Annual Report 2006

Institut für Pharmakologie (PKI)

der Universität Bern

Department of Pharmacology,

University of Bern

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An online copy of this report can be obtained at http://www.pki.unibe.ch/

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1. Introduction

1.1. Vorwort

Dies ist der sechste umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat sich auch im Jahr 2006 bemüht, seine Aufgaben in Lehre und Forschung innerhalb der Medizinischen Fakultät vorbildlich zu erfüllen. Die Pharmakologie besitzt eine Brückenfunktion zwischen biologischer Grundlagen- und klinischer Forschung. Das PKI arbeitet deshalb eng mit den verschiedensten Kliniken des Inselspitals und mit anderen Forschungseinrichtungen der Universität Bern zusammen. Damit wollen wir helfen, die klinische Forschung sowie die Aus-, Weiter- und Fortbildung an der Medizinischen Fakultät zu stärken. Zum anderen sind wir an der Zusammenarbeit mit Firmen interessiert, wie die weiter hinten aufgeführten gegenwärtigen Kontakte der einzelnen Forschungsgruppen zeigen. Auch im Jahr 2006 trugen wir dazu bei, die Kommunikation zwischen Wissenschaftlern und Öffentlichkeit zu fördern. Dazu dienten u.a. die Vernissagen, die viele Gäste in das PKI lockten.

Das Jahr 2006 war von bedeutenden Veränderungen in unserem Institut geprägt. Nachdem die Herren Prof. Porzig (28.2.2005), Prof. Honegger (30.9.2005) und Prof. Stucki (31.12.2005) bereits im Jahr 2005 altershalber zurücktraten, zog die Gruppe Prof. Sigel am 1.3.2006 in das Institut für Biochemie und Molekulare Medizin der Universität um. Als Nachfolgerin von Herrn Prof. Porzig trat Frau Prof. Andrea Huwiler ihre Stelle am 1.2.2006 an. Als neue DozentInnen nahmen Frau PD Dr. Shida Yousefi (1.1.2006) und Herr Prof. Uwe Zangemeister-Wittke (1.11.2005) ihre Tätigkeit auf.

Neben unserer regulären Lehrtätigkeit im 3. Studienjahr Medizin sowie neben der Ausbildung der ZahnmedizinerInnen sind wir aktiv innerhalb der interfakultären Graduate School for Cellular and Biomedical Sciences tätig. Prof. Simon ist Mitglied der Betreuungskommission „Medizinische Biologie“ innerhalb dieses Ausbildungsprogramms für Doktorandinnen und Doktoranden. Dazu kommen zusätzliche Bildungsangebote in Form von Seminaren (Fortschritte in der Pharmakologie), praktischen Kursen (Frau PD Dr. Yousefi) und einer Summer School (Prof. Simon). Diese Bildungsangebote werden weitgehend aus eigenen finanziellen Mitteln bzw. Sponsorengeldern bestritten. Im Institut arbeiten gegenwärtig 16 DoktorandInnen (10 PhD, 6 MD), und eine Doktorandin hat im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2006 insgesamt 31 Originalarbeiten sowie 15 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >150). MitarbeiterInnen des Instituts wurden zu insgesamt 36 Vorträgen bzw. Seminaren eingeladen. PD Dr. Shida Yousefi und Dr. Sebastien Conus wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 4 Mitarbeiter mit namhaften Beiträgen des Schweizerischen Nationalfonds unterstützt. Zahlreiche Persönlichkeiten besuchten das Institut und hielten Forschungsseminare. Der Berner Immunologie-Club erfreut sich, auch durch die aktive Hilfe aus dem PKI, einer grossen Beliebtheit. Ein von Prof. Simon und Prof. Brunner (Institut für Pathologie) organisierter Kongress über Apoptose zog ca. 200 Teilnehmer aus dem In- und Ausland an. Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

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

Ein grosses Problem ist die zu geringe finanzielle Unterstützung unseres Instituts zur Aufrechterhaltung der Infrastruktur. Insbesondere bei der Bezahlung von Reparaturen kommen wir immer wieder in finanzielle Probleme. Dies hat sich leider auch nach Abschluss eines Leistungsvertrag zwischen der Medizinischen Fakultät und dem PKI nicht geändert.

Ich danke allen Mitarbeitern und Mitarbeiterinnen für ihren Einsatz, welcher auch im Jahr 2006 zu einer Bilanz beitrug, die internationalen Massstäben gerecht wird. Ebenso danke ich allen Sponsoren und Freunden des Instituts.

Prof. Dr. med. Hans-Uwe Simon
Direktor

Bern, Februar 2007

1.2. Foreword

This is the sixth comprehensive report of the Department of Pharmacology of the University of Bern. Our department has worked hard to fulfil its tasks in teaching and research within the Medical Faculty in 2006 in high quality. Pharmacology plays an important role in both basic biological science and clinical research. The Department of Pharmacology wants to succeed in both areas and, therefore, maintains intense contacts with several clinics of the University Hospital (Inselspital) as well as with different research institutes of the University of Bern. In doing so, we hope to strengthen both translational 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. In addition, we further tried to promote communication between scientists and the public in 2006. The organization of art exhibitions within our institute is an example for these efforts.

The year 2006 was again characterized by important changes in our department. Following the retirement of Prof. Porzig (Febr. 28, 2005), Prof. Honegger (Sept. 30, 2005), and Prof. Stucki (Dec. 31, 2005), Prof. Sigel moved with his group in the Institute of Biochemistry and Molecular Medicine of the University of Bern (March 1, 2006). Prof. Andrea Huwiler, who started her work on February 1, 2006, is succeeding Prof. Porzig. As new principal investigators, we recruited PD Dr. Shida Yousefi (Jan. 1, 2006) and Prof. Uwe Zangemeister-Wittke (Nov. 1, 2005) to the institute.

In addition to regular teaching within the third study year of medical students and our teaching of dental students, we are actively involved within the graduation program for MD/PhD students of the University of Bern. In 2005, the Graduate School for Cellular and Biomedical Sciences was founded by the Medical, Natural Sciences, and Veterinary Medical Faculties, and Prof. Simon is member of the tutoring committee “Medical Biology” within this school. Additional teaching activities outside the medical curriculum, such as seminars (Progress in Pharmacology), practical courses (PD Dr. Yousefi), and a summer school (Prof. Simon) were provided. Importantly, these additional events were financed exclusively by external sponsors. Currently, 10 PhD students and 6 MD students work at the PKI and one student successfully finished her graduate study in 2006.

In 2006, members of the Department of Pharmacology published 31 original and 15 review articles in international peer-reviewed journals (the sum of the “impact factors” is more than

150). Co-workers of the institute were invited to 36 lectures or seminars. PD Dr. Shida Yousefi and Dr. Sebastien Conus received research prizes. Four co-workers are currently supported by grants of the Swiss National Science Foundation. Several prominent researchers visited the institute and presented seminars. An international congress on Apoptosis with approximately 200 participants was organized by Prof. Simon and Prof. Brunner (Dept. of Pathology, Univ. of Bern). In summary, research plays an important role at the PKI and is performed at a high level.

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

One major problem is the financial support of the institute within the ordinary budget of the Medical Faculty that is not sufficient to keep the infrastructure in shape and running. In particular, we always have problems if a certain instrument needs to be repaired. The situation also did not change following signing a contract between the Medical Faculty and the PKI.

I thank all co-workers for their hard work that contributed to the success of the PKI in 2006. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, February 2007

2. Staff 2006

Director

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

Deputy Director

Prof. Dr. Andrea Huwiler, PhD (since February 2006)

Permanent Members

Prof. Dr. Andrea Huwiler, PhD (since February 2006)
Prof. em. Dr. Harald Reuter, MD
Prof. Dr. Erwin Sigel, PhD (until February 2006)
Prof. Dr. Hans-Uwe Simon, MD, PhD
PD Dr. Shida Yousefi, PhD
Prof. Dr. Uwe Zangemeister-Wittke, PhD

Scientific Staff

Dr. Nicola Andina, MD, PhD student
Roland Baur, head technician (until February 2006)
Eva Bettler, MD student* (since August 2006)
Dr. Sébastien Conus, PhD
Arezoo Daryadel, PhD student*
Dr. Frauke Döll, PhD (since September 2006)*
Mistianne Feeney, research fellow (since April 2006)
Elena Federzoni, PhD student (since December 2006)
Pascale Grzonka, MD student* (since August 2006)
Dr. Barbara Geering, PhD (since October 2006)
Grace Gordon, technician (since May 2006)
Susanne Hösli, MD student* (since August 2006)
Antanas Januskevicius, research fellow (June 1 - July 17, 2006)
Simone Hildbrand, technician (since April 2006)
Ganna Kostylina, PhD student
Kuldeep Kaur, PhD student (until February 2006)
Evelyne Kozlowski, technician
Dipak Makey, PhD student (since July 2006)
Cristina Mihalache, PhD student (since November 2006)
Dr. Vera Preller, MD (May 1 - July 15, 2006)
Susanne Probst, technician
Annika Quast, PhD student (since August 2006)
Dr. Shuyu Ren, PhD (since April 2006)
Dr. Souzan Salemi, PhD
Inès Schmid, head technician
Kelly Tan, PhD student* (until February 2006)
David Troi, MD student*
Jennifer Wittwer, MD student* (since August 2006)
Dr. Stephan von Gunten, MD, PhD (until September 2006)

