process. Addition of eotaxin to blood eosinophils containing IL-13 resulted in a rapid release of this cytokine. Eosinophil-derived IL-13 was functional as it increased surface expression of the low-affinity IgE receptor (CD23) on purified B cells. In conclusion, human eosinophils are able to produce and release functional IL-13 in eosinophilic inflammatory responses.
See original publication No. 2.

Inhibition of inflammatory effector functions of granulocytes by petasins
O.A.R. Thomet, U.N. Wiesmann, K. Blaser, H.-U. Simon
(Collaboration with the Dept. of Metabolic Diseases, Children's Hospital, University of Bern, Bern, Switzerland)
Following preclinical studies, which we have published in 2001, suggested that an extract of petasites hybridus (Ze339) blocks LT synthesis in monocytes and granulocytes. We therefore performed a clinical study with an extract of Petasites hybridus (Ze 339) in allergic rhinitis. Patients suffering received three times a day two tablets of Ze339 standardized to 8 mg petasins within a time period of one week. After 5 days of treatment, Ze339 significantly improved primary end points which were day- and nighttime nasal symptoms. Nasal resistance, which was measured by rhinomanometry, gradually decreased as a consequence of Ze339 treatment reaching normal levels after five days (rhinomanometry: from 403.5 +/- 62.0 ml to

844.8 +/- 38.8 ml). Levels of inflammatory mediators in nasal fluids and serum were measured 90 minutes after drug administration every day in the morning. After 5 days of treatment, a significant reduction of histamine (from 153.7 ± 32.1 pg/ml to 53.0 ± 8.4 pg/ml) and LT levels (LTB_4: from 313.1 ± 46.5 pg/ml to 180.6 ± 32.2 pg/ml; cysteinyl-LT: from 137.0 ± 42.2 pg/ml to 70.1 ± 16.5 pg/ml) could be observed. Moreover, quality-of-life scores significantly improved. The drug had no effect on the distribution of lymphocyte subpopulations in the blood as well as on the capacity of blood leukocytes to generate cytokines and lipid mediators. These results suggests that Ze339 is effective in treating allergic rhinitis patients by decreasing levels of nasal inflammatory mediators.
See original publication No. 3.

Peripheral blood mononuclear cells from extrinsic and intrinsic atopic dermatitis patients demonstrate increased capacity of generating interleukin-13 but differ in their potential of synthesising interferon-

D. Simon, 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)
A subgroup of patients with atopic dermatitis (AD) are known to have normal total and specific IgE levels and negative skin prick tests towards common environmental allergens. This form of the disease has been termed intrinsic AD (IAD). Although allergic mechanisms appear to be important, the pathogenesis of both extrinsic and intrinsic forms of the disease is unknown. We have compared the cytokine production pattern of peripheral blood mononuclear cells (PBMC) from extrinsic AD (EAD), IAD, and normal control individuals. PBMC were stimulated with anti-CD3 and/or anti-CD28 monoclonal antibodies (mAb) and cytokine production was measured by immunoassays in supernatants of 24-h cultures. Compared to healthy subjects and IAD patients, stimulated PBMC from EAD patients produced less interferon (IFN)-. However, stimulated PBMC from both EAD and IAD patients produced more interleukin (IL)-13 than PBMC from control individuals. Moreover, IL-5 production was significantly increased in IAD but not in EAD patients. Therefore, the underlying mechanism leading to increased differentiation of T helper (Th) 2 cells may involve a deficient capacity in producing IFN- in EAD but not in IAD patients. IL-13 may be a key cytokine in the pathogenesis of both EAD and IAD.
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 □-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.

High serum TARC levels in the lymphocytic variant of the hypereosinophilic syndrome
A. de Lavareille, F. Roufosse, P. Schmid, A.-S. Roumier, L. Schandene, E. Cogan, H.-U. Simon, M. Goldman
(Collaboration with the Department of Immunology, University of Brussel, Brussels, Belgium)
The idiopathic hypereosinophilic syndrome (HIS) is secondary to expansion of an IL-5-producing T cell subset in a subgroup of patients. As this variant is associated with an increased risk for development of T cell lymphoma, early identification of such patients is critical to adequate management. Although the Th2-like cells often bear an aberrant surface phenotype and can be readily detected by flow cytometry, we now show that lymphocyte phenotyping may be normal in some cases. In contrast, measurement of serum thymus and activation-regulated chemokine (TARC) levels consistently shows increased values in patients with this condition compared to other patients with the IHS, and could therefore represent a useful diagnostic tool.
See original publication No. 6.

Calpain-1 regulates Bax and subsequent Smac-dependent caspase-3 activation in neutrophil apoptosis
F. Altznauer, A. Cavalli, S. Conus, 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.

