Annual Report 2007

Institut für Pharmakologie (PKI)

der Universität Bern

Institute of Pharmacology,

University of Bern

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1. Introduction

1.1. Vorwort

Dies ist der siebente umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat sich auch im Jahr 2007 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 2007 trugen wir dazu bei, die Kommunikation zwischen Wissenschaftlern und Öffentlichkeit zu fördern. Dazu dienten u.a. eine Vernissage, die viele Gäste in das PKI lockte.

Das Jahr 2007 war davon geprägt, dass sich die neuen Forschungsgruppen (Frau Prof. Huwiler, Frau PD Dr. Yousefi und Herr Prof. Zangemeister-Wittke) im Institut fest etabliert haben und eine erfolgreiche Forschung durchführen. Unsere Verpflichtungen in der Lehre wurde auch nach den altersbedingten Rücktritten der ehemaligen Dozenten nahtlos wahrgenommen.

Neben unserer regulären Lehrtätigkeit im 3. Studienjahr Medizin sowie neben der Ausbildung der ZahnmedizinerInnen sind Herr Prof. Simon und Frau PD Dr. Yousefi zusätzlich auch in die Ausbildung von Studenten der Biologie (Naturwissenschaftliche Fakultät der Universität Bern) einbezogen. Die Dozenten des PKI sind ausserdem 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 und Sponsorengeldern bestritten. Im Institut arbeiten gegenwärtig 17 DoktorandInnen (10 PhD, 7 MD), und zwei Doktorandinnen haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2007 insgesamt 26 Originalarbeiten sowie 15 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >250). MitarbeiterInnen des Instituts wurden zu insgesamt 30 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. Lauterburg (Institut für Klinische Pharmakologie) organisierter Pharmakologie-Kongress zog ca. 180 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 als Präsident der SGEP. Die SGEP initiierte einen neuen Kurs innerhalb eines M.Sc. Programms für Drug Development Sciences. Hierzu werden auch Veranstaltungen in Bern angeboten (Prof. Huwiler, Prof. Simon). Prof. Simon wurde in 2007 zum Präsidenten der Union der Schweizerischen Gesellschaften für Experimentelle Biologie (USGEB) und zum Präsidenten der European Cell Death Organization (ECDO) gewählt.

Ich danke allen Mitarbeitern und Mitarbeiterinnen für ihren Einsatz, welcher auch im Jahr 2007 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 2008

1.2. Foreword

This is the seventh comprehensive report of the Institute of Pharmacology of the University of Bern. Our institute has worked hard to fulfil its tasks in teaching and research within the Medical Faculty in 2007 at high quality. Pharmacology plays an important role in both basic biological science and clinical research. The Institute 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 2007. The organization of an art exhibition within our institute is an example for these efforts.

The year 2007 was characterized by the further strengthening of the new groups (Prof. Huwiler, PD Dr. Yousefi, and Prof. Zangemeister-Wittke) that perform research at a high level. After the retirement of three former professors, all teaching responsibilities within the medical and natural sciences student programs were smoothly taken over by new members of the PKI.

In addition to regular teaching within the third study year of medical students and our teaching of dental students, Prof. Simon and PD Dr. Yousefi are additionally involved in M.Sc. programmes newly established for students studying Biology at the Natural Sciences Faculty of our university. We are also 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 7 MD students work at the PKI and two students successfully finished her PhD graduate study in 2007.

In 2007, members of the Institute of Pharmacology published 26 original and 15 review articles in international peer-reviewed journals (the sum of the “impact factors” is more than

250). Co-workers of the institute were invited to 30 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. The Bern Immunology Club (BIC) is also thanks to our contribution highly active and successful. A national congress (with international participants) of the Swiss Society of Pharmacology and Toxicology (SSPT) was organized by Prof. Simon and Prof. Lauterburg (Institute of Clinical Pharmacology, Univ. of Bern) and attracted approximately 180 individuals interested in Pharmacology. 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. The SSEP initiated a new course within a M.Sc. program for Drug Development Sciences. Here, we offer new teaching events in Bern (Prof. Huwiler, Prof. Simon). Prof. Simon was elected as President of the Union of the Swiss Societies for Experimental Biology (USSEB) as well as President of the European Cell Death Organization (ECDO) in 2007.

I thank all co-workers for their hard work that contributed to the success of the PKI in 2007. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, February 2008

2. Staff 2007

Director

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

Deputy Director

Prof. Dr. Andrea Huwiler, PhD

Permanent Members

Prof. Dr. Andrea Huwiler, PhD
Prof. em. Dr. Harald Reuter, MD*
Prof. Dr. Hans-Uwe Simon, MD, PhD
PD Dr. Shida Yousefi, PhD
Prof. Dr. Uwe Zangemeister-Wittke, PhD
PD Dr. Peter Späth, PhD*

Scientific Staff

Dr. Nicola Andina, MD, PhD student
Karima Berard Ettoli, research fellow* (since July 2007)
Eva Bettler, MD student*
Dr. Sébastien Conus, PhD
Dr. Frauke Döll, PhD* (until January 2007)
Mistianne Feeney, research fellow (until July 2007)
Elena Federzoni, PhD student
Stephanie Felder, MD student* (since August 2007)
Dr. Barbara Geering, PhD*
Grace Gordon, technician
Anna Greening, PhD student* (since October 2007)
Pascale Grzonka, MD student*
Zhaouye He, PhD student (since September 2007)
Susanne Hösli, MD student*
Simone Hildbrand, technician
Dr. Sajid Hussain, PhD* (since April 2007)
Ganna Kostylina, PhD student (until July 2007)
Evelyne Kozlowski, technician
He Liu, PhD student* (since September 2007)
Dipak Maskey, PhD student
Cristina Mihalache, PhD student
Susanne Probst, technician
Annika Quast, PhD student
Dr. Shuyu Ren, PhD
Dr. Benjamin Sakem, PhD* (since June 1, 2007)
Dr. Souzan Salemi, PhD
Inès Schmid, head technician
Dr. Jan Schmidt-Mende, MD, PhD (since February 2007)
Stephanie Schwalm, PhD student* (since October 2007)

Manuel Simon, PhD student (since November 2007)
David Troi, MD student*
Jennifer Wittwer, MD student*
Thomas von Rütte, MD student*
Dr. Johannes Winkler, PhD*
Dr. Cuiyan Xin, PhD*
Dr. Xu Xu, PhD* (since March 2007)
Dr. Algirdas Ziogas, PhD (until October 2007)

External University Teachers

Dr. Sibylle Bürgi, PhD*
PD Dr. Armand Cachelin, MD, PhD*
Prof. Dr. Irena Mlinaric, PhD* (Visiting Professor of the University of Bern)
Prof. Dr. Josef Pfeilschifter, MD (Visiting Professor of the University of Bern)