Thomas von Rütte, MD student*
Dr. Cuiyan Xin, PhD (since July 2006)*
Dr. Algirdas Ziogas, PhD

External University Teachers

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

Guest scientists

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

External Computer Support

Faton Shala* (until June 2006)
Dominik Wyss*

Office

Erika Fritsche, head secretary
Sandra Suter, head secretary (since September 2006)
Peggy Shala, secretary (until June 2006)
Anita Dähler, secretary (since June 2006)

Franziska Marti*, secretary to Prof. Reuter

Workshop

Hans Andres

House Keeping

Mariter Vieites
Isa Conforti

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

3. Teaching Activities
3.1. Lectures

Lectures for medical students

Date	Lecturer	Titel of the lecture
Jan 9, 2006	Prof. Hartmut Porzig	Antiarrhytmika
Jan 18, 2006	Prof. Hartmut Porzig	Beeinflussung der kontraktilen Herzfunktion durch Pharmaka
Jan 30, 2006	Prof. Hartmut Porzig	Diuretika
Feb 13, 2006	Prof. Hartmut Porzig	Grundlagen der Homöopathie
April 24, 2006	Dr. Stephan von Gunten	Zucker-Antidiabetika
April 24, 2006	Dr. Stephan von Gunten	Fett-Lipidsenker
April 24, 2006	Dr. Stephan von Gunten	Gicht
May 01, 2006	Prof. Andrea Huwiler	Antiepileptika
May 08, 2006	Prof. Andrea Huwiler	Lokalanästhetika
May 22, 2006	Prof. Andrea Huwiler	Therapie von Morbus Parkinson und Alzheimer
May 24, 2006	Prof. Andrea Huwiler	Nebenniere
May 30, 2006	Prof. Andrea Huwiler	Schilddrüse
May 31, 2006	Prof. Andrea Huwiler	Narkosemittel
June 12, 2006	Prof. Andrea Huwiler	Angriffspunkte von Psychopharmaka
June 14, 2006	Prof. Andrea Huwiler	Neuroleptika
June 14, 2006	Prof. Andrea Huwiler	Angststörungen
June 19, 2006	Prof. Andrea Huwiler	Antidepressiva
June 21, 2006	Prof. Andrea Huwiler	Der alte Patient: - Pharmakologie und Toxikologie
June 26, 2006	Prof. Andrea Huwiler	Schmerz und Analgesiologie
July 12, 2006	Prof. Hans-Uwe Simon	Immunmodulation
Oct 25, 2006	Prof. Hans-Uwe Simon	Pharmakodynamik 1

Oct 30, 2006	Prof. Hans-Uwe Simon	Pharmakodynamik 2
Nov 01, 2006	Prof. Hans-Uwe Simon	Einführung in die Toxikologie
Nov 09, 2006	Prof. Hans-Uwe Simon	Entzündungshemmung
Nov 09, 2006	Prof. Hartmut Porzig	Signalübertragung im autonomen Nervensystem (2. Stj. Medizin)
Nov 29, 2006	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Dec 13, 2006	Prof. Uwe Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Dec 13, 2006	Prof. Uwe Zangemeister-Wittke	Wirkprinzipien der Antihypertensiva
Dec 20, 2006	Prof. Uwe Zangemeister-Wittke	Antiarrhythmika

Lectures for dental students (Coordinator: Prof. U. Zangemeister-Wittke)

Date	**Lecturer**	**Title of the lecture**
March 27, 2006	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Einführung, Rezeptoren
March 29, 2006	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Dosis-Wirkungskurven
April 03, 2006	Prof. Hans-Uwe Simon	Antagonisten / Applikation / Aufnahme
April 05, 2006	Prof. Uwe Zangemeister-Wittke	First pass / Verteilung / Elimination
April 10, 2006	Prof. Uwe Zangemeister-Wittke	Arzneimittelmetabolismus
April 12, 2006	Prof. Uwe Zangemeister-Wittke	Gesamtkinetik / Dosierung
April 24, 2006	Prof. Andrea Huwiler	Interaktionen / Pharmakogenetik, allg.
April 26, 2006	Dr. Sibylle Bürgi	Antibiotika I
May 1, 2006	Dr. Sibylle Bürgi	Antibiotika II

May 3, 2006	Dr. Sibylle Bürgi	Antibiotika III
May 8, 2006	Dr. Sibylle Bürgi	Lokalanästhetika
May 10, 2006	Dr. Sibylle Bürgi	Insulin, orale Antidiabetika
May 15, 2006	PD Dr. K. Baltensperger	Sympathikus
May 17, 2006	PD Dr. K. Baltensperger	Kreislaufpräparate I
May 22, 2006	PD Dr. K. Baltensperger	Kreislaufpräparate II
May 24, 2006	PD Dr. Peter Späth	Orale Antikoag./Plättchenhemmer
May 29, 2006	PD Dr. Armand Cachelin	Immunsuppression
May 31, 2006	PD Dr. Armand Cachelin	Starke Analgetika
June 7, 2006	PD Dr. Roger Zühlke	Schwache Analgetika I
June 12, 2,,6	PD Dr. Roger Zühlke	Schwache Analgetika II
June 14, 2006	PD Dr. Roger Zühlke	Psychopharmaka
June 19, 2006	PD Dr. Roger Zühlke	Magensäurehemmung
June 21, 2006	PD Dr. Roger Zühlke	Lokale Präparate
June 26, 2006	Prof. Uwe Zangemeister-Wittke	Examensvorbereitung
June 28, 2006	Prof. Andrea Huwiler	Benzodiazepine

Lectures for students of the Natural Sciences Faculty

Date	**Lecturer**	**Title of the lecture**
April 19, 2006	Prof. Hans-Uwe Simon	Regulation der Granulozyten-Apoptose

3.2. Coordination PBL Medical Students, 3rd year (2006/2007)

Core group:
Prof. Andrea Huwiler

Representatives of Pharmacology in teaching blocks:
Prof. Andrea Huwiler (blocks VI and VII)
Prof. Uwe Zangemeister-Wittke (blocks III and IV)
Dr. Jan Schmidt-Mende (block V)
Prof. Hans-Uwe Simon (blocks I, II, and VIII)

3.3. Tutorials (study year 2006/2007)

Medical students 3rd year:
Dr. Nicola Andia
Dr. Sébastien Conus
Dr. Souzan Salemi
PD Dr. Shida Yousefi
Dr. Algirdas Ziogas

3.4. Inaugural Lectures

Date	Lecturer	Title
March 29, 2006	Prof. Andrea Huwiler	Sphingolipids: their contribution to inflammatory processes
April 4, 2006	PD Dr. Shida Yousefi	Identification of a new calpain-mediated apoptotic pathway
July 18, 2006	Prof. Uwe Zangemeister-Wittke	Cancer drug resistance and the perspective of targeted therapy

3.5. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan 11, 2006	PD Dr. Mübeccel Akdis Swiss Institute of Allergy and Asthma Research, Davos	Immune mechanisms of allergic inflammation
Jan 13, 2006	Dr. Eleonora Simeoni Experimental Surgery Department, CHUV, Lausanne	Chemokines and chemokine receptors in heart transplantation
Jan 18, 2006	Dr. Julia Rajtarova Kinderspital, Zürich	Oligonucleotide-mediated targeted gene repair of X-linked granulomatous Disease
Jan 25, 2006	Prof. Hans-Dieter Volk Institut für Medizinische Immunologie, Charité, Berlin (D)	Immunoregulation in sepsis
Feb 1, 2006	Prof. Primus Mullis Universitäts-Kinderklinik Bern	Autosomal dominant growth hormone definiciency: What can we learn from it?
Feb 8, 2006	Dr. Alfonso Martin – Fontecha Institute for Research in Biomedicine, Bellinzona	Cell traffic in activated lymph nodes
Feb 13, 2006	Dr. Christina Nassenstein Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover (D)	Neurotrophins and their receptores in allergic asthma
Feb 22, 2006	Dr. Alexandre Arcaro Institute Clinical Chemistry, Kinder-spital, Zürich	Targetin IFG-1 receptor and PI3K signaling in pediatric malignancies
March 10, 2006	Dr. Vera Preller Hochgebirgsklinik, Davos-Wolfgang	CD26 control of CNS inflammation and autoimmunity