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

R. Baumann, C. Casaulta, D. Simon, S. Conus, 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 human peripheral blood neutrophils express the putative intracellular MIF receptor JAB-1 and that recombinant MIF delays apoptosis of these cells *in vitro*. The 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.

Neutrophil apoptosis is associated with a 22-kDa isoform of ASP

S. Yousefi, A. Ziemiecki, I. Schmid, T. Brunner, H.-U. Simon

(Collaboration with the Departments of Clinical Research and Pathology, University of Bern, Switzerland)

Apoptosis Specific Protein (ASP) has been reported to be associated with the process of apoptosis in several cell lines, although its function has not been understood. We, therefore, intend to understand ASP functions in neutrophils under normal and inflammatory conditions. Neutrophils expressed mRNA for ASP and levels of expression were not influenced by inflammatory cytokines (which block neutrophil apoptosis) or agonistic anti-Fas receptor antibodies (which induce apoptosis in these cells). Protein expression was performed using several monoclonal and polyclonal anti-ASP antibodies raised against recombinant ASP. Whereas the monoclonal ASP antibody recognized a 33-kDa protein in freshly isolated blood neutrophils and in addition a 28-kDa protein in neutrophil populations containing apoptotic cells, we observed a 22-kDa protein in the latter cell population using the polyclonal ASP antibody. The polyclonal antibody did not detect any ASP in freshly purified neutrophils. Specificity was proven by preincubation with recombinant ASP in each case. Preliminary data suggest that the 28-kDa ASP is a fragment of full-length 33-kDa protein, which is cleaved by caspases in the process of apoptosis. The appearance of the 22-kDa protein might be a transcriptional event and its role in apoptotic pathways is currently under investigation in our laboratory.

Original publications

1. I. Daigle, S. Yousefi, M. Collona, D.R. Green, H.-U. Simon:
Death receptors bind SHP-1 and block cytokine-induced anti-apoptotic signaling in neutrophils.
Nat. Med. 8 (2002), 61-67.

2. P. Schmid-Grendelmeier, F. Altznauer, B. Fischer, C. Bizer, A. Straumann, G. Menz, K. Blaser, B. Wüthrich, H.-U. Simon:
Eosinophils express functional IL-13 in eosinophilic inflammatory diseases.
J. Immunol. 169 (2002), 1021-1027.

3. O.A.R. Thomet, A. Schapowal, I.V.W.M. Heinisch, U.N. Wiesmann, H.-U. Simon:
Anti-inflammatory activity of an extract of Petasites hybridus in allergic rhinitis.
Int. Immunopharmacol. 2 (2002), 997-1006.

4. D. Simon, S. Borelli, L.R. Braathen, H.-U. Simon:
Peripheral blood mononuclear cells from IgE- and non-IgE associated allergic atopic eczema/dermatitis syndrome (AEDS) demonstrate increased capacity of generating interleukin-13 but differ in their potential of synthesising interferon-□.
Allergy 57 (2002), 431-435.

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., in press.

6. A. de Lavareille, F. Roufosse, P. Schmid-Grendelmeier, A.-S. Roumier, L. Schandené, E. Cogan, H.-U. Simon, M. Goldman:
High derum thymus and activation-regulated chemokine levels in the lymphocytic variant of the hypereosinophilic syndrome.
J. Allergy Clin. Immunol. 110 (2002), 476-479.

7. H. Danz, S. Stoyanova, O.A.R. Thomet, H.-U. Simon, G. Dannhardt, H. Ulbrich, M. Hamburger:
Inhibitory activity of tryptanthrin on prostaglandin and leukotriene synthesis.
Planta Med. 68 (2002), 875-880.

8. S. Russmann, H.U. Iselin, D. Meier, A. Zimmermann, H.-U. Simon, P. Caduff, J. Reichen:
Acute hepatitis associated with montelukast.
Hepatology, in press.

Review articles

1. H.-U. Simon:

Die Neutralisation von Interleukin-5 als therapeutisches Konzept bei allergischen Entzündungen.
Allergologie 25 (2002), 19-23.

2. S. Yousefi, H.-U. Simon:
Granulocyte apoptosis: death by a secreted lipocalin?
Cell Death Differ. 9 (2002), 595-597.

3. O.A.R. Thomet, H.-U. Simon:
Petasins in the treatment of allergic diseases: Results of preclinical and clinical studies.
Int. Arch. Allergy Immunol. 129 (2002), 108-112.

4. H.-U. Simon:
The neutralization of interleukin-5 as a therapeutic concept in allergic inflammation.
Sarcoidosis Vasc. Diffuse Lung Dis. 19 (2002), 25-28.