Guest scientists

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

External Computer Support

Dominik Wyss*

Office

Sandra Suter, head secretary
Anita Dähler, secretary

Franziska Marti*, secretary to Prof. Reuter
Tamara Haeberlin*, Zurich, USGEB secretary to Prof. Simon
Veronique Vandevoorde*, Ghent, ECDO secretary to Prof. Simon

Workshop

Hans Andres

House Keeping

Mariter Vieites
Isa Conforti

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

Members of the Institute of Pharmacology of the University of Bern in February 2008.
From left and below: First raw: Evelyne Kozlowski, Cristina Mihalache, Souzan Salemi, Shida Yousefi, Jan Schmidt-Mende, Elena Federzoni, Johannes Winkler, Andrea Huwiler, Harald Reuter, Hans-Uwe Simon. Second raw: David Troi, Benjamin Sakem, Sandra Suter, Hans Andres, Barbara Geering, Inès Schmid, Xu Xu, Cuiyan Xin, Lotte P. Hofmann. Third raw: Nicola Andina, Annika Quast, Dipak Maskey, Peter Späth, Anita Dähler, Mirjam Kummer, Sébastien Conus, Isa Conforti, Grace Gordon, Shuyu Ren, Anna Greening, Stephanie Schwalm, Uwe Zangemeister-Wittke.

3. Teaching Activities
3.1. Lectures

Lectures for medical students

Date	Lecturer	Titel of the lecture
Jan. 8, 2007	PD Dr. Peter Späth	Antithrombotische Therapie II & Antikoagulantien
Feb. 5, 2007	Prof. Uwe Zangemeister-Wittke	Diuretika
April 23, 2007	Dr. Jan Schmidt-Mende	Zucker-Antidiabetika
April 25, 2007	Dr. Jan Schmidt-Mende	Fett-Lipidsenker, Gicht
May 09, 2007	Prof. Andrea Huwiler	Antiepileptika
May 16, 2007	Prof. Andrea Huwiler	Lokalanästhetika
May 16, 2007	Prof. Andrea Huwiler	Therapie von Morbus Parkinson und Demenz
May 21, 2007	Prof. Andrea Huwiler	Nebenniere
May 23, 2007	Prof. Andrea Huwiler	Nebenschilddrüse
June 6, 2007	Prof. Andrea Huwiler	Pharmakologie der Narkotika / Anästhesie 1
June 11, 2007	Prof. Andrea Huwiler	Angriffspunkte von Psychopharmaka
June 13, 2007	Prof. Andrea Huwiler	Neuroleptika
June 18, 2007	Prof. Andrea Huwiler	Angststörungen
June 18, 2006	Prof. Andrea Huwiler	Antidepressiva
June 20, 2007	Prof. Andrea Huwiler	Der alte Patient: - Pharmakologie und Toxikologie
June 25, 2007	Prof. Andrea Huwiler	Schmerz und Analgesiologie 1
June 27, 2007	Prof. Andrea Huwiler	Schmerz und Analgesiologie 2
July 11, 2007	Prof. Hans-Uwe Simon	Immunmodulation
Sept. 19, 2007	Prof. Hans-Uwe Simon	Pharmakodynamik 1

Sept. 24, 2007	Prof. Hans-Uwe Simon	Pharmakodynamik 2
Sept. 26, 2007	Prof. Hans-Uwe Simon	Einführung in die Toxikologie
Oct. 3, 2007	Prof. Hans-Uwe Simon	Entzündungshemmung
Oct. 24, 2007	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Nov. 6, 2007	Prof. Uwe Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Nov. 6, 2007	Prof. Uwe Zangemeister-Wittke	Wirkprinzipien der Antihypertensiva
Nov. 14, 2007	Prof. Uwe Zangemeister-Wittke	Antiarrhythmika
Nov. 19, 2007	PD Dr. Peter Späth Prof. Uwe Zangemeister-Wittke	Antithrombotische Therapie II & Antikoagulantien
Nov. 28, 2007	Prof. Uwe Zangemeister-Wittke	Behandlung der Herzinsuffizienz und Angina Pectoris
Dec. 10, 2007	Prof. Uwe Zangemeister-Wittke	Diuretika

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

Date	**Lecturer**	**Title of the lecture**
March 19, 2007	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Einführung, Rezeptoren
March 21, 2007	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Dosis-Wirkungskurven
March 26, 2007	Prof. Hans-Uwe Simon	Antagonisten / Applikation
March 26, 2007	Prof. Uwe Zangemeister-Wittke	Aufnahme / Verteilung
March 28, 2007	Prof. Uwe Zangemeister-Wittke	Arzneimittelmetabolismus / Elimination
April 4, 2007	Prof. Uwe Zangemeister-Wittke	Gesamtkinetik / Dosierung

April 11, 2006	Prof. Andrea Huwiler	Interaktionen / Pharmakogenetik, allg.
April 16, 2007	Prof. Uwe Zangemeister-Wittke	Vegetatives Nervensystem
April 18, 2007	Prof. Uwe Zangemeister-Wittke	Herz-Kreislaufpräparate
April 23, 2007	Prof. A. Huwiler	Narkose-/Beruhigungsmittel
April 25, 2007	Dr. Sibylle Bürgi	Lokalanästhetika
April 30, 2007	Dr. Sibylle Bürgi	Antibiotika I
May 2, 2007	Dr. Sibylle Bürgi	Antibiotika II
May 7, 2007	Dr. Sibylle Bürgi	Insulin, orale Antidiabetika
May 9, 2007	PD Dr. Peter Späth	Orale Antikoag./Plättchenhemmer
May 14, 2007	PD Dr. Armand Cachelin	Immunsuppression
May 16, 2007	PD Dr. Armand Cachelin	Schwache Analgetika I
May 21, 2007	PD Dr. Armand Cachelin	Starke Analgetika
May 23, 2007	Dr. Jan Schmidt-Mende	Magensäurehemmung
June 4, 2007	Dr. Jan Schmidt-Mende	Psychopharmaka
June 6, 2007	Prof. Uwe Zangemeister-Wittke	Examensvorbereitung

Lectures: Cellular and Molecular Immunology (Coordinator: Prof. B. Stadler)

Date	**Lecturer**	**Title of the lecture**
Nov. 22, 2007	Prof. Hans-Uwe Simon	Immunomodulators and immune response modifiers

External teaching activities: University of Zurich (Molecular Medicine)

Date	**Lecturer**	**Title of the lecture**
April 26-27, 2007	Prof. Uwe Zangemeister-Wittke	Introduction into tumor biology