March 15, 2006	Dr. Doriano Fabbro Novartis, Basel	20 years protein kinase inhibitors as therapeutic agents lessons learned
March 29, 2006	Dr. Barbara Geering Ludwig Institute for Cancer Research, London (UK)	Regulation of class IA phosphoinositide 3-kinases
April 12, 2006	Prof. Daniel Hoessli Dept. of Pathology, University of Geneva	Signalling in lymphoma cells
April 19, 2006	Dr. Bart Hendriks University Children's Hospital, Zürich	Identification, isolation and maintenance of human epidermal stem cells
April 26, 2006	Dr. Mario P. Tschan Dept. of Clin. Research University of Bern	A splice variant of the tumor suppressor hDMP1 promotes cellular proliferation
May 23, 2006	Dr. Urs Christen Inst. of General Pharmacology, Univ. of Frankfurt/M. (D)	Initiation, acceleration and abrogation of autoimmune disease: Role of the pro-inflammatory chemokine CXCL10 (IP-10)
May 24, 2006	Dr. Fabienne Tacchini-Cottier Dept. of Biochemistry, University of Lausanne	Role of neutrophils in the immunoregulation of infection with L. major
June 7, 2006	Prof. Gerd Geisslinger Inst. of Clin. Pharmacology, Univ. of Frankfurt/M. (D)	Clinical pharmacological aspects of opioids
June 16, 2006	Dr. Andreina Bruno University of Palermo (I)	Leptin and apigenin: antagonists in the apoptotic pathways
July 5, 2006	Dr. Markus Neef Institute of Clinical Pharmacology, University of Bern	Antifibrotic strategies in esperimental liver cirrhosis
July 19, 2006	Prof. Robert Friis Dept. of Clin. Research University of Bern	sFRP4; a peculiar modulator of Wnt signaling associated with an onset of apoptosis, but also with tumor progression
Aug 22, 2006	Dr. Jan Schmidt-Mende Karolinska Institutet Stockholm (S)	Apoptosis in the Myelodysplastic Syndrome

Oct 11, 2006	Dr. Keith Hoek Dept. of Dermatology University Hospital, Zürich	Metastatic potential in melanoma
Oct 25, 2006	Prof. Jörg Huwiler Institute of Pharma Technology, FH Nordwestschweiz	Drug targeting using antibody-conjugated liposomes
Dec 20, 2006	Dr. Nelly Marmy Conus Cancer Center, Melbourne, Australia	Biomarker analysis of tumour response to targeted therapies

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

3.6. Bern Immunology Club (BIC)

Date	Teacher	Title of the seminar
Jan 25, 2006	Prof. Hans-Dieter Volk Institut für Medizinische Immunologie, Charité, Berlin (D)	Immunoregulation in sepsis
Feb 22, 2006	Prof. Burkhard Becher Dept. Neuroimmunology, University of Zürich	Antigen recognition in the CNS: What does the liver have to do with it?
March 29, 2006	Prof. Andrea Huwiler	Sphingolipids: their contribution to inflammatory processes
April 26, 2006	Prof. Beat Imhof Dept. Pathology, University of Geneva	The role of JAM-C in angiogenesis and immune response
May 31, 2006	Dr. Thomas Geiser Dept. of Pneumology, University of Bern	Alveolar repair in pulmonary fibrosis
June 28, 2006	Prof. Annette Oxenius ETH Zurich	T cell immunity during acute and chronic viral infections
Aug 13-15, 2006	5th International Summer School	

Sep 27, 2006	Dr. Federica Sallusto Institute for Biomedical Research, Bellinzona	Cell traffic in lymph nodes during immune responses
Oct 25, 2006	Prof. Antonius Rolink Developmental and Molecular Immunology, Basel	Molecular mechanisms guiding lymphocyte development
Nov 29, 2006	Prof. Pedro Romero CHUV, Lausanne	Naturally acquired T cell immunity to melanoma associated antigens and modulation by vaccination in cancer patients
Dec 13, 2006	Prof. Hans-Uwe Simon	Highlights of the year in clinical and experimental immunology: Cytokine storm - A life-threatening adverse effect associated with antibody treatment

For the program of the Bern Immunology Club (BIC), please consult the following website:
http://www.bic.unibe.ch/content/index_eng.html

3.7. Academic Degrees

Nathalie Boulineau, Dr. phil.
Thesis: On the subunit isoforms of the $GABA_A$ receptor
Institute of Pharmacology, Bern, March 10, 2006

Uwe Zangemeister-Wittke, Prof. Dr.
Titularprofessor,
University of Bern, May 2006

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

Group members: Simone Hiltbrand, technician[1]
Dr. Shuyu Ren, PhD[1]
Dr. Cuiyan Xin, PhD[1]
Dr. Frauke Döll, PhD[1,2]
Sabine Klawitter, PhD student[1,2]
Dr. Tanja Emmler, PhD[2]
Anna Greening, PhD student[2]
Stefanie Schwalm, PhD student[2]
Lotte P. Hofmann, Vet.med., PhD student[2]
Isolde Römer, technician[2]
Svetlana Bubnova, technician[2]
Luise Reinsberg, technician[2]

[1]Dept. of Pharmacology, University of Bern.
[2]Institut für Allgemeine Pharmakologie und Toxikologie, Universität Frankfurt/Main.

Our research is focused on sphingolipids and their contribution to physiological processes and pathological diseases. On the one side sphingolipids including ceramide, sphingosine 1-phosphate, sphingosylphosphorylcholine and the therapeutically used FTY720 are used to identify signal transduction pathways mediated by these lipids which may point to novel functions of these lipids. On the other side the regulation of sphingolipid-generating and -degrading enzymes (neutral ceramidase, sphingosine kinases) are investigated to understand under which conditions a certain sphingolipid is accumulating in the cell to exert a function. The major goal is it to identify novel therapeutic targets within the sphingolipid cascades which may turn useful in the treatment of diseases characterized by abnormal cell growth and/or death.

The immunomodulatory FTY720 and its phosphorylated derivative activate the Smad signalling cascade and upregulate connective tissue growth factor (CTGF) and collagen type IV expression in renal mesangial cells

C. Xin, S. Ren, W. Eberhardt, J. Pfeilschifter, A. Huwiler

1.--The immunomodulating agent FTY720 is a substrate for the sphingosine kinase and the phosphorylated form is able to bind to sphingosine 1-phosphate (S1P) receptors. In this study, we show that exposure of renal mesangial cells to phospho-FTY720 leads to a rapid and transient activation of several protein kinase cascades, including the mitogen- and stress-activated protein kinases. The nonphosphorylated FTY720 also increased MAPK phosphorylation, but with a reduced potency and a more delayed time course. In addition, phospho-FTY720 and FTY720 are able to increase phosphorylation of Smad proteins which are classical members of the transforming growth factor-beta (TGF-beta) signalling device,

thus suggesting a crosstalk between FTY720 and TGF-beta signalling. 2.--Pretreatment with the S1P(3) receptor antagonist suramin inhibits FTY720 and phospho-FTY720-induced Smad phosphorylation, whereas pertussis toxin pretreatment, which blocks G(i/0) proteins, has no effect on Smad phosphorylation. 3.--Since TGF-beta is a potent profibrotic cytokine in mesangial cells and upregulates the connective tissue growth factor (CTGF) and collagen as important hallmarks in the fibrotic sequelae, we investigated whether FTY720 and phospho-FTY720 are able to mimic these effects of TGF-beta. Indeed, FTY720 and phospho-FTY720 markedly upregulate CTGF and collagen type IV protein expressions. In addition, the tissue inhibitor of metalloproteinase-1 is transcriptionally activated by FTY720, whereas cytokine-induced matrix metalloproteinase-9 is down-regulated by FTY720. 4.--Depletion of the TGF-beta receptor type II by the siRNA transfection technique blocks not only Smad phosphorylation but also CTGF upregulation. Similarly, Smad-4 depletion by siRNA transfection also abrogates CTGF upregulation induced by FTY720 and phospho-FTY720. 5.--In summary, our data show that FTY720 and phospho-FTY720 not only activate the Smad signalling cascade in mesangial cells, but also upregulate the expression of CTGF and collagen. These findings suggest that FTY720 may have additional effects besides the established immunomodulatory action and, importantly, a profibrotic activity has to be considered in future experimental approaches.