5. G. Menz, R. Buhl, A. Gillissen, P. Kardos, H. Matthys, R. Pfister, E.W. Russi, H.-U. Simon, C. Vogelmeier, R. Wettengel, H. Worth, K.F. Rabe:
Difficult to manage asthma: Clinical phenotypes and principles of therapy.
Pneumologie 56 (2002), 132-137.

6. S. Yousefi, H.-U. Simon:
SHP-1: A regulator of neutrophil apoptosis.
Sem. Immunol., in press.

7. H.-U. Simon:
Neutrophil apoptosis pathways and their modifications in inflammation.
Immunol. Rev., in press.

Book chapters

1. H.-U. Simon, F. Levi-Schaffer:
Eosinophils maintain their capacity to degranulate upon repetitive stimulation with the same agonist. In: New Trends in Allergy V (Eds. J. Ring, H. Behrendt, D. Vieluf); Springer-Verlag, Berlin, Heidelberg, 2002, p. 85-91.

2. 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.

3. 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).
Filing in USA und UK

Group Prof. Jörg Stucki

Group member: Dr. Clemens Wagner, PhD

Chromokinetics of metabolic pathways
J. Stucki
Some methods to study and intuitively understand steady state flows in complicated metabolic pathways are investigated. For this purpose a suitable decomposition of complex metabolic schemes into smaller subsystems was used. These independent subsystems were then interpreted as basic colors of a chromatic coloring scheme. The mixture of these colors allows an intuitive picture of how a steady state in a metabolic pathway can be understood. Furthermore, actions of drugs can be more easily investigated on this basis. An anaerobic variant of pyruvate metabolism in rat liver mitochondria was used as a simple example. Possible implementations of existing algorithms were realized.

Elementary modes of chemical reaction networks
C. Wagner
A chemical reaction network can be represented as a time derivative of concentration, which is equal to the stoichiometry matrix times the flows. If we only consider steady states of the system the time derivative becomes zero and any solution for the flows lies in the null space of the stoichiometry matrix. Using linear algebra the integer null space of the stoichiometry matrix can be determined by standard methods. We define an elementary mode as a linear combination of null space basis vectors with a minimal set of flows. This new definition leads to an algorithm, which first calculates the null space basis vectors and by a combination of these vectors in pairs the elementary modes of the systems. The condition for each combination is that the contributions of both vectors to a flow cancel each other. Every combination obtained in such a way is tested against its elementary property. If we have already collected a flow vector, which set of flows is contained in the set of flows of the actually calculated one, then this flow vector is eliminated. In a final step all those flux vectors are selected as elementary modes of the system, which fulfill the sign restrictions. In contrast to earlier publications we show that the algorithm also works if some of the reactions are reversible.

Neurodynamics
C. Wagner
Visual inputs reach the primary visual cortex V1 via the thalamic lateral geniculate nucleus. The network in V1 represents the first stage of cortical processing in the visual pathway and neurons in V1 detect i.e. edge direction, velocity and color. They are arranged in different layers, whereby the axons from the thalamus point to cells in layer IV. Simple Cells in layer IV code for orientation. Each of these cells is characterized by a tuning curve, which relates the frequency of firing to the angle of an edge in the visual field. Beside the horizontal structure of layers, the network in V1 is organized in columns with a high density of internal connections and a low density of connections between the columns. Furthermore, neurons in V1 project their axons to higher levels of visual processing. The visual system and particularly V1 is one of the best studied neural networks. This advantage was used, on the one hand, by taking network topology from morphological analysis and on the other hand, by testing the results of computer simulations against experimental data. The goal of our

work is to explore the relationship between network topology and network properties like synchronization and information flow.

Collective behaviour in neuronal networks

R. Stoop, C. Wagner
(Collaboration with the Institute of Neuroinformatics, ETHZ, Zürich, Switzerland)

Neurons in the cat visual cortex revealed a characteristic collective bursting behaviour upon visual stimulation by random dots and square wave gratings. We simulated a small representation of this network in order to explore the effect of feedback connections and of inputs on the network output. The network consists of 80 excitatory and 20 inhibitory globally coupled neurons. For excitation the model neurons were derived from a reconstructed cat spiny stellate neuron from layer IV of the striate cortex. The geometry of the cells was simplified to obtain an eight-compartment version. The morphology of inhibitory neurons was obtained from a reconstructed basket cell and the $GABA_A$ type inhibitory synapses were placed on the soma of excitatory neuron. The network architecture shows recurrent connected excitatory and inhibitory neurons that receive feed-forward input. The computation was performed using the NEURON simulation environment. Although the isolated neurons are no intrinsic bursters the neurons of the network revealed collective bursting, which was induced by the recurrent connections. The time series of the network output were embedded into an 8 dimensional space and noise cleaned. For both types of neurons we determined the correlation dimension and the Lyapunov exponents. Probably due to the strong coupling the determined parameters are very similar, the correlation dimension is approximately 3.5 and the Lyapunov exponents are about (0.5 0.15 0 –1). The two positive values indicate the presence of hyperchaos. The measurements from the cat visual cortex show characteristic plateau regions in a log-log plot (correlations vs. sphere radius) of the spike train, which could be nicely reproduced by the simulations. The plateau region separates the different time scales of the system. For a constant feed forward input the network shows simple bursting behaviour with two time scales, the inner burst intervals and the inter burst intervals. Further plateaux are induced when we used a synchronized square wave input with 5 different pulse durations, which were randomly selected. In the asynchronous case the results are very similar, however the plateaux start to decline. The two simulations correspond to experiments using square wave grating (synchronous input) and random dot stimulation (asynchronous input) as visual input. Again a nice correspondence between simulations and experiments was found. In summary, we found collective behaviour and low dimensional chaos in a recurrent network of the visual cortex. Randomness in the visual input seems to be translated to multiscale bursting of the network output.