3.2. Coordination PBL Medical Students, 3rd year (2007/2008)

Core group:
Prof. Andrea Huwiler

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

3.3. Tutorials (study year 2007/2008)

Medical students 3rd year:
Dr. Nicola Andina
Dr. Sébastien Conus
Dr. Barbara Geering
Dr. Souzan Salemi
Dr. Jan Schmidt-Mende
PD Dr. Shida Yousefi

PhD students,
Graduate School for Cellular and Biochemical Sciences:
PD Dr. Shida Yousefi

Medical students 1st year,
Wahlpraktikum "Konfokale Mikroskopie" (Dec. 2007 – May 2008):
Dr. Sebastien Conus
Prof. Dr. Hans-Uwe Simon

3.4. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan. 24, 2007	Dr. Yitzhak Zimmer Dept. Clin. Research, University of Bern	The Met RTK system and DNA repair – a novel molecular pathway and target for radiosensitization
Febr. 6, 2007	M.Sc. He Liu University of Freiburg, Freiburg / Breisgau (D)	The role of hematopoietic RhoGTPase, RhoH, in the IL-3 mediated signaling in BaF3 cell line and in the differentation in murine bone marrow derived mast cells
April 24, 2007	Dr. Claudio Vallan Institute of Pathology, University of Bern	Using FlowJo to automating flow cytometric analyses
May 2, 2007	Prof. Olivier Staub Dept. of Pharmacology and Toxicology, University of Lausanne	The balance between ubiquitylation and deubiquitylation controls transepithelial Na-transport in the kidney
May 9, 2007	Prof. Leonardo Scapozza Pharmaceutical Sciences, University of Geneva	Druggability of tyrosine kinases; How conformation and time influence inhibitors' pharmacology
June 27, 2007	Prof. Liliana Schäfer Inst. of Pharmacology, Univ. of Frankfurt/M. (D)	Decorin- and Biglycan-signaling in inflammation and fibrosis
Aug. 09, 2007	Prof. Ilana Nathan Dept. of Clin. Bio-chemistry, Ben Gurion University of of the Negev, Beer Sheva (ISR)	Substituted arylethylenes as anticancer agents; mode of action in induction of cell death
Aug. 10, 2007	Prof. Angela Haczku Dept. of Medicine, University of Pensylvania Philadelphia (USA)	Role and regulation of lung collectins in allergic airway inflammation
Oct. 2, 2007	Prof. U. Förstermann Institute of Pharmacol., Univ. of Mainz (D)	Vascular oxidative stress: Pathophysiological importance and pharmacological reversal
Oct. 24, 2007	Dr. Nicole Gross Paediatric Oncology Research DMCP, CHUV, Lausanne	Role of CXCR4 in the development and agressive behaviour of human neuroblastoma

Nov. 14, 2007	Dr. Daniel Gerlich Institute of Biochemistry, ETH Zürich	Automated 4-D live microscipy to study human cell division
Dec. 5, 2007	Prof. Urs Rüegg Pharmaceutical Sciences, University of Geneva	Pharmacology of Muscular Dystrophy

3.5. Bern Immunology Club (BIC)

Date	Teacher	Title of the seminar
Jan. 31, 2007	Prof. Dr. Gerd Folkers Collegium Helveticum, University of Zürich / ETH Zürich	Minisimposium Immunology: Learning the important by studying the unimportant?
Febr. 14, 2007	Prof. Klaus Ley University of Virginia, Charlottesville, USA	Neutrophil regulatory T cells: role of IL-17 and IL-23
March 28, 2007	Prof. Thomas Brunner Institut of Pathology, University of Bern	How intestinal glucocorticoid production regulates local immune responses
April 4, 2007	Prof. Hans-Uwe Simon (Chair)	IVIG: Clinical use and mechanisms of action
	Prof. T. Hunziker	Use of IVIG for dermatological disorders
	Dr. S. Miescher	Mechanisms of action of IVIG – still a black box?
	Dr. I. Andresen	Efficacy and safety of SCIG therapy
April 25, 2007	Dr. Werner Held Ludwig Institute for Cancer Research, Lausanne/Epalinges	Self-control of natural killer cells
May 30, 2007	Prof. Josef Pfeilschifter Institute of Pharmacology, University of Frankfurt/M, Frankfurt (D)	Regulation of gene expression by nitric oxide in renal mesangial cell

June 27, 2007	Dr. Burkard Ludewig Kantonsspital, St. Gallen	Innate immune responses against coronaviruses or immunophathogenesis of atherosclerosis
Aug. 12-14, 2007	Prof. Hans-Uwe Simon and Faculty	6th International Summer School, Heiligenschwendi (CH)
Aug. 29, 2007	Prof. Cezmi Akdis Swiss Institute of Allergy and Asthma Research (SIAF), Davos	Mechanisms of allergic disease
Sept. 26, 2007	Dr. Jean Pieters Biozentrum, Basel	Deciphering the signaling pathways regulating host immunity against mycobaterial Infections: Maintaining the balance
Oct. 17, 2007	Dr. Claudio Vallan Institute of Pathology, University of Bern	Flow measurements with the new generation of cytometers: From the basics to pretty complicated stuff
Oct. 31, 2007	Dr. Markus Manz Institute Research Biomedicine (IRB), Bellinzona	Dendritic cell differentiation and homeostasis
Nov. 28, 2007	Prof. Michael Detmar ETH Zürich	(Lymph)angiogenesis in inflammation and cancer progression

For the current program of the Bern Immunology Club (BIC), please consult the following website:
http://www.bic.unibe.ch/content/teaching/bic_lectures_08/index_eng.html

3.6. Academic Degrees

Ganna Kostylina, Dr. phil.
Thesis: Neutrophil apoptosis mediated by nicotinic acid receptors.
Institute of Pharmacology, Bern, June 2007
Supervisor: Prof. Hans-Uwe Simon

Arezoo Daryadel, Dr. phil.
Thesis: Expression and function of MIF and RhoH/TTF in neutrophils.
Institute of Pharmacology, Bern, October 2007
Supervisors: Prof. Hans-Uwe Simon, PD Dr. Shida Yousefi

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

Group members: Simone Hildbrand, technician[1]
Dr. Shuyu Ren, PhD[1]
Dr. Cuiyan Xin, PhD[1]
Dr. Xu Xu, PhD[1]
Dr. Benjamin Sakem, PhD[1]
Dr. Frauke Döll, PhD[1,2]
Sabine Klawitter, PhD student[1,2]
Anna Greening, PhD student[1,2]
Stephanie Schwalm, PhD student[1,2]
Dr. Tanja Emmler, PhD[2]
Dr. Alexander Koch, PhD[2]
Lotte P. Hofmann, Vet.med., PhD student[2]
Ankathrin Förster, PhD student[2]
Isolde Römer, technician[2]
Svetlana Bubnova, technician[2]
Luise Reinsberg, technician[2]

[1]Institute 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.