See original publication No. 1

Histamine increases sphingosine kinase-1 expression and activity in the human arterial endothelial cell line EA.hy 926 by a PKC-alpha-dependent mechanism

A. Huwiler, F. Döll, S. Ren, S. Klawitter, A. Greening, I. Römer, S. Bubnova,
L. Reinsberg, J. Pfeilschifter

Sphingosine 1-phosphate (S1P) is a potent mitogenic signal generated from sphingosine by the action of sphingosine kinases (SKs). In this study, we show that in the human arterial endothelial cell line EA.hy 926 histamine induces a time-dependent upregulation of the SK-1 mRNA and protein expression which is followed by increased SK-1 activity. A similar upregulation of SK-1 is also observed with the direct protein kinase C activator 12-O-tetradecanoylphorbol-13-acetate (TPA). In contrast, SK-2 activity is not affected by neither histamine nor TPA. The increased SK-1 protein expression is due to stimulated de novo synthesis since cycloheximide inhibited the delayed SK-1 protein upregulation. Moreover, the increased SK-1 mRNA expression results from an increased promoter activation by histamine and TPA. In mechanistic terms, the transcriptional upregulation of SK-1 is dependent on PKC and the extracellular signal-regulated protein kinase (ERK) cascade since staurosporine and the MEK inhibitor U0126 abolish the TPA-induced SK-1 induction. Furthermore, the histamine effect is abolished by the H1-receptor antagonist diphenhydramine, but not by the H2-receptor antagonist cimetidine. Parallel to the induction of SK-1, histamine and TPA stimulate an increased migration of endothelial cells, which is prevented by depletion of the SK-1 by small interfering RNA (siRNA). To appoint this specific cell response to a specific PKC isoenzyme, siRNA of PKC-alpha, -delta, and -epsilon were used to selectively downregulate the respective isoforms. Interestingly, only depletion of PKC-alpha leads to a complete loss of TPA- and histamine-triggered SK-1 induction and cell migration. In summary, these data show that PKC-alpha activation in endothelial cells by histamine-activated H1-receptors, or by direct PKC activators leads to a sustained upregulation of the SK-1 protein expression and activity which, in turn, is critically involved in the mechanism of endothelial cell migration.

See original publication No. 2

Extracellular nucleotides induce migration of renal mesangial cells by upregulating sphingosine kinase-1 expression and activity

S. Klawitter, L.P. Hofmann, J. Pfeilschifter, A. Huwiler

Background and purpose: Extracellular nucleotides act as potent mitogens for renal mesangial cells (MC). In this study we determined whether extracellular nucleotides trigger additional responses in MCs and the mechanisms involved. Experimental approach: MC migration was measured after nucleotide stimulation in an adapted Boyden-chamber. Sphingosine kinase-1 (SK-1) protein expression was detected by Western blot analysis and mRNA expression quantified by real-time PCR. SK activity was measured by an in vitro kinase assay using sphingosine as substrate.Key results: Nucleotide stimulation caused biphasic activation of SK-1, but not SK-2. The first peak occurred after minutes of stimulation and was followed by a second delayed peak after 4-24 h of stimulation. The delayed activation of SK-1 is due to increased SK-1 mRNA steady-state levels and de novo synthesis of SK-1 protein, and depends on PKC and the classical MAPK cascade. To see whether nucleotide-stimulated cell responses require SK-1, we selectively depleted SK-1 from cells by using small-interference RNA (siRNA). MC migration is highly stimulated by ATP and UTP; this is mimicked by exogenously added S1P. Depletion of SK-1 by siRNA drastically reduced the effect of ATP and UTP on cell migration but not on cell proliferation. Furthermore, MCs isolated from SK-1-deficient mice were completely devoid of nucleotide-induced migration. Conclusions and implications: These data show that extracellular nucleotides besides being mitogenic also trigger MC migration and this cell response critically requires SK-1 activity. Thus, pharmacological intervention of SK-1 may have impacts on situations where MC migration is important such as during inflammatory kidney diseases.

See original publication No. 3

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5. C. Xin, A. Ren, W. Eberhardt, J. Pfeilschifter, A. Huwiler: The immunomodulatory agent FTY720 exerts anti-inflammatory capacity in renal mesangial cells and suppresses cytokine-induced secretory phospholipase A2 expression.
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We are interested in the precise features of chronic inflammatory responses. Several diseases serve as models to study such processes. In particular, we investigate pathogenic mechanisms of the following diseases: Atopic dermatitis, idiopathic eosinophilia, eosinophilic esophagitis, cystic fibrosis, sepsis, and cancer. Our research goal is the identification of new drug targets for future therapeutic approaches in these diseases. Besides the pathogenic aspects of our research, we have developed several in vitro and in vivo test systems to determine potential effects of a given drug on the immune system. Moreover, we are involved in several clinical drug studies. Our research requires a network of physician-scientists from many different clinics. Most of the participating groups are located at the Medical Faculty of the University of Bern. Results of these collaborative interactions are seen in the following abstracts, which briefly describe our research activities in 2006.

Immunologic and functional evidence for anti-Siglec-9 autoantibodies in intravenous immunoglobulin preparations

S. von Gunten, A. Schaub, M. Vogel, B.M. Stadler, S. Miescher, H.-U. Simon
(Collaboration with the Department of Immunology, University of Bern, Switzerland)

Human intravenous immunoglobulin (IVIg) preparations are increasingly used for the treatment of autoimmune diseases. Earlier work demonstrated the presence of autoantibodies against Fas in IVIg, suggesting that IVIg might be able to induce caspase-dependent cell death in Fas-sensitive cells. In this study, we demonstrate that Sialic acid-binding immunoglobulin-like lectin (Siglec)-9 represents a surface molecule on neutrophils

that is activated by IVIg, resulting in both caspase-dependent and caspase-independent forms of cell death in these cells. Neutrophil death was mediated by naturally occurring anti-Siglec-9 autoantibodies that are present in IVIg. Moreover, the efficacy of IVIg-mediated neutrophil killing was enhanced by the pro-inflammatory cytokines granulocyte/macrophage colony-stimulating factor (GM-CSF) and interferon (IFN)-γ, and this additional cell death required reactive oxygen species (ROS) but not caspases. Anti-Siglec-9 autoantibody depleted IVIg failed to induce this caspase-independent neutrophil death. These findings contribute to our understanding of how IVIg preparations exert their immunoregulatory effects under pathologic conditions and may provide a possible explanation for the neutropenia that is sometimes seen in association with IVIg therapy.
See original publication No. 1

Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis

S. Yousefi, R. Perozzo, I. Schmid, A. Ziemiecki, T. Schaffner, L. Scapozza, T. Brunner, H.-U. Simon

(Collaboration with the Pharmaceutical Biochemistry Group, School of Pharmaceutical Sciences, EPGL, University of Geneva, and Departments of Clinical Research and Pathology, University of Bern, Switzerland)

Autophagy-related gene (Atg) 5 is a gene product required for the formation of autophagosomes. We report here that Atg5, besides the promotion of autophagy, enhances the susceptibility towards apoptotic stimuli. Enforced expression of Atg5 sensitized tumor cells to anticancer drug treatment both in vitro and in vivo. In contrast, silencing the Atg5 gene with short interfering RNA (siRNA) resulted in partial chemotherapy resistance. Apoptosis was associated with calpain-mediated Atg5 cleavage, resulting in a 24-kDa N-terminal cleavage product. Atg5 cleavage was seen independent from the cell type and the apoptotic stimulus, suggesting that calpain activation and Atg5 cleavage are general phenomena of apoptotic cells. Truncated Atg5 translocated from the cytosol to mitochondria, associated with the anti-apoptotic molecule Bcl-x_L, and triggered cytochrome c release and caspase activation. Taken together, calpain-mediated Atg5 cleavage provokes apoptotic cell death and therefore represents a molecular link between autophagy and apoptosis, a finding with potential importance for clinical anticancer therapies.
See original publication No. 2

Targeting survivin via a PI3K but not c-Akt/PKB by anticancer drugs in immature neutrophils

S. Martinelli, G. Kostylina, V. Niggli, C. Baumann, M.F. Fey, H.G. Wendel, S.W. Lowe, S. Yousefi, H.-U. Simon

(Collaboration with the Departments of Pathology and Medical Oncology, University of Bern, Switzerland, and Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA)

Myelosuppression is the most common unwanted side effect associated with the administration of anticancer drugs and infections remain a common cause of death in chemotherapy-treated patients. Several mechanisms of the cytotoxicity of these drugs have been proposed and may synergistically operate in a given cell. Survivin expression has been associated with cancer, but recent reports suggest that this molecule is also expressed in several immature and mature hematopoietic cells. Here, we provide evidence that treatment of immature neutrophils with anticancer drugs reduced endogenous survivin levels causing apoptosis. The anticancer drugs did not directly target survivin, instead they blocked the activity of phosphatidylinositol-3-OH kinase (PI3K), which regulated survivin expression and apoptosis in these cells. Strikingly, and in contrast to other cells, this pathway did not involve the serine/threonine kinase c-akt/PKB. Moreover, in combination with anticancer drug therapy, rapamycin did not induce increased myelosuppression in an experimental

lymphoma mouse model. These data suggest that drugs, which block either c-akt/PKB or signaling molecules located distal to c-akt/PKB may preferentially induce apoptosis of cancer cells as they exhibit no cytotoxicity for immature neutrophils.
See original publication No. 3

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

E. M. Vassina, S. Yousefi, D. Simon, C. Zwicky, S. Conus, H.-U. Simon
(Collaboration with the Departments of Dermatology and Hematology, University of Bern, Switzerland)