Synchronization and network topology

R. Stoop, C. Wagner
(Collaboration with the Institute of Neuroinformatics, ETHZ, Zürich, Switzerland)

Synchronization of neural networks is thought to be one of the possibilities how distant parts of the brain exchange information. Due to potentiation and depression of synaptic connections the topology of the network evolves. We explore the question whether a network with appropriate learning rules evolves into an architecture, which is able to show synchronization. To find the synchronized state, our approach uses a Hebbian learning rule, where the difference between the state variables of two oscillators is used either to strengthen or to weaken the synaptic couplings. We run simulations of networks with 100 chaotic oscillators (logistic maps), which represent

the dynamics of neurons. The initial conditions of the maps were randomly selected from the interval (0,1) and the interaction strength between the oscillators was initially in the range where synchronization does not occur (0.1). Starting with a globally coupled network some of the connection strengths become zero and reduce the connectivity in the network. In the synchronized state the network revealed a connection density of 85% compared to the globally coupled network. It is well known that the latter synchronize for coupling strengths larger than 0.5. We observed that in our networks, with a reduced number of connections, the mean interaction of all inputs to an oscillator also assumes a value of 0.5. This suggests a compensatory mechanism whereby some of the inputs recompense for others. The transition of the network to the synchronized state is of an all-or-non type.

Chaos control

R. Stoop, C. Wagner

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

Many simulations have shown that low dimensional chaos eventually occurs in neuronal network dynamics. This gives rise to study chaos control methods for these networks, which reduce the complex motion of the system on a chaotic attractor to a periodic one. Oscillating behavior in neural networks is one of the major ingredients of the binding hypothesis. There are many different chaos control methods available, however most of them lack the property of simplicity. Based on experiments we further developed a method, which controls systems on an unstable periodic orbit (UPO) of a chaotic attractor by simple limiters. This approach has the additional advantage that a targeting algorithm, which moves the system close to the orbit, becomes idle. We have recently shown that the method works nicely for 1d systems. Now, we extended the approach to 2d systems (Henon map) and to continuous systems (Lorentz system). For a 2d map we explored two different approaches. First, 2 limiters were used, each for one coordinate. By a proper setting of these limiters the unstable periodic orbits of the Henon attractor can be found. Second, we used a single limiter, which was tilted in order to determine the UPO's. The analysis revealed that the stable manifold of a fixed point of the orbit always lies in a certain range of tilt angle of the limiter. The dynamics of the Lorentz system was reduced to a Poincare section and controlled by applying a modified 2d control algorithm.

Information transfer in neuronal networks

R. Stoop, C. Wagner

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

The neurons in the primary visual cortex are arranged in columns. Within a column the neurons code for the same feature, i.e. orientation, in the visual field. Therefore, an object in the visual field with different edges activates different columns in V1. However, the brain still does not know that these detected edges belong to the same object. There is a lot of experimental evidence that this is done by synchronization, which led to the binding hypothesis. For fast recognition of objects the information of activation must be rapidly distributed in the network. Therefore, we investigated the speed of information transfer in networks with the ability to synchronize. We used a scale-free linear network of chaotic oscillators, which has a high connection density to its closest neighbors and a few connections to neurons far away (fractal coupling). In order to determine the speed of information flow we perturbed the central cluster (column) and followed the spreading of the perturbation in the network. There are two competing effects, which determine the velocity of perturbation. First, due to the exponential divergence of adjacent initial conditions of chaotic oscillators any

distortion will be exponentially amplified. Second, in the case of diffusive coupling, the coupling scheme leads to a Gaussian spreading of perturbations. The slope of the line where both terms cancel each other determines the speed of information transfer. We compared the velocity of perturbation in diffusively and in fractally coupled networks with the same number of connections. As a major result we observed an enhanced speed of information transfer in fractally coupled networks. It is well known that diffusion can be represented as a Markov process. We applied this theory to the fractally coupled network and determined the diffusion coefficient. Indeed, as in the case of diffusive coupled networks, the speed of information is determined by the diffusion coefficient. The enhancing effect can now be explained in terms of a diffusion process. Fast diffusion is obtained when the system hops over a large distance in a single step. These long jumps correspond to the long range connections in the network. The short range connections are necessary to obtain synchronized behaviour. But the possibility to make a short jump reduces the probability for the large jumps. In summary, fast information transfer in synchronized networks require a connection density with a rapid decay of short range connections and a long tail for long range connections.