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. 1

FTY720 suppresses interleukin-1beta-induced secretory phospholipase A2 expression in renal mesangial cells by a transcriptional mechanism.

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

FTY720 is a potent immunomodulatory prodrug that is converted to its active phosphorylated form by a sphingosine kinase. Here we have studied whether FTY720 mimicked the action of sphingosine-1-phosphate (S1P) and exerted an anti-inflammatory potential in renal mesangial cells. EXPERIMENTAL APPROACH: Prostaglandin E(2) (PGE(2)) was quantified by an enzyme-linked immunosorbent-assay. Secretory phospholipase A(2) (sPLA(2)) protein was detected by Western blot analyses. mRNA expression was determined by Northern blot analysis and sPLA(2)-promoter activity was measured by a luciferase-reporter-gene assay. KEY RESULTS: Stimulation of cells for 24 h with interleukin-1beta (IL-1beta) is known to trigger increased PGE(2) formation which coincides with an induction of the mRNA for group-IIA-sPLA(2) and protein expression. FTY720 dose-dependently suppressed IL-1beta-induced IIA-sPLA(2) protein secretion and activity in the supernatant. This effect is due to a suppression of cytokine-induced sPLA(2) mRNA expression which results from a reduced promoter activity. As a consequence of suppressed sPLA(2) activity, PGE(2) formation is also reduced by FTY720. Mechanistically, the FTY720-suppressed sPLA(2) expression results from an activation of the TGFbeta/Smad signalling cascade since inhibition of the TGFbeta receptor type I by a specific kinase inhibitor reverses the FTY720-mediated decrease of sPLA(2) protein expression and sPLA(2) promoter activity. In summary, our data show that FTY720 was able to mimic the anti-inflammatory activity of TGFbeta and blocked cytokine-triggered sPLA(2) expression and subsequent PGE(2) formation. Thus, FTY720 may exert additional in vivo effects besides the well reported immunomodulation and its anti-inflammatory potential should be considered.

See original publication No. 2

Prolactin upregulates sphingosine kinase-1 expression and activity in the human breast cancer cell line MCF7 and triggers enhanced proliferation and migration.

F. Döll, J. Pfeilschifter, A. Huwiler

Sphingosine kinases (SK) catalyze the formation of sphingosine-1-phosphate (S1P) which plays a crucial role in cell growth and survival. Here, we show that prolactin (PRL)

biphasically activates the SK-1, but not the SK-2 subtype, in the breast adenocarcinoma cell-line MCF7. A first peak occurs after minutes of stimulation and is followed by a second delayed activation after hours of stimulation. A similar biphasic effect on SK-1 activity is seen for 17beta-estradiol (E(2)). The delayed activation of SK-1 derives from an upregulated mRNA and protein expression and is due to increased SK-1 promoter activity and mechanistically involves STAT5 activation as well as protein kinase C and the classical mitogen-activated protein kinases. Furthermore, glucocorticoids also block both hormone-induced SK-1 expression and activity. Functionally, long-term stimulation of MCF7 cells with PRL or E(2) is well known to trigger increased cell proliferation and migration. Both hormone-induced cell responses critically involve SK-1 activation since the depletion of SK-1, but not SK-2, by siRNA transfection abolishes the hormone-induced cell proliferation and migration. In summary, our data show that PRL and E(2) cause a pronounced delayed SK-1 activation which is due to increased gene transcription, and critically determines the capability of cells to grow and move. Thus, the SK-1 may represent a novel attractive target for anti-tumor therapy.
See original publication No. 3

Sphingosylphosphorylcholine acts in an anti-inflammatory manner in renal mesangial cells by reducing interleukin-1beta-induced prostaglandin E2 formation.
C. Xin, S. Ren, W. Eberhardt, J. Pfeilschifter, A. Huwiler
Sphingosylphosphorylcholine (SPC) is a bioactive lipid that binds to G protein-coupled-receptors and activates various signaling cascades. Here, we show that in renal mesangial cells, SPC not only activates various protein kinase cascades but also activates Smad proteins, which are classical members of the transforming growth factor-beta (TGFbeta) signaling pathway. Consequently, SPC is able to mimic TGFbeta-mediated cell responses, such as an anti-inflammatory and a profibrotic response. Interleukin-1beta-stimulated prostaglandin E(2) formation is dose-dependently suppressed by SPC, which is paralleled by reduced secretory phospholipase A(2) (sPLA(2)) protein expression and activity. This effect is due to a reduction of sPLA(2) mRNA expression caused by inhibited sPLA(2) promoter activity. Furthermore, SPC upregulates the profibrotic connective tissue growth factor (CTGF) protein and mRNA expression. Blocking TGFbeta signaling by a TGFbeta receptor kinase inhibitor causes an inhibition of SPC-stimulated Smad activation and reverses both the negative effect of SPC on sPLA(2) expression and the positive effect on CTGF expression. In summary, our data show that SPC, by mimicking TGFbeta, leads to a suppression of proinflammatory mediator production and stimulates a profibrotic cell response that is often the end point of an anti-inflammatory reaction. Thus, targeting SPC receptors may represent a novel therapeutic strategy to cope with inflammatory diseases.
See original publication No. 4

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Review article

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Book contribution

1. **A. Huwiler**: Drug discovery and evaluation: Pharmacological assays. 3rd edition, volumes 1 and 2 (Ed. H.G. Vogel); Springer Verlag, Berlin – Heidelberg – New York, 2008.

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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, hypereosinophilic syndromes, 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 2007.

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 Institute of Immunology, University of Bern; CSL Behring, Bern, and School of Life Sciences, University of Dundee, UK)

Background: 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. Objective: To address the question whether IVIg preparations contain anti-sialic acid-binding Ig-like lectin-8 (Siglec-8) autoantibodies. Methods: 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. Results: 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. Conclusion: IVIg preparations contain natural anti-Siglec-8 autoantibodies. Clinical implications: Anti-Siglec-8 autoantibodies present in IVIg preparations may have therapeutic relevance in autoimmune and allergic diseases, respectively, such as Churg-Strauss syndrome.