The exact molecular mechanisms leading to the clinical picture of hypereosinophilic syndrome (HES) are unknown. Here, we show that cultured eosinophils purified from blood of HES patients exhibit delayed spontaneous death and relative resistance towards ceramide- but not CD95-mediated death. The subsequent investigation of members of the inhibitor of apoptosis (IAP) family revealed that HES but not normal eosinophils expressed high levels of cellular (c)IAP-2 and survivin. X-linked IAP (XIAP) was usually present in both HES and normal eosinophils. The eosinophil hematopoietins IL-3, IL-5, and granulocyte/macrophage colony-stimulating factor (GM-CSF) increased the expression of cIAP-2, survivin, and XIAP in normal eosinophils in vitro. In the blood of HES patients, we observed increased concentrations of IL-3 and/or IL-5, suggesting that these cytokines are, at least partially, responsible for the elevated levels of cIAP-2 and survivin in the eosinophils of these patients. Utilizing a cell-free system in which caspase-3 was activated in eosinophil cytosolic extracts by addition of cytochrome *c*, immunodepletion of cIAP-2, survivin, and XIAP, respectively, resulted in accelerated caspase activation. These data suggest that some members of the IAP family including survivin are regulated by survival cytokines and inhibit the caspase cascade in HES eosinophils. The cytokine-dependent mechanism of delayed eosinophil apoptosis described here may also apply to other eosinophilic diseases.
See original publication No. 4

Epidermal caspase-3 cleavage associated with interferon-γ-expressing lymphocytes in acute atopic dermatitis lesions

D. Simon, R.L.P. Lindberg, E. Kozlowski, L.R. Braathen, H.-U. Simon
(Collaboration with the Department of Dermatology, University of Bern, and Departments of Research and Neurology, University Hospitals Basel, Switzerland)

Keratinocyte apoptosis mediated by Fas/Fas ligand molecular interactions and subsequent caspase activation is believed to play an important role in the pathogenesis of atopic dermatitis (AD), in particular for the formation of spongiosis. To estimate epidermal caspase activation in normal and AD skin under in vivo conditions, we analyzed caspase-3 cleavage by immunohistology. In normal skin as well as non-lesional AD skin, we detected caspase-3 cleavage in single cells of the basal layer. In contrast, in acute lesional AD skin, we obtained not only evidence for increased expression of cleaved caspase-3 in keratinocytes of the basal layer, we also observed caspase-3 cleavage in one or more layers of the spinous cell layer, in particular in spongiotic areas. Short-term topical treatment of the skin lesions with tacrolimus or pimecrolimus abolished the expression of cleaved caspase-3 in the spinous layer. Moreover, epidermal caspase-3 cleavage correlated with the numbers of dermal interferon (IFN)-γ expressing CD4+ and CD8+ lymphocytes in skin lesions of AD patients, supporting the view that IFN-γ is important for the activation of proapoptotic pathways in keratinocytes. This is also confirmed by the observation of increased Fas expression on keratinocytes in acute AD lesions that was markedly reduced following topical calcineurin inhibitor treatment. These data suggest that caspase-3 cleavage in the spinous layer of the

epidermis is a pathologic event contributing to spongiosis formation in AD, whereas cleavage of caspase-3 in basal cells might represent a physiologic mechanism within the process of epidermal renewal.
See original publication No. 5

Intravenous immunoglobulin preparations contain anti-Siglec-8 autoantibodies
S. von Gunten, M. Vogel, A. Schaub, B.M. Stadler, S. Miescher, P.R. Crocker, H.-U. Simon (Collaboration with the Department of Immunology, University of Bern, Switzerland, and Division of Cell Biology and Immunology, School of Life Sciences, University of Dundee, Dundee, UK)
Human intravenous immunoglobulin (IVIg) preparations are used for the treatment of autoimmune and allergic diseases. Natural autoantibodies are believed to contribute to IVIg-mediated anti-inflammatory effects. To address the question whether IVIg preparations contain anti-sialic acid-binding Ig-like lectin-8 (Siglec-8) autoantibodies. The presence of possible anti-Siglec-8 autoantibodies in IVIg preparations was first examined by functional eosinophil death and apoptosis assays. Specificity of IVIg effects was shown by depleting anti-Siglec-8 autoantibodies from IVIg. Binding of purified anti-Siglec-8 autoantibodies to recombinant Siglec-8 was demonstrated by an immunodot assay. IVIg exerts cytotoxic effects on purified human blood eosinophils. Both potency and efficacy of the IVIg-mediated eosinophil killing effect was enhanced by interleukin-5 (IL-5), granulocyte/macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and leptin. Similarly, inflammatory eosinophils obtained from patients suffering from the hypereosinophilic syndrome (HES) demonstrated increased Siglec-8 cytotoxic responses when compared to normal blood eosinophils. Pharmacologic blocking experiments indicated that the IVIg-mediated additional eosinophil death in the presence of cytokines is largely caspase-independent, but depends on reactive oxygen species (ROS). Anti-Siglec-8 autoantibody-depleted IVIg failed to induce caspase-independent eosinophil death. Taken together, these data suggest that IVIg preparations contain natural anti-Siglec-8 autoantibodies.
See original publication No. 6

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*Joint supervision together with Prof. Dr. H.-U. Simon.

We are interested in molecular mechanisms regulating apoptosis and autophagy, in particular in cells of the immune system. We obtained evidence that both apoptosis and autophagy play important roles in the regulation of immune responses. In addition, we study extracellular killing mechanisms of eosinophils that might be related to cell death.

Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis
S. Yousefi, R. Perozzo, I. Schmid, A. Ziemiecki, T. Schaffner, L. Scapozza, T. Brunner, H.-U. Simon
(Collaboration with the Pharmaceutical Biochemistry Group, School of Pharmaceutical Sciences, EPGL, University of Geneva, and Departments of Clinical Research and Pathology, University of Bern, Switzerland)
Autophagy-related gene (Atg) 5 is a gene product required for the formation of autophagosomes. We report here that Atg5, besides the promotion of autophagy, enhances the susceptibility towards apoptotic stimuli. Enforced expression of Atg5 sensitized tumor cells to anticancer drug treatment both in vitro and in vivo. In contrast, silencing the Atg5 gene with short interfering RNA (siRNA) resulted in partial chemotherapy resistance. Apoptosis was associated with calpain-mediated Atg5 cleavage, resulting in a 24-kDa N-terminal cleavage product. Atg5 cleavage was seen independent from the cell type and the apoptotic stimulus, suggesting that calpain activation and Atg5 cleavage are general phenomena of apoptotic cells. Truncated Atg5 translocated from the cytosol to mitochondria, associated with the anti-apoptotic molecule Bcl-x_L, and triggered cytochrome c release and caspase activation. Taken together, calpain-mediated Atg5 cleavage provokes apoptotic cell death and therefore represents a molecular link between autophagy and apoptosis, a finding with potential importance for clinical anticancer therapies.
See original publication No. 1

Apoptotic neutrophils release macrophage migration inhibitory factor upon stimulation with tumor necrosis factor-a
A. Daryadel, R.F. Grifone, H.-U. Simon, S. Yousefi
Macrophage migration inhibitory factor (MIF) is an important cytokine involved in the regulation of innate immunity and present at increased levels during inflammatory responses. Here, we demonstrate that mature blood and tissue neutrophils constitutively express MIF as a cytosolic protein not associated with azurophil granules. Functionally active MIF, but not proteases stored in azurophil granules, was released from apoptotic neutrophils following short-term tumor necrosis factor (TNF)-α stimulation in a caspase-dependent manner and prior to any detectable phagocytosis by monocyte-derived

macrophages. Moreover, TNF-α - mediated MIF release was blocked by glyburide and propenicide, both inhibitors of ATP-binding cassette (ABC)-type transporters, suggesting that this transporter system is activated during neutrophil apoptosis. Taken together, apoptotic mature neutrophils release MIF upon short-term TNF-α stimulation, suggesting that apoptosis may not always occur without the induction of pro-inflammatory mechanisms. **See original publication No. 2**

Eosinophils form extracellular traps in bacterial and parasitic infectious diseases
S. Yousefi, R. F. Grifone, A. Straumann, G. J. Gleich, H.-U. Simon
(Collaboration with the Department of Dermatology, University of Utah, Salt Lake City, USA, and Department of Gastroenterology, Kantonsspital Olten, Olten, Switzerland)
Eosinophils are considered as proinflammatory effector cells, which may be helpful in the defense against bacteria and parasites. Here, we demonstrate that activated eosinophils release granule and nuclear proteins, which form extracellular fibers. Similar structures have previously been described following activation of neutrophils and called neutrophil extracellular traps (NETs). We further show that eosinophil extracellular traps (EETs) bind and kill bacteria. EETs were identified in vivo in the course of bacterial and parasitic infections, respectively. Thus, eosinophils contribute to innate immune responses in tissues by inhibition of pathogen spreading and, subsequently, by pathogen killing.

Original publications

1. S. Yousefi, R. Perozzo, I. Schmid, A. Ziemiecki, T. Schaffner, L. Scapozza, T. Brunner, H.-U. Simon: Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis.
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Hormon Res. 65 (2006), 132-141.