Original publications

1. C. Wagner, J.W. Stucki:
Construction of an associative memory using unstable periodic orbits of a chaotic attractor.
J. Theor. Biol. 215 (2002), 375 – 384.

2. R. Stoop, D. Blank, A. Kern, J.-J. v.d. Vyver, M. Christen, S. Lecchini, C. Wagner:
Collective bursting in layer IV, synchronization by small thalamic inputs and recurrent connections.
Cogn. Brain Res. 13 (2002), 293 – 304.

Book chapter

1. C. Wagner, R. Stoop:
Enhanced information flow in a chain of fractally coupled chaotic clusters
In: “Frontiers in Artificial Intelligence and Applications: Knowledge-based Intelligent Information Engineering Systems”, Eds. E. Damiani, R.J. Howlett, L.C. Jain, N. Ichalkaranje, IOS Press, Amsterdam, Vol. 82 (2002), p. 905 – 909.

4.2. Congress Invitations

Dr. Sabine Baumann

Union of the Swiss Societies for Experimental Biology (USGEB), Lugano (CH), March 07-08, 2002;
$GABA_A$ receptor subunit arrangement and function explored by covalent subunit linkage.

Prof. Ulrich E. Honegger

European Conference on Epilepsy, Workshops on basic research, Madrid (Spain), October 6-10, 2002;
Mode of actions of antiepileptics.

European Conference on Epilepsy, Workshops on basic research, Madrid (Spain), October 6-10, 2002;
Side effects of antiepileptics.

Prof. Erwin Sigel

12th Neuropharmacology Conference "$GABA_A$ Receptors in Cellular and Network Excitability", satellite meeting to the annual meeting of the Society for Neuroscience, Orlando, Florida, USA, Oct. 31 – Nov. 02, 2002;
The $GABA_A$ receptor: covalently linked subunits and ligand binding sites.

Prof. Hans-Uwe Simon

58th Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI), New York (USA), March 1-6, 2002;
Introducing apoptosis pathways.

Annual Meeting of the Swiss Society of Allergology and Immunology (SSAI), Lugano (CH), March 14-16, 2002;
Clinical and immunological effects of low-dose interferon-□ treatment in patients with corticosteroid unresponsive asthma.

43th Congress of the German Society of Pneumology and 22th Meeting of the German Society of Allergology and Clinical Immunology, Bochum (D), March 13-16, 2002;
Programmierter Zelltod und Zytokine.

European Academy of Allergology and Clinical Immunology, XXI. Congress; Symposium of the World Allergy Forum, Naples (I), June 1-5, 2002;
Cytokines and cytokine receptor antagonists.

Asthma – vom Labor in die Praxis, Bern (CH), June 06, 2002;
Immunologischer Überblick über die Pathogenese des Asthmas.

Villa Vigoni Meeting on Cell Death; Menaggio (I), June 26-29, 2002;

Apoptosis pathways in neutrophils.

Immunodermatological Workshop; Fevik (Norway), August 2-4, 2002;
Immunological mechanisms in atopic dermatitis.

Immunologie-Tag Bern: „New Aspects in Immunopharmacology“; Bern (CH),
September 19, 2002;
Antikörpertherapien.

First Cell Death and Differentiation & Fourth International SASS Foundation Conference,
Apoptosis in Cancer and Infection, Capri (I), October 6-10, 2002;
Calpain-1 regulates Bax and subsequent Smac-dependent caspase 3 activation in neutrophil apoptosis.

10th Euroconference on Apoptosis, Paris (F), October 10-12, 2002;
Death of immune cells in inflammatory responses.

Allergologie-Kurs, Hannover (D), November 15-16, 2002;
Physiologie des Immunsystems.

Allergologie-Kurs, Hannover (D), November 15-16, 2002;
Immunologische Grundlagen allergischer Erkrankungen.

Allergologie-Kurs, Hannover (D), November 15-16, 2002;
In-vitro-Diagnostik allergischer Erkrankungen.

Austrian Society for Allergology and Immunology, Annual Meeting, Innsbruck (A);
November 21-23, 2002;
Pathogenic and therapeutic roles of cytokines in asthma.