See original publication No. 1

Neutrophil apoptosis mediated by nicotinic acid receptors (GPR109A)

G. Kostylina, D. Simon, M.F. Fey, S. Yousefi, H.-U. Simon
(Collaboration with the Institute of Medical Oncology, University of Bern)

GPR109A (HM74A) is a G_i-protein coupled receptor, which is activated by nicotinic acid (NA), a lipid-lowering drug. Here, we demonstrate that mature human neutrophils, but not eosinophils, express functional GPR109A receptors. The induction of the GPR109A gene appears to occur late in the terminal differentiation process of neutrophils, since a mixed population of immature bone marrow neutrophils did not demonstrate evidence for its expression. NA accelerated apoptosis in cultured neutrophils in a concentration-dependent manner, as assessed by phosphatidylserine (PS) redistribution, caspase-3 activation, and DNA fragmentation assays. The pro-apoptotic effect of NA was abolished by pertussis toxin (PTX), which was used to block G_i-proteins, suggesting a receptor-mediated mechanism. Activation of GPR109A by NA resulted in decreased levels of cAMP, most likely due to G_i-mediated inhibition of adenylyl cyclase activity. NA-induced apoptosis was reversed by the addition of cell-permeable cAMP, pointing to the possibility that reduced cAMP levels promote apoptosis in neutrophils. Distal mechanism involved in this process may include the post-translational modification of members of the Bcl-2 family, such as dephosphorylation of pro-apoptotic Bad and anti-apoptotic Mcl-1 proteins. Taken together, following maturation in the bone marrow, neutrophils express functional GPR109A receptors, which might be involved in the regulation of neutrophil numbers. Moreover, this study identified a new cellular target of NA and future drugs activating GPR109A receptors, the mature neutrophil.

See original publication No. 2

Anti-CD20 (rituximab) treatment improves atopic eczema

D. Simon, S. Hösli, G. Kostylina, N. Yawalkar, H.-U. Simon
(Collaboration with the Department of Dermatology, University of Bern)

Background: Atopic eczema (AE) is a chronic inflammatory skin disorder characterized by eczematous skin lesions, pruritus, and typical histopathological features. Objective: We asked whether depletion of B cells by monoclonal anti-CD20 antibody therapy (rituximab) would improve severe AE. Methods: Six patients (4 females and 2 males) with severe AE received two intravenous applications of rituximab, each 1000 mg, two weeks apart. To evaluate the efficacy of rituximab, we monitored clinical parameters (EASI, pruritus), total and allergen-specific IgE levels, skin histology, as well as inflammatory cells and cytokine expression in the skin and peripheral blood before and after therapy (ClinicalTrials.gov Identifier: NCT00267826). Results: All patients showed an improvement of their skin symptoms within 4 to 8 weeks. The EASI significantly decreased (before therapy: 29.4 ± 4.3; week 8: 8.4 ± 3.6; $p<0.001$). Histological alterations, such as spongiosis, acanthosis, and dermal infiltrate, including T and B cell numbers, also dramatically improved. However, whereas blood B cells were below detectable levels as a consequence of rituximab administration, skin B cells were reduced by approximately 50% only. Expression of interleukin (IL)-5 and IL-13 was reduced after therapy. Moreover, whereas allergen-specific IgE levels were not altered, we observed a slight reduction in total IgE concentrations in blood. Conclusions: B cells play a major role in AE pathogenesis. Treatment with an anti-CD20 antibody leads to an impressive improvement of AE in patients with severe disease. Clinical implication: Rituximab is a drug that can be used in severe AD. Further clinical studies are recommended.

See original publication No. 3

Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation

S. Conus, R. Perozzo, T. Reinheckel, C. Peters, L. Scapozza, S. Yousefi, H.-U. Simon
(Collaboration with the School of Pharmaceutical Sciences, EPGL, University of Geneva, and Institute of Molecular Medicine and Cell Research, University of Freiburg, Freiburg i. Br., Germany)

In the resolution of inflammatory responses, neutrophils rapidly undergo apoptosis. We report here a new pro-apoptotic pathway in which cathepsin D directly activates caspase-8. Cathepsin D is released from azurophilic granules in neutrophils in a caspase-independent but reactive oxygen species (ROS)-dependent manner. Under inflammatory conditions, the translocation of cathepsin D in the cytosol is blocked. Pharmacological or genetic inhibition of cathepsin D resulted in delayed caspase activation and reduced neutrophil apoptosis. Cathepsin D deficiency or lack of its translocation in the cytosol prolongs innate immune responses in experimental bacterial infection and in septic shock. Thus, we identified a new function of azurophilic granules, which regulate, besides their role in bacterial defense mechanisms, the life-span of neutrophils and therefore the duration of innate immune responses through the release of cathepsin D.

See original publication No. 4

Original publications

1. S. von Gunten, M. Vogel, A. Schaub, B.M. Stadler, S. Miescher, P. Crocker, **H.-U. Simon**: Intravenous immunoglobulin preparations contain anti-Siglec-8 autoantibodies.
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6. D. Simon, L.R. Braathen, **H.-U. Simon**: Increased lipopolysaccharide-induced tumour necrosis factor-α, interferon-γ and interleukin-10 production in atopic dermatitis.
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    Endocrinology 148 (2007), 45-53.

11. B. Berent-Maoz, S. Salemi, D. Mankuta, **H.-U. Simon**, F. Levi-Schaffer: TRAIL mediated signaling in human mast cells: the influence of IgE-dependent activation.
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13. L.L. Belyanskaya, A. Ziogas, S. Hopkins-Donaldson, S. Kurtz, **H.-U. Simon**, R. Stahel, U. Zangemeister-Wittke: TRAIL-induced survival and proliferation of SCLC cells is mediated by ERK and dependent on TRAIL-R2/DR5 expression in the absence of caspase-8.
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6. **H.-U. Simon**, J. Cools: Novel approaches to therapy of hypereosinophilic syndromes.
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Book chapters

1. **H.-U. Simon**: Hypereosinophilic syndromes. In: Allergy and Allergic Diseases, 2nd edition (Eds. A.B. Kay, A. Kaplan, J. Bousquet, P. Holt); Blackwell Publishing, Oxford, 2008, in press.

2. **H.-U. Simon**: Regulation of cell survival. In: Middleton's Allergy: Principles and Practice, 7th edition (Eds. N.F. Adkinson, W.W. Busse, B.S. Bochner, S.T. Holgate, E.F.R. Simons, R.F. Lemanske Jr.); MOSBY Elsevier, Edinburgh – London – New York – Oxford – Philadelphia – St. Louis – Sydney – Toronto, 2008, in press.

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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. To understand gene functions, we established a lentiviral gene transfer technology in our institute that can be used to modify the expression of genes in *in vitro* and *in vivo* experimental systems. We are also interested in new questions of granulocyte biology.