Book chapters

1. S. Yousefi, S. Martinelli, F. Altznauer, E. Vassina, H.-U. Simon: Survivin – a key regulator of neutrophil and eosinophil survival. In: From genes to phenotypes: the basis of future allergy management. (Eds. J. Bienenstock, J. Ring, A.G. Togias); Hogrefe & Huber Publishers, Cambridge, Göttingen, 2006.
Allergy Clin. Immunol. Int.: J. World Allergy Org. 17, suppl. 2 (2005), 26-28.

2. D. Simon, E. Vassina, S. Yousefi, E. Kozlowski, L.R. Braathen, H.-U. Simon: Reduced numbers of cytokine-expressing inflammatory cells in atopic dermatitis after topical tacrolimus treatment. In: From genes to phenotypes: the basis of future allergy management. (Eds. J. Bienenstock, J. Ring, A.G. Togias); Hogrefe & Huber Publishers, Cambridge, Göttingen, 2006.
Allergy Clin. Immunol. Int.: J. World Allergy Org. 17, suppl. 2 (2005), 115-117.

Group Prof. Dr. Uwe Zangemeister-Wittke

Group members: Dr. Algirdas Zogas, PhD
Annika Quast, PhD student
Susanne Probst, technician
Sajid Hussain, PhD student[1]
Patricia Martin-Killias, PhD student[1]
Adriana Oliveira dos Santos, PhD student[1] (until March 2006)

[1]Department of Biochemistry, University of Zurich

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

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

In our tumor targeting program we have developed tumor-selective drug delivery systems based on recombinant antibodies and synthetic protein ligands directed against tumor-associated antigens. An EpCAM-specific single-chain immunotoxin is currently in phase III oncology trials and other developments for targeted cancer therapy such as tumor-targeted nanovesicles and new toxin formulations are under investigation. As a recent innovative step towards improved tumor targeting, we have developed fully synthetic designed ankyrin repeat proteins (DARPins). These proteins lack intramolecular cysteines, can be expressed in large amounts in E. coli shake flasks and are highly stable even at temperatures well above 70°C. These new targeting ligands with specificity against EpCAM will replace our scFv in future drug delivery systems.

Antisense-mediated ML-IAP downregulation sensitizes G361 melanoma cells to cisplatin

P. Mousavi-Shafaei, A.A. Ziaee, E. Azizi, U. Zangemeister-Wittke

(Collaboration with the Institute of Biochemistry and Biophysics, Tehran University of Medical Sciences, Tehran, Iran)

Malignant melanoma is an aggressive form of skin cancer that is highly resistant to conventional therapies. The melanoma inhibitor of apoptosis protein is a potent inhibitor of apoptosis and is overexpressed in melanoma cells, but undetectable in most normal tissues including melanocytes. We designed 20-mer phosphorothioate antisense oligonucleotides complementary to five putatively single-stranded sites on the melanoma inhibitor of apoptosis protein mRNA and investigated their ability to sensitize G361 melanoma cells to cisplatin. Inhibition of melanoma inhibitor of apoptosis protein mRNA and protein expression were measured by real-time polymerase chain reaction and immunoblotting. Cell viability and apoptosis were quantitated by colorimetric viability assays and by annexin V staining, respectively. Oligonucleotide M706 was identified as the most efficient antisense sequence which downregulated melanoma inhibitor of apoptosis protein mRNA and protein levels in G361 cells by 68 and 78%, respectively. The specificity of target downregulation was confirmed using scrambled sequence control oligonucleotides that only marginally decreased melanoma inhibitor of apoptosis protein expression. Whereas downregulation of melanoma inhibitor of apoptosis protein moderately inhibited cell growth by 26%, in combination with cisplatin, this resulted in a supra-additive effect with almost 57% reduction in G361 cell viability compared with cisplatin alone (17%) ($P<0.05$). Cell death was mainly due to apoptosis as demonstrated by a 3- to 4-fold increase in annexin V-positive cells and typical morphological changes compared with controls. In summary, we describe a new antisense oligonucleotide that efficiently downregulates melanoma inhibitor of apoptosis protein expression and sensitizes melanoma cells to cisplatin.

See original publication No. 1

Chemosensitization of carcinoma cells using EpCAM-targeted liposomal bcl-2/bcl-xL antisense

S. Hussain, A. Pluckthun, T.M. Allen, U. Zangemeister-Wittke

(Collaboration with the Department of Biochemistry, University of Zurich, Switzerland)

Nanoscale drug delivery systems, such as sterically stabilized immunoliposomes binding to internalizing tumor-associated antigens, can increase therapeutic efficacy and reduce toxicity to normal tissues compared with nontargeted liposomes. The epithelial cell adhesion molecule (EpCAM) is of interest as a ligand for targeted drug delivery because it is abundantly expressed in solid tumors but shows limited distribution in normal tissues. To generate EpCAM-specific immunoliposomes for targeted cancer therapy, the humanized single-chain Fv antibody fragment 4D5MOCB was covalently linked to the exterior of coated cationic liposomes. As anticancer agent, we encapsulated the previously described antisense oligonucleotide 4625 specific for both bcl-2 and bcl-xL. The EpCAM-targeted immunoliposomes (SIL25) showed specific binding to EpCAM-overexpressing tumor cells, with a 10- to 20-fold increase in binding compared with nontargeted control liposomes. No enhanced binding was observed on EpCAM-negative control cells. On cell binding, SIL25 was efficiently internalized by receptor-mediated endocytosis, ultimately leading to down-regulation of both bcl-2 and bcl-xL expression on both the mRNA and protein level, which resulted in enhanced tumor cell apoptosis. In combination experiments, the use of SIL25 led to a 2- to 5-fold sensitization of EpCAM-positive tumor cells of diverse origin to death induction by doxorubicin. Our data show the promise of EpCAM-specific drug delivery systems, such as antisense-loaded immunoliposomes, for targeted cancer therapy.

See original publication No. 2

Original publications

1. P. Mousavi-Shafaei, A.A. Ziaee, E. Azizi, U. Zangemeister-Wittke: Antisense-mediated ML-IAP downregulation sensitizes G361 melanoma cells to cisplatin. Anti-cancer drugs 17 (2006), 1031-1039.

2. S. Hussain, A. Pluckthun, T.M. Allen, U. Zangemeister-Wittke: Chemosensitization of carcinoma cells using EpCAM-targeted liposomal bcl-2/bcl-xL antisense. Mol. Cancer Ther. 5 (2006), 3170-3180.

3. K. Yamanaka, P. Rocchi, H. Miyake, L. Fazli, A. So, U. Zangemeister-Wittke, M.E. Gleave: Induction of apoptosis and enhancement of chemosensitivity in human prostate cancer LNCaP cells using bispecific antisense oligonucleotide targeting Bcl-2 and Bcl-xL genes. BJU Int. 97 (2006), 1300-1308.

4. S. Hopkins-Donaldson, L. Belyanskaya, S. Kurtz, B. Sigrist, U. Zangemeister-Wittke, R. Stahel: p53-induced apoptosis occurs in the absence of p14ARF in malignant pleural mesothelioma. Neoplasia 8 (2006), 551-559.

5. S. Kubetzko, E. Balic, R. Waibel, U. Zangemeister-Wittke, A. Plückthun: PEGylation and multimerization of the anti-p185HER-2 single-chain Fv 4D5: effects on tumor targeting. J. Biol. Chem. 281 (2006), 35186-35201.

Review articles

1. V. Wacheck, U. Zangemeister-Wittke: Antisense molecules for targeted cancer therapy. Crit. Rev. Oncol. Hematol. 59 (2006), 65-73.

2. U. Zangemeister-Wittke, A. Huwiler: Antisense targeting of Mcl-1 has therapeutic potential in gastric cancer. (commentary) Cancer Biol. Ther. 5 (2006), 1355-1356.

3. U. Zangemeister-Wittke: Krebsbehandlung mit Antisensemolekülen. Wissenschaftliche Aspekte und klinische Perspektiven. Der Onkologe, in press.

Book chapter

1. H.-U. Simon, U. Zangemeister-Wittke: Apoptosis, regulation and clinical implications. In Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine (Ruckpaul K. Ganten D., ed.), Springer-Verlag GmbH & Co. KG, Heidelberg, Germany, p. 85-91, 2006. ISBN978-3-540-44244-8 (Print) 978-3-540-29623-2 (Online).

2. J.G. Edwards, U. Zangemeister-Wittke, K.J. O'Byrne: Growth and survival factors in malignant pleural mesothelioma (MPM). Malignant Pleural Mesothelioma. Oxford University Press., in press.

New patent application/PCT

U. Zangemeister-Wittke, C. Di Paolo: Methods for treating cancer using an improved immunotoxin. January, 2006. 171643 (File 3539/1).

Additional publications by former PKI principal investigators

Original publications

1. S.F. Muhlebach, G. Karlaganis, U.E. Honegger: Kinectic assessment of persistent halogenated xenobiotics in cell culture models: comparison of mono- and poly-halogenated compounds.
   Chemosphere 62 (2006), 1838-1845.