World Congress of Immunopathology, Singapore, December 2-6, 2002;
Molecular mechanisms controlling granulocyte numbers and activation inflammation.

Dr. Clemens Wagner

6th International Conference on Knowledge-based Intelligent Information &
Engineering Systems. Podere d Ombriano, Crema (I); September 16 – 18, 2002;
Enhanced information flow in a chain of fractally coupled chaotic clusters.

Dr. Shida Yousefi

III-Bern International Summer School; Wilderswil (CH), Aug. 30 – Sept. 02, 2002;
A new player in the apoptotic machinery.

4.3. Seminar Invitations

Dr. Kurt Baltensperger

Live Cell Imaging Workshop at the EPF Lausanne and Zeiss User Meeting,
Lausanne (CH); Oct. 10, 2002;
Estimation of cell surface associated *versus* internal receptor protein by confocal microscopy and image quantification.

Prof. Ulrich E. Honegger

Pharma Center, University of Basel (CH); May 22, 2002;
guest of Prof. Dr. W. Schaffner
Pharmakologische in vitro-Tests zur Untersuchung von Phytopharmaka Wirkungen.

Ostschweizer Kinderspital, St.Gallen (CH); June 27, 2002; guest of PD Dr. Ch. Kind and Dr. M. Weissert;
Phytotherapie – ein aktueller Forschungszweig der Pharmakologie.

Apothekerverein des Kantons Bern, Fortbildungsveranstaltungen;
Bern und Biel (CH); July 3 and 4, 2002;
Reaktionen auf Interaktionen.

Gesundheitsdepartement Kanton St. Gallen, Kantonsspital St. Gallen (CH);
Sept. 19, 2002; Symposium on ADHS;
Neuropharmakologie der Stimulantien, im speziellen von Ritalin.

Neurologists continuation weekend, Sils-Maria (CH);October 18-20, 2002;
Modes of action of central acting drugs.

SVEPTA Continuation Course, Department of Pharmacology Bern (CH);
October 10, 2002;
Mode of action of antiepileptic drugs.

Regionalgerichte Bern-Laupen, Trachselwald; Amtshaus Bern (CH);
October 31, 2002;
Drogen-Abhängigkeit und Behandlung von Suchtkranken.

Prof. Hartmut Porzig

Institut für Infektionskrankheiten, Universität Bern, Bern (CH); May 31, 2002; guest of Prof. M. Täuber.
G-protein-mediated signals in the development of human hematopoietic cells.

Prof. Hans-Uwe Simon

Klinik für Rheumatologie, Klinische Immunologie und Allergologie, Inselspital, Bern (CH); Jan. 11, 2002; guest of Prof. Dr. M. Seitz;
Apoptose und Entzündung.

Institut für Infektionskrankheiten, Universität Bern, Bern (CH); February 01, 2002; guest of Prof. Dr. M. Täuber;
Neutrophil apoptosis in health and disease.

American Academy of Allergy Asthma & Immunology, 58th Annual Meeting, New York (USA); March 03, 2002;
Effector functions of eosinophils in allergic inflammation.

American Academy of Allergy Asthma & Immunology, 58th Annual Meeting, New York (USA); March 04, 2003;
Role of apoptosis in allergic inflammation.

Institut für Medizinische Immunologie, Charité, Humboldt-Universität Berlin, Berlin (D); July 04, 2002; guest of Prof. Dr. H.-D. Volk;
Apoptosis in neutrophils: From death receptors to phosphatases, calpains, and beyond.

Bern Immunology Club; October 03, 2002;
Apoptosis and inflammation.

4.4. Organization of Meetings and Courses

Dr. Kurt Baltensperger

Kick-off meeting: "Introduction the Imaris Image Analysis Station".
Bern, Sept. 4, 2002

Course on “Image acquisition, deconvolution, 3D representation and image quantification using Huygens and Imaris”. Sept. 17-19, 2002

Prof. Hans-Uwe Simon

Allergologie-Kurs (together with Dr. A. Schapowal, Landquart, and Prof. Dr. M. Zierhut, Tübingen); Davos (CH), February 22-23, 2002

2nd Swiss Apoptosis Meeting (together with PD Dr. T. Brunner, Bern);
Bern (CH), August 22-23, 2002

EU COST 844 Meeting: Genomics and Proteomics in Apoptosis Research (together with PD Dr. T. Brunner); Bern, August 24, 2002

Scientific symposium: Factors that drive inflammation, Bern (CH), August 30, 2002

III-Bern International Summer School; Wilderswil (CH), August 30 – Sept. 02, 2002

Immunologie-Tag Bern: „New Aspects in Immunopharmacology“ (together with Prof. Dr. P. Villiger and Prof. Dr. M. Seitz); Bern (CH), September 19, 2002

10th Euroconference on Apoptosis of the European Cell Death Organization (ECDO) (Member of the International Advisory Board); Paris (F), October 10 –12, 2002

Bern Immunology Club (together with the other founder members); Bern, October 3, 31; November 28; December 19, 2002

Dr. Shida Yousefi

Workshop on RNA-Purification and RT-PCR (together with Prof. Dr. H.-U. Simon). Bern, February 19-20, 2002

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon

58th Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI); Session: “Apoptosis pathways”; New York (USA), March 1-6, 2002.