Expression of CD95 on mature leukocytes of MRL/*lpr* mice after transplantation of genetically modified bone marrow stem cells

E. Federzoni, G. Gordon, S. Müller, I. Schmid, H.-U. Simon, S. Yousefi
(Collaboration with the Department of Clinical Research, University of Bern)

Bone marrow transplantation (BMT) is commonly used for the treatment of severe haematological and immunological diseases. For instance, the autoimmune lymphoproliferative syndrome (ALPS) caused by a complete expression defect of CD95 (Fas, APO-1) can be cured by allogeneic BMT. However, since this therapy may not generate satisfactory results when only partially compatible donors are available, we were interested in the development of a potential alternative treatment by using lentiviral gene transfer of a normal copy of CD95 cDNA in hematopoietic stem cells. Here, we show that this approach applied to MRL/*lpr* mice results in the expression of functional CD95 receptors on the surface of lymphocytes, monocytes, and granulocytes. This suggests that correction of CD95 deficiency can be achieved by gene therapy.

See original publication No. 1

Catapult-like release of mitochondrial DNA by eosinophils contributes to anti-bacterial defense

S. Yousefi, N. Andina, E. Kozlowski, I. Schmid, A. Straumann, G.J. Gleich, H.-U. Simon
(Collaboration with the Department of Gastroenterology, Kantonsspital Olten and Department of Dermatology, University of Utah, Salt Lake City, USA)

Although eosinophils are considered as being useful in defense mechanisms against parasites, their exact function(s) in innate immunity remains unclear. The aim of this study was to elucidate the role of eosinophils infiltrating the gastrointestinal tract. We show here that lipopolysaccharide (LPS) from gram-negative bacteria activates interleukin (IL)-5 primed eosinophils to release mitochondrial DNA in a reactive oxygen species (ROS) dependent manner, but independent of eosinophil death. Strikingly, the process of DNA release occurs with high speed in a catapult-like manner in less than 1 second. In the

extracellular space, the mitochondrial DNA and the granule proteins form extracellular structures able to bind and kill bacteria both in vitro and under inflammatory conditions in vivo. These data suggest a novel mechanism of eosinophil-mediated innate immune responses that might be important to maintain the intestinal barrier function following inflammation-associated epithelial cell damage preventing the host from uncontrolled invasion of bacteria.

Original publications

1. E. Federzoni, G. Gordon, S. Müller, I. Schmid, H.-U. Simon, **S. Yousefi**: Expression of CD95 on mature leukocytes of MRL/lpr mice after transplantation of genetically modified bone marrow stem cells.
   Immunol. Lett., in press.

2. G. Kostylina, D. Simon, M.F. Fey, **S. Yousefi**, H.-U. Simon: Neutrophil apoptosis mediated by nicotinic acid receptors (GPR109A).
   Cell Death Differ. 15 (2008), 134-142.

3. S. Salemi, **S. Yousefi**, D. Lochmatter, A. Eble, J. Deladoey, I.C. Robinson, H.-U. Simon, P.E. Mullis: Isolated autosomal dominant growth hormone deficiency (IGHD II): Stimulating mutant GH-1 gene expression drives GH-1 splice-site selection, cell proliferation and apoptosis.
   Endocrinology 148 (2007), 45-53.

Review article

1. **S. Yousefi**, H.-U. Simon: Apoptosis regulation by autophagy gene 5.
   Crit. Rev. Oncol. Hematol. 63 (2007), 241-244.

2. **S. Yousefi**, H.-U. Simon: Taxol therapy revisited.
   Blood 110 (2007), 3492.

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Our research is focused on translational aspects in molecular oncology. A major goal is to investigate anti-apoptosis as a mechanism of drug resistance in lung cancer, and to identify survival pathways and their regulators for targeted intervention. Since recently, we have also investigated the role of hypoxia and of sphingosine kinases in the positive regulation of cell survival, proliferation and migration.

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 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 pathway.

In our tumor targeting program we have developed tumor-selective drug delivery systems based on recombinant high affinity antibodies 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 nanoparticles and new site-specifically activated toxin formulations are under investigation. As a recent innovative step towards improved tumor targeting, we have developed fully synthetic designed ankyrin repeat proteins (DARPins) against EpCAM. 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. Using further affinity matured DARPins, new generations of immunotoxins and nanovesicular drug delivery systems are under development.

Anti-tumor activity of a novel EpCAM-targeted nanovesicular drug delivery system

S. Hussain, A. Plückthun, T.M. Aellen, U. Zangemeister-Wittke
(Collaboration with the Departement of Biochemistry, University of Zürich, Switzerland)

Site-specific delivery of anticancer agents to tumors represents a promising therapeutic strategy because it increases efficacy and reduces toxicity to normal tissues compared with untargeted drugs. Sterically stabilized immunoliposomes (SIL), guided by antibodies that specifically bind to well internalizing antigens on the tumor cell surface, are effective nanoscale delivery systems capable of accumulating large quantities of anticancer agents at the tumor site. The epithelial cell adhesion molecule (EpCAM) holds major promise as a target for antibody-based cancer therapy due to its abundant expression in many solid tumors and its limited distribution in normal tissues. We generated EpCAM-directed immunoliposomes by covalently coupling the humanized single-chain Fv antibody fragment 4D5MOCB to the surface of sterically stabilized liposomes loaded with the anticancer agent doxorubicin. In vitro, the doxorubicin-loaded immunoliposomes (SIL-Dox) showed efficient cell binding and internalization and were significantly more cytotoxic against EpCAM-positive tumor cells than nontargeted liposomes (SL-Dox). In athymic mice bearing established human tumor xenografts, pharmacokinetic and biodistribution analysis of SIL-Dox revealed long circulation times in the blood with a half-life of 11 h and effective time-dependent tumor localization, resulting in up to 15% injected dose per gram tissue. These favorable pharmacokinetic properties translated into potent antitumor activity, which resulted in significant growth inhibition (compared with control mice), and was more pronounced than that of doxorubicin alone and nontargeted SL-Dox at low, nontoxic doses. Our data show the promise of EpCAM-directed nanovesicular drug delivery for targeted therapy of solid tumors.

See original publication No. 1

TRAIL-induced survival and proliferation of SCLC cells is mediated by ERK and dependent on TRAIL-R2 expression in the absence of caspase-8

L.L. Belyanskaya, S. Hopkins-Donaldson, S. Kurtz, H.-U. Simon, R. Stahel,
U. Zangemeister-Wittke
(Collaboration with the Departement of Medical Oncology, University of Zurich)

Small cell lung cancer (SCLC) is characterized by an aggressive phenotype and acquired resistance to a broad spectrum of anticancer agents. TNF-related apoptosis-inducing ligand (TRAIL) has been considered as a promising candidate for safe and selective induction of tumor cell apoptosis without toxicity to normal tissues. Here we report that TRAIL failed to induce apoptosis in SCLC cells and instead resulted in an up to 40% increase in proliferation. TRAIL-induced SCLC cell proliferation was mediated by extracellular signal-regulated kinase 1 and 2, and dependent on the expression of surface TRAIL-receptor 2 (TRAIL-R2) and lack of caspase-8, which is frequent in SCLC. Treatment of SCLC cells with interferon-gamma (IFN-gamma) restored caspase-8 expression and facilitated TRAIL-induced apoptosis. The overall loss of cell proliferation/viability upon treatment with the IFN-gamma-TRAIL combination was 70% compared to TRAIL-only treated cells and more than 30% compared to untreated cells. Similar results were obtained by transfection of cells with a caspase-8 gene construct. Altogether, our data suggest that TRAIL-R2 expression in the absence of caspase-8 is a negative determinant for the outcome of TRAIL-based cancer therapy, and provides the rationale for using IFN-gamma or other strategies able to restore caspase-8 expression to convert TRAIL from a pro-survival into a death ligand.