2. G.M. De Marchis, S. Burgi, U. Kientsch, U.E. Honegger: Vitamin E reduces antidepressant-related beta-adrenoceptor down-regulations in cultured cells. Compareable effects on St. John's Wort and tricyclic antidepressant treatment.
   Planta Med. 72 (2006), 1436-1437.

3. A. Vichalkovski, I. Kotevic, N. Gebhardt, R. Kaderli, H. Porzig: Tyrosine kinase modulation of protein kinase C activity regulates G protein-linked Ca^{2+} signaling in leukemic hematopoietic cells
   Cell Calcium 39 (2006), 517-528.

4. R. Baur, F. Minier, E. Sigel: A GABA(A) receptor of defined subunit composition and positioning: concatenations of five subunits.
   FEBS Lett. 580 (2006), 1616 – 1620.

4.2. Congress Invitations

Dr. Sebastien Conus

4th Swiss Apoptosis Meeting, Bern (CH), August 24-25, 2006;
Cathepsin D is a key initiator protease during neutrophil apoptosis.

Workshop of the Microscopy Imaging Center (MIC), University of Bern, Bern (CH), December 12, 2006;
Confocal microscopy as a tool to follow intracellular mechanisms.

Dipl. Biol. Sabine Klawitter

Annual meeting of the German Society of Pharmacology and Toxicology (DGPT), Mainz (D), April 5, 2006;
Regulation of sphingosine kinase-1 by extracellular nucleotides.

Prof. Harald Reuter

International Symposium “25 Years of Giga-Seal Patch Clamping”
(Academia Europaea, Klaus Tschira Foundation, Heidelberg (D).

Internationales Menschenrechtsforum Luzern „Menschenrechte und Bildung“, Luzern (CH), May 31 – June 1, 2006.

Friedrich-Miescher-Institut, Basel (Scientific Advisory Board Meeting), Murten (CH), September 21 – 25, 2006.

International Council of the “Israeli-Palestinian Science Organization”, UNESCO, Paris (F) November 7 – 10, 2006.

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie, Bern (CH), January 26, 2006;
Strategien der Immunmodulation bei Erkrankungen des Menschen.

First International Workshop on Animal Models in Cell Death Signaling & Cancer (“Death in the Alps”), Obergurgl (A), January 25-29, 2006;
Atg5 is a pro-apoptotic molecule upon cleavage by calpain.

Universitätsspital Basel, Allergologische Fortbildung, Basel (CH), March 16, 2006;
Pathophysiologie der eosinophilen Entzündung.

XXV. Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Vienna (A), June 10-14, 2006;
Understanding asthma.

XXV. Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Vienna (A), June 10-14, 2006;
Eosinophil esophagitis.

Workshop on Apoptosis “Signalling in DNA damage and cell death”, Loveno di Menaggio (I), June 25-28, 2006;
A new pro-apoptotic pathway involving calpain and Atg5.

4th Swiss Apoptosis Meeting, Bern (CH), August 24-25, 2006;
Apoptosis regulation by autophagy gene 5.

Highlights in Allergy and Asthma, In Honor of Prof. Kurt Blaser,
Davos (CH), October 22-23, 2006;
Eosinophils in allergic inflammation.

Haut und Ernährung: Von (A)llergien bis (Z)inkmangel, Dermatologische Klinik, Inselspital, Universität Bern, Bern (CH), November 9, 2006;
Leptin – ein multifunktionelles Hormon.

8. Leipziger Umweltsymposium: Umweltmedizin ein Grenzgebiet zur Allergologie,
Leipzig (D), November 24-25, 2006;
Rolle der Eosinophilen bei allergischen Erkrankungen; Pathogenese – Diagnostik – Therapie.

PD Dr. Shida Yousefi

5th International conference on cystein proteinases and their inhibitors: From structure to regulation and biology, Portoroz (Slovenia), Sept. 2-6, 2006;
Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis.

Prof. Uwe Zangemeister-Wittke

1st International Symposium on EpCAM Function and Clinical Application, Schloss Höhenried bei München (D), June 15-17, 2006;
EpCAM-Specific immunotoxins and liposomal drug delivery systems for targeted cancer therapy.

Annual meeting of the Swiss Society of Pharmacology and Toxicology (SSPT), CHUV, Lausanne (CH), October 5-6, 2006;
Cancer therapy using antibodies and synthetic protein ligands.

4.3. Seminar Invitations

Prof. Andrea Huwiler

Novartis, Wien (A); March 22, 2006; guest of Dr. Andreas Billich:
Regulation of sphingosine kinase-1 in tumor and non-tumor cells.

Novartis, Basel (CH); April 11, 2006; guest of Dr. Doriano Fabbro:
Regulation of sphingosine kinase-1 in tumor and non-tumor cells.

Evening guest lecture: Retreat of the Pharmazentrum Frankfurt (D), Rauischholzhausen (D); October 30, 2006; guest of Prof. Dr. Josef Pfeilschifter:
In vivo functions of sphingosine kinases.

Prof. Hans-Uwe Simon

American Academy of Allergy Asthma & Immunology, 62nd Annual Meeting, Miami Beach (FL, USA); March 5, 2006;
Apoptosis and inflammation.

Clinic of Visceral and Transplantation Surgery, University of Bern, Bern (CH); March 18, 2006; guest of Prof. Dr. Daniel Candinas:
Apoptosis and its role in inflammation.

Institut für Pharmakologie und Klinische Pharmakologie, Universität Düsseldorf, Düsseldorf (D); May 17, 2006; guest of Prof. Dr. Karsten Schrör:
Autophagy and apoptosis: Identification of an intracellular switching factor.

GlaxoSmithKline AG, Münchenbuchsee (CH); July 6, 2006; guest of Dr. Daniel Berger:
Eosinophilic esophagitis.

Institut für Zellbiologie, Universität Bern, Bern (CH); November 20, 2006;
guest of Prof. Dr. Thomas Seebeck:
Calpain-mediated pro-apoptotic mechanisms.

Institut für Molekulare Medizin und Zellforschung, Universität Freiburg i.Br. (D);
November 20, 2006; guest of Prof. Dr. Christoph Borner:
Atg5 – a molecular switch between autophagy and apoptosis.

Sonderforschungsbereich 415, Universität Kiel, Kiel (D); December 7, 2006;
guest of Prof. Dr. Holger Kalthoff:
A new pro-apoptotic pathway involving calpain and Atg5.

Bern Immunology Club, Bern (CH); December 13, 2006;
Cytokine storm: A life-threatening adverse effect associated with antibody treatment.

PD Dr. Shida Yousefi

Department of Pathology, University of Bern, Bern (CH), special course on apoptosis; August 28, 2006; guest of Prof. Dr. Thomas Brunner:
Non-caspase proteases and cell death.

Prof. Uwe Zangemeister-Wittke

Department of Pathology, University of Bern, Bern (CH); March 22, 2006;
guest of Prof. Dr. Christoph Müller:
Regulation of anti-apoptosis in small cell lung lung cancer.

Institute of Chemotherapy Research, Georg Speyer Haus, Frankfurt/M. (D); April 27, 2006;
guest of Prof. Dr. Winfried Wels:
Anti-apoptosis in small cell lung cancer mediated by chemotherapy and TRAIL.

Klinisch-Biochemisches Kolloquium am Universitätskinderspital Zürich, Zürich (CH);
November 7, 2006; guest of Dr. Alexandre Arcaro:
Anti-apoptosis in small cell lung cancer mediated by anti-cancer agents.

4.4. Organization of Meetings and Courses

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology (SSPT):
Fortschritte in der Pharmakologie – Immunsystem; Bern (CH), January 26, 2006

5th III-Bern International Summer School; Heiligenschwendi (CH), August 13-15, 2006

4th Meeting of the Swiss Apoptosis Meeting (together with T. Brunner);
Bern (CH), August 24-25, 2006

Teaching course: Basics in apoptosis signalling (together with T. Brunner);
Bern (CH), August 28, 2006

Bern Immunology Club (together with the other founder members); Dept. of Pharmacology, University of Bern, one meeting in each month of 2006

PD Dr. Shida Yousefi

DKF, PKI, PIAF - Course in immunofluorescent staining, confocal microscopy, and image analysis. Bern (CH), May 10 – 12, 2006.

4.5. Invited Chairperson at Congresses

Prof. Andrea Huwiler

Annual meeting of the German Society of Pharmacology and Toxicology (DGPT); Session: “Biochemische Pharmakologie”; Mainz (D), April 5, 2006.

Prof. Hans-Uwe Simon

Symposium der Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie; Morning session; Bern (CH), January 26, 2006.

4th EAACI GA^{2}LEN Davos meeting (European Academy of Allergol. and Clin. Immunology); Session III: “Inflammatory cells and mediators”; Grainau (D), February 16-19, 2006.