Annual Meeting of the Swiss Society of Allergology and Immunology (SSAI); Session: “Inflammation”; Lugano (CH), March 14-16, 2002.

XXI. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Session: “Immunodermatology”; Naples (I), June 1-5, 2002.

XXI. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Session: “Chemokines and chemokine receptors in allergic inflammation”; Naples (I), June 1-5, 2002.

Second Swiss Apoptosis Meeting; Session: “Apoptosis pathways”; Bern (CH), August 22-24, 2002.

First Cell Death and Differentiation & Fourth International SASS Foundation Conference, Apoptosis in Cancer and Infection; Session 11: “Receptors III; Infection II”; Capri (I), October 6-10, 2002.

3. Allergologie-Seminar; Session: “Grundlagen allergischer Erkrankungen”; Hannover (D), November 5-6, 2002.

4.6. Referee Work for Peer-Reviewed Journals

Prof. Ulrich E. Honegger

Biochemical Pharmacology
Planta Medica
Swiss Medical Weekly

Prof. Hartmut Porzig

N-S Arch Pharmacol
Brain Res

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

J Clin Invest
J Immunol
Blood
Cell Death Differ
J Leukocyte Biol
Apoptosis
Int Arch Allergy Immunol
J Allergy Clin Immunol
Oncogene
Allergy
Clin Exp Allergy
Clin Exp Immunol
Int J Hyg Environ Health
Biochem Pharmacol
J Pharm Pharmacol
Eur Respir J
Life Science

J Invest Dermatol
Swiss Med Wkly
Cytokine
Eur J Immunol
Proc Natl Acad Sci USA
J Hepatol
Exp Dermatol
DMW
Respiration
Z ärztl Fortbild Qual.sich (ZaeFQ)
Am J Pathol
J Biochem Biophys Meth
Environm Toxicol
American Journal of Physiology - Cell Physiology

4.7. Referee Work for Grant Bodies

Prof. Erwin Sigel

Swiss National Science Foundation
Wellcome Trust
Medical Research Council (MRC)
Austrian Foundation for the Advancement of Science

Prof. Hans-Uwe Simon

Wellcome Trust
Medical Research Council (MRC)
British Asthma Campaign
BONFOR-Program, University of Bonn (D)
The Netherlands Organization for Scientific Research (NWO)
Medizinische Fakultät der Universität Tübingen, *fortüne*-Programm

Prof. Hartmut Porzig

United States-Israel Binational Science Foundation (BSF)

4.8. Awards

Dr. Sabine Baumann

Bürgi-Preis 2002

5. Administrative, Advisory, and Honorary Posts

Dr. Kurt Baltensperger

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

Information Technology Coordinator at the PKI

Roland Baur

Coordinator for radioactive work at the PKI

Prof. Ulrich E. Honegger

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 Kommission Grundstudium der Medizinischen Fakultät der Universität Bern

Mitglied der Arzneimittelkommission des Schweizerischen Apothekerverbandes

Wissenschaftlicher Beirat des Apothekervereins des Kantons Bern

Member of the GlaxoSmithKline Advisory Board for Epilepsy

Member of the Zeller Medical Advisory Board

Prof. Hartmut Porzig

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

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

Member of the Swiss working group: “Nachwuchsförderung/Akademische Qualifikationen”

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

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)

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”

Member of the Executive Committee of the European Academy of Allergology and Clinical Immunology (EAACI)

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)

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)

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

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 could be purchased. It was financed through an extraordinary grant (CHF 88'000.00) of the Medical Faculty. During the past year the confocal microscope has been used by a total of 24 different users with 12 different affiliations. It was in operation for approximately 500 hours with an average session time of 3 hours. The facility for confocal microscopy and image analysis is operated by Dr. K. Baltensperger. It provides training for new users, and technical and scientific support. The operator's time spent for the facility amounted to over 400 work hours.