See original publication No. 2

Original publications

1. S. Hussain, A. Plückthun, T.M. Allen, **U. Zangemeister-Wittke**: Anti-tumor activity of a novel EpCAM-targeted nanovesicular drug delivery system.
   Mol. Cancer Ther. 6 (2007), 3019-3027.

2. L.L. Belyanskaya, S. Hopkins-Donaldson, S. Kurtz, H.-U. Simon, R. Stahel, **U. Zangemeister-Wittke**: TRAIL-induced survival and proliferation of SCLC cells is mediated by ERK and dependent on TRAIL-R2 expression in the absence of caspase-8.
   Lung Cancer, in press.

3. S. Giorgini, D. Trisciuoglio, C. Gabellini, M. Desideri, L. Castellini, C. Colarossi, **U. Zangemeister-Wittke**, G. Zupi, D. Del Bufalo: Modulation of bcl-xL in Tumor Cells Regulates Angiogenesis through CXCL8 Expression.
   Mol. Cancer Res. 5 (2007), 761-771.

Review articles

1. **U. Zangemeister-Wittke**: Krebsbehandlung mit Antisensemolekülen. Wissenschaftliche Aspekte und klinische Perspektiven.
   Der Onkologe 13 (2007), 256-262.

2. A. Huwiler, **U. Zangemeister-Wittke**: Targeting the conversion of ceramide to sphingosine 1-phosphate as a novel strategy for cancer therapy.
   Crit. Rev. Oncol. Hematol. 63 (2007), 150-159.

Book chapter

1. **U. Zangemeister-Wittke**, H.-U. Simon: Myelosuppression in Encyclopedia of Cancer, Second Edition, Springer Verlag, in press.

Patent application/PCT

U. Zangemeister-Wittke, C. Di Paolo: Methods for treating cancer using an exotoxin A moiety having a furin cleavage site replaced with a caner-associated protease site cleaved by MMP-2 or MMP-9. US Patent No: 11/816,477, EU Patent No 06723047.4 – August 16, 2007.

Additional publications of PKI members

PD Dr. Peter Späth

Original publications
(published work from previous lab)

1. V. Wahn, **P. Späth**: Komplementdefekte.
   Allergologie 30 (2007), 99-105.

2. D. Pöhlau, H. Przuntek, M. Sailer, M. Bethke, J. Koehler, N. König, C. Heesen, **P. Späth**, I. Andresen: Intravenous immunoglobulin in primary and secondary chronic progressive multiple sclerosis: a randomized placebo controlled multicentre study.
   Mult. Scler. 13 (2007), 1107-1117

Book chapter
(work performed in PKI)

1. **P.J. Späth**, C. Kempf: Herstellung von intravenös verabreichbaren Immunglobulinen und Pathogensicherheit. In: Klinischer Einsatz von Immunglobulinen, 4. Auflage (Ed V. Wahn); UNI-MED Verlag 2007, Bremen, p. 28-47

Dr. Souzan Salemi
(published work from previous labs)

1. **S. Salemi,** A. Aeschlimann, U. Wollina, R.E. Gay, B.A. Michel, S. Gay, H. Sprott: Up-regulation of delta-opioid receptors and kappa-opioid receptors in the skin of fibromyalgia patients.
   Arthritis Rheum. 56 (2007), 2464-2466.

2. V. Petkovic, **S. Salemi**, E. Vassella, E. Karamitopoulou-Diamantis, U.J. Meinhardt, C.E. Flück, P.E. Mullis: Leydig-cell tumour in children: variable clinical presentation, diagnostic features, follow-up and genetic analysis of four cases.
   Horm. Res. 67 (2007), 89-95.

4.2. Congress Invitations

Dr. Sebastien Conus

15th Euroconference on Apoptosis (ECDO); Portoroz (SL), Oct. 26-31, 2007;
Cathepsin D initiates neutrophil apoptosis and its inhibition blocks the resolution of inflammation.

Prof. Andrea Huwiler

Joint Meeting of the German and Danish Pharmacology Societies, Kopenhagen (DK), June 21 - 22, 2007;
Hypoxia in lipid signalling in cardiovascular disease.

Prof. Harald Reuter

Wahl zum Ehrenmitglied der Schweizerischen Gesellschaft für Experimentelle Pharmakologie (SGEP)

Delegierter der Akademien der Wissenschaften Schweiz an das "Biennual Meeting des International Human Rights Network of Academies and Scholarly Societies", Sri Lanka, April 4 - 7, 2007

Council Meeting der "Israeli-Palestinian Science Organization" (IPSO), World Science Forum, Budapest , November 7 - 9, 2007

Advisory Board Meetings: Venetian Institute of Molecular Medicine, Padua, April 16 - 17, 2007; Friedrich Miescher Institut, Basel-Grindelwald, September 19-21, 2007

Prof. Hans-Uwe Simon

Annual Congress of the Swiss Society of Allergology and Immunology (SSAI), Basel (CH), April 19-20, 2007;
Eosinophilia and vasculitis.

Graduate School for Cellular and Biomedical Sciences, University of Bern; Signal Transduction Course, Curzutt, Monte Carasso (CH), June 4-5, 2007;
The mitochondrial death pathway and its regulation in diseases.

XXVI. Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Göteborg (S), June 9-13, 2007;
Hypereosinophilic syndromes – novel concepts and treatment options.

Workshop on Apoptosis “Programmed cell death”, Loveno di Menaggio (I), June 23-27, 2007;
Critical role for cathepsin D in neutrophil apoptosis.

5th Biennial Congress of the International Eosinophil Society (IES), Snowbird, Utah (USA), July 19-22, 2007;
Extracellular traps generated by granulocytes – effector function of viable cells or result of a new form of cell death?

Department of Clinical Research, University of Bern: Abschieds-Symposium Robert Friis, Bern (CH), August 31, 2007;
Death of granulocytes – physiologic and pathologic aspects.