62nd Annual Meeting of the American Academy of Allergy Asthma & Immunology; Workshop 5805: “Mucosal immunity in the 21st century”; Miami Beach (FL, USA), March 3-7, 2006.

4th Scientific Meeting des MD-PhD Programms der Schweizerischen Akademie der Medizinischen Wissenschaften (SAMW); Sitzung: Oral presentations I and II; Tagungszentrum Leuenberg bei Hölstein (CH), March 19-21, 2006.

Annual Congress of the Swiss Society for Allergology and Immunology (SSAI); Symposium A3: Immunotherapy; ETH Zurich, Zurich (CH), March 30-31, 2006.

26th Symposium of the Collegium Internationale Allergologium (CIA); Poster session: Effector cells; Malta, May 5-10, 2006.

XXV. Congress of the Eur. Academy of Allergol. and Clin. Immunol. (EAACI); Oral Abstract Session 16: “Asthma pathogenesis evaluated in patients”; Vienna (A), June 10-14, 2006.

XXV. Congress of the Eur. Academy of Allergol. and Clin. Immunol. (EAACI); Poster Session: “Inflammatory cells and mediators II - eosinophils”; Vienna (A), June 10-14, 2006.

Workshop on Apoptosis “Signalling in DNA damage and cell death”; Afternoon session on June 26, 2006; Loveno di Menaggio (I), June 25-28, 2006.

14th Euroconference on Apoptosis; Session 7: “Cell death pathways”; Cagliari, Sardinia (I), Sept. 30 – Oct. 4, 2006.

4.6. Referee Work for Peer-Reviewed Journals

Prof. Andrea Huwiler

Biochim. Biophys. Acta
Blood
Br. J. Pharmacol.
Carcinogenesis
Circ. Res.
Clin. Chem. Lab. Med.
Diabetologica
Eur. J. Pharmacol.
Exp. Cell Res.
FEBS Lett.
Hormone and Metabol. Res.
J. Biol. Chem.
J. Cell. Biochem.
J. Cell. Physiol.
J. Exp. Pharmacol. Ther.
Kidney and Blood Pressure Research
Kidney Int.
Naunyn Schmiedeb. Arch. Pharmacol.
Planta Medica

Prof. Hans-Uwe Simon

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

Prof. Uwe Zangemeister-Wittke

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

4.7. Referee Work for Grant Bodies

Prof. Andrea Huwiler

Deutsche Forschungsgemeinschaft (DFG)
Norwegischer Forschungsrat (NFR)

Prof. Hans-Uwe Simon

Swiss National Science Foundation (SNF)
Deutsche Forschungsgemeinschaft (DFG)
Landesstiftung Baden-Württemberg, Stuttgart
Science Foundation Irland (SFI)
The Wellcome Trust, London, UK
Medical Research Council (MRC)
Italian Association for Cancer Research (AIRC)

Prof. Uwe Zangemeister-Wittke

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

4.8. Awards

Dr. Sebastien Conus

1st Poster Prize
4th Swiss Apoptosis Meeting
(Bern, August 24 – 25, 2006)

PD Dr. Shida Yousefi

Novartis Poster Prize (1st Prize)
Swiss Society of Pharmacology and Toxicology (SSPT)
(Lausanne, October 5 – 6, 2006)

5. Administrative, Advisory, and Honorary Posts

Dr. Sebastien Conus

Webmaster of the PKI (since January 2006)

Prof. Harald Reuter

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

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

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

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

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

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

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

Prof. Hans-Uwe Simon

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

Member of the Ethics Committee, European Academy of Allergology and Clinical Immunology (EAACI), 2003-2007

Member of the Board of the Immunology Section of the European Academy of Allergology and Clinical Immunology (EAACI), June 2003-2007

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

Member of the Immunomodulation Committee (Workshops) of the American Academy of Allergy, Asthma and Immunology (AAAAI), 2004-2008

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), 2001-2008

Member of the Council of the Swiss Society of Pharmacology and Toxicology (SSPT), 2002-2008

President of the Swiss Society of Pharmacology and Toxicology (SSPT), 2004-2007

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

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

President of the Swiss Society of Experimental Pharmacology (SSEP), 2005-2008

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

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

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

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

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

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

Member of the Advisory Board of Novartis Pharma Schweiz AG “Xolair”, 2005-2006

Member of the Advisory Board, Foundation pour la recherche et le traitement des maladies respiratoires, Lausanne, since 2006

Associate Editor, Allergy

Section Editor, Apoptosis

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

Member of the Scientific Board, Allergologie

Member of the Editorial Board, Clinical and Experimental Allergy

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

Member of the Advisory Board, Allergo-Journal

Member of the Advisory Editorial Board, Planta Medica

Member of the Editorial Board, Cell Death and Differentiation

Member of the Editorial Board, Journal Allergy Clinical Immunology

PD Dr. Shida Yousefi

Coordinator for radioactive work at the PKI

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

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

Coordinator for PC work at the PKI

Prof. Uwe Zangemeister-Wittke

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

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

Member of the Editorial Board of the journal Oligonucleotides

Consultant for Defined Health Inc., NJ, USA

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

Biosafety Coordinator PKI (since December 2005)

Information Technology Coordinator at the PKI (since December 2005)

6. Services

6.1. Confocal Microscopy

The facility belongs to the **Department of Clinical Research (DKF)** of the University of Bern. It hosts a Zeiss laser scanning microscope (LSM410), which may be used by members of the Medical Faculty at a small charge (CHF 10 per h). Together with the Image analysis station, it was in operation in 2006 for approximately 300 hours. The facility for confocal microscopy and image analysis was operated by PD Dr. S. Yousefi. Under the supervision of the coordinator, a whole team of qualified individuals provided training for new users, as well as technical and scientific support. The DKF compensated this work by providing the salary for one Ph.D. student of our institute. During the past year the confocal microscope has been used by 23 different research groups. In 2006, the operator and her team spent for the facility approximately 400 hours. In general, the usage of this facility decreased compared to the years before, most likely due to the fact that the instrument is too old (it has been used since 1993). It is planned that the LSM410 is replaced by a new confocal microscope in 2007.

6.2. Flow Cytometry

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

7. Public Work

7.1. Art Exhibitions

Eva Bigler & Tara Wilkinson, Bern, Switzerland
Vernissage: June 15, 2006

Jürg Marti, Bern, Switzerland
Vernissage: November 2, 2006

8. Sponsors

8.1. Research Grants

Prof. Andrea Huwiler

Swiss National Science Foundation (grant No. 3100A0-111806/1)
Deutsche Forschungsgemeinschaft (grant No. HU842/4-1)
Wilhelm Sander-Stiftung (No. 2005.094.1)
Novartis Stiftung (06B43)
Stiftung zur Förderung der wissenschaftlichen Forschung an der Universität Bern

Prof. Hans-Uwe Simon

Swiss National Science Foundation (grant No. 310000-107526)
OPO-Foundation, Zurich (CH)
Stanley Thomas Johnson Foundation, Bern (CH)
Bernische Krebsliga, Bern (CH)
GlaxoSmithKline, Greenford (UK)
Roche Pharma (Schweiz) AG, Reinach (CH)
Essex Chemie AG, Lucerne (CH)

PD Dr. Shida Yousefi

Swiss National Science Foundation (grant No. 31-068449.02)
Stiftung zur Förderung der wissenschaftlichen Forschung an der Universität Bern

Prof. Uwe Zangemeister-Wittke

Swiss National Science Foundation (grant No. 3100AO-103726)
Krebsliga Zürich
Legat der Krebskommission Zürich (interdisciplinary research networking)
Sassella-Stiftung of the Zürcher Kantonalbank
Werner und Hedy Berger-Janser-Stiftung (as from December 2006)

8.2. Meetings

5th III-International Summer School, Heiligenschwendi (CH), August 13-15, 2006

Allergomed, Therwil
AstraZeneca AG, Zug
Becton Dickinson Biosciences, Allschwil
CSL Behring AG, Bern
Essex Chemie AG, Luzern
GlaxoSmithKline AG, Münchenbuchsee
Novartis Pharma (Schweiz) AG, Bern
Pfizer AG, Zürich
Programm für die Interfakultäre Ausbildung des Forschungsnachwuchses der Univ. Bern
USGEB

4th Swiss Apoptosis Meeting, Bern (CH), August 24-25, 2006

Alexis Corporation, Lausen
Catalys AG, Wallisellen
Cell Signaling Technologies, Allschwil
Fluka Chemie GmbH, Buchs
Juro Supply GmbH, Lucerne
LabForce AG, Nunningen
LuBioScience GmbH, Lucerne
VWR International AG, Lucerne
Institute of Pathology, University of Bern

8.3. Seminars „Progress in Pharmacology“

AstraZeneca AG, Zug
CSL Behring AG, Bern
Pfizer AG, Zürich
Vifor AG, Villars-sur-Glâne

8.4. Travel Support

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Support of PD Dr. Shida Yousefi
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8.5. Other Support

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