6.2. Flow Cytometry

A service is provided for analyzing potential pathogenic mechanisms of eosinophilic disorders and other chronic 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. Day of the Open Door at PKI

September 12, 2002

7.2. Academic Celebration

The institute organized an academic celebration (**Akademische Feier**) associated with a **day of the open door** on September 12, 2002, to thank all the individuals who helped us in the renovation of our building. The program is printed here one more time:

P R O G R A M M

Musik ***J. Haydn: Londoner-Trio Nr. 1 C-Dur***

- Allegro moderato
- Andante
- Finale, Vivace

Begrüssung ***Prof. Dr. Hans-Uwe Simon***
Direktor des Pharmakologischen Instituts

Ansprache ***Prof. Dr. Christoph Schäublin***
Rektor der Universität Bern

Ansprache ***Prof. Dr. Emilio Bossi***
Dekan der Medizinischen Fakultät

Musik ***W. A. Mozart: Wiener-Serenade Nr. 1 C-Dur***

- Allegro
- Adagio
- Menuetto
- Rondo Allegro

Akademische Rede ***Prof. em. Dr. Marcel H. Bickel***
„Zur Geschichte der Pharmakologie in Bern“

Musik ***J. Haydn: Londoner-Trio Nr. 2 G-Dur***

- Andante, Allegro
- Allegro

Apéro

Musikerinnen ***Martina Keletic****, Flöte* ***Ilona Naumova****, Geige* ***Anna Katharina Trauffer****, Cello*

7.3. Art Exhibitions

Christine Johne, Munich, Germany
Bern, August 29, 2002

Nadine Arioli, Davos, Switzerland
Bern, November 21, 2002

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)

Josephine Clark-Fonds für Forschung auf dem Gebiete der Medizin

Prof. Ulrich E. Honegger

Bundesamt für Umwelt, Wald und Landschaftsschutz (BUWAL) (until February 2002)

Zeller Medical AG, Romanshorn (CH)

Prof. Hartmut Porzig

Schweizerische Krebsliga (together with K. Baltensperger, grant No. SKL 778-2-1999)

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)

GENION, Hamburg (D)

Prof. Hans-Uwe Simon

Swiss National Science Foundation (grant No. 31-58916.99)

OPO-Foundation, Zurich (CH)

Bernische Krebsliga (together with S. Yousefi)

Prof. Jörg Stucki

Swiss National Science Foundation (grant No. 31-49745.96) (until March 2002)

Dr. Shida Yousefi

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

Bernische Krebsliga (together with H.-U. Simon)

Novartis-Stiftung

Stiftung zur Förderung der wissenschaftlichen Forschung an der Universität Bern

8.2. Meetings

Agilent Technologies Germany, Heilbronn
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

Allergomed, Therwil
III-Bern International Summer School, Bern, August 30 – September 02, 2002

Amersham Biosciences, Dübendorf
III-Bern International Summer School, Bern, August 30 – September 02, 2002

Apotech, Epalinges
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

International Scientific Symposium: Factors that drive inflammation.
Bern, August 30, 2002

Applera Europe B.V., Rotkreuz
III-Bern International Summer School, Bern, August 30 – September 02, 2002

AstraZeneca AG, Zug
III-Bern International Summer School (major sponsor), Bern, August 30 – September 02, 2002

Becton Dickinson Biosciences, Allschwil
III-Bern International Summer School (major sponsor), Bern, August 30 – September 02, 2002

Catalys AG, Wallisellen
Workshop on RNA-Purification and RT-PCR; Bern, February 19-20, 2002

2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

III-Bern International Summer School, Bern, August 30 – September 02, 2002

Cell Signaling Technology (c/o Bioconcept, Allschwil)
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

COST: EU action 844 – Switzerland
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

DAKO Diagnostics AG, Zug
III-Bern International Summer School, Bern, August 30 – September 02, 2002

Fluka Chemie GmbH, Buchs
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

Grogg Chemie, Stettlen
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

INTEGRA BIOSCIENCES, Wallisellen
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

JURO Supply GmbH, Lucerne
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

LabForce, Nuningen
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

LUCERNACHEM, Lucerne
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

VWR International (c/o JURO Supply GmbH), Lucerne
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

Institute of Pathology, University of Bern
2nd Swiss Apoptosis Meeting, Bern, August 22-23, 2002

Max und Elsa Beer-Brawand-Fonds, University of Bern
International Symposium: Factors that drive inflammation, Bern, August 30, 2002

Novartis Pharma AG, Bern
III-Bern International Summer School, Bern, August 30 – September 02, 2002

TRIMEDAL AG, Brüttisellen
III-Bern International Summer School, Bern, August 30 – September 02, 2002

8.3. Travel Support

COST: EU action 844 - Switzerland
Support of S. Yousefi, ECDO meeting in Paris, October 2002

ZLB Bioplasma AG, Bern
Support of F. Altznauer, AAAAI meeting 2002 in New York, March 2002

8.4. Other Support

Bürgi fund
Seminar series of the institute