35. Kongress der Deutschen Gesellschaft für Rheumatologie, Hamburg (D), Sept. 19-22, 2007;
Gibt es das Hypereosinophile Syndrom? Neue Erkenntnisse aus der Immunologie und Molekularbiologie.

Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Onkologie; 13th SSH Hematology Course, Basel (CH), Oct. 5-9, 2007;
HES/CEL: diagnostic and treatment options.

89. Jahresversammlung der Schweizerischen Gesellschaft für Dermatologie und Venerologie (SGDV), Haut und Immunsystem; Bern (CH), Oct. 18-20, 2007;
Eosinophile: IL-5 und sonst nichts?

International Workshop: Naturally occurring antibodies in health and disease; Bern (CH), Oct. 19-20, 2007;
Natural anti-Siglec-8 and anti-Siglec-9 autoantibodies in IVIg preparations.

15th Euroconference on Apoptosis (ECDO); Portoroz (SL), Oct. 26-31, 2007;
Non-caspase proteases in cell death.

World Allergy Congress 2007; Bangkok (Thailand), Dec. 2-6, 2007;
Eosinophilic gastrointestinal disease.

World Allergy Congress 2007; Bangkok (Thailand), Dec. 2-6, 2007;
Do eosinophils matter in asthma?

PD Dr. Peter Späth

Congress of the Romanian Society of Allergy and Clinical Immunology, Târgu Mures, (Romania), April 26 – 28, 2007;
Hereditary Angio-Oedema (HAE) as part of non-allergic angio-oedema and primary immunodeficiencies – The Bern experience.
& Replacement therapies in primary antibody deficiency syndromes.

5th C1 Inhibitor Deficiency Workshop, Budapest (Hungary), May 31 – June 3, 2007;
Closing remarks.

6. Summer School der Charité, Berlin (Germany), Aug. 31 – Sept. 2, 2007;
Sind IVIG Prionen-sicher?

PD Dr. Shida Yousefi

Meeting of the Swiss Society of Pharmacology and Toxicology, Bern (CH), Sept. 27-28, 2007;
Novel mutations in the FIP1L1-PDGFRA fusion gene resulting in imatinib resistance.

Prof. Uwe Zangemeister-Wittke

24th International Conference on Advances in the Application of Monoclonal Antibodies in Clinical Oncology, Limassol, Cyprus, June 17 - 20, 2007;
Development of EpCAM-specific designed ankyrin repeat proteins for targeted drug delivery to solid tumours.

4.3. Seminar Invitations

Prof. Andrea Huwiler

Dept. Nephrology and Clinical Immunology, University of Aachen (D); July 25, 2007; guest of Prof. Mertens:
Anti-inflammatory actions of sphingolipids.

University of Frankfurt, Rauischholzhausen (D); Oct. 16, 2007; guest of Prof. Pfeilschifter:
Anti-inflammatory actions of sphingolipids.

Prof. Hans-Uwe Simon

Pfizer AG, Zurich (CH); Febr. 2, 2007; guest of Dr. Ralph Studer:
Cytokine storm: A life-threatening adverse effect associated with antibody treatment.

American Academy of Allergy Asthma & Immunology, Annual Meeting,
San Diego (CA, USA); Febr. 27, 2007;
Eosinophil - mast cell interactions in allergic diseases.

Department of Cell Biology and Morphology, University of Lausanne, Lausanne (CH); April 26, 2007; guest of Prof. Peter Clarke:
Atg5 – a molecular switch between autophagy and apoptosis.

Department of Pathology and Immunology, University of Geneva, Geneva (CH); June 18, 2007; guest of Prof. Daniel Hoessli:
Cathepsin D initiates neutrophil apoptosis and its inhibition blocks the resolution of inflammation.

Department of Hematology, University Hospital Basel, Basel (CH); Oct. 17, 2007; guest of Prof. A. Gratwohl:
Hypereosinophilic syndromes: Pathophysiologic, diagnostic and therapeutic aspects.

PD Dr. Peter Späth

Symposium in Honour of Hans U. Lutz' Retirement, Zurich (Switzerland); June 29, 2007;
Between innate and adaptive immunity.

Curs Internaţional Multicentric de Alergologie şi Immunolgie Clinică, Târgu Mures (Romania), October 8 – 12, 2007;
A review of selected non-haematological, non-AIDS-related autoimmune diseases.

PD Dr. Shida Yousefi

Klinisch-Biochemisches Kolloquium, University of Zurich, Zurich (CH), Nov. 6, 2007; guest of Dr. A. Arcaro:
Regulation of autophagy and apoptosis by Atg5.

4.4. Organization of Meetings and Courses

Prof. Andrea Huwiler

Annual Meeting of the USGEB; Workshop 9: “Novel approaches in anti-inflammatory drug therapy”; Basel, March 13 -14, 2007.

Annual Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT); Session: “Tumorpharmacology: from bench to bedside”; Bern, September 27 - 28, 2007.

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology (SSPT):
Fortschritte in der Pharmakologie – Endokrines System; Bern (CH), January 25, 2007.

Teaching course, Graduate School of the University of Bern: Signal transduction (together with T. Brunner, Bern; C. Frei, Zurich; M. Molinari, Bellinzona; M. Thelen, Bellinzona); Curzutt (CH), June 4-5, 2007.

Pre-Meeting Workshop of the 5th Biennial Congress of the International Eosinophil Society, Consensus Research Definition for HES (together with A. Klion, NIH, Bethesda); Snowbird, Utah (USA), July 18, 2007.

6th III-Bern International Summer School, Heiligenschwendi (CH); August 12-14, 2007.

Meeting of the Swiss Society of Pharmacology and Toxicology (together with B. Lauterburg, Bern); Bern (CH), Sept. 27-28, 2007.

Bern Immunology Club (together with the other founder members); Institute of Pharmacology, University of Bern, one meeting in each month of 2007

PD Dr. Shida Yousefi

DKF, PKI, PIAF - Course in immunofluorescent staining, confocal microscopy, and image analysis. Bern (CH), October 9 – 10, 2007.

4.5. Invited Chairperson at Congresses

Prof. Andrea Huwiler

Joint Meeting of the German and Danish Pharmacology Societies; Session: Genetically modified animals in drug discovery; Kopenhagen, June 22, 2007

Prof. Hans-Uwe Simon

Symposium der Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie; Session: Diabetes mellitus; Bern (CH), January 25, 2007.

Society meets science: Avenues for research and interaction (Meeting of the Branco Weiss fellowship); Session: Impacts of society on science; Zurich (CH), January 29, 2007.

XXVI. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Session: Eosinophilia, does it matter?; Göteborg (S), June 9-13, 2007.

XXVI. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Session: Mechanisms of the allergic response I; Göteborg (S), June 9-13, 2007.

5th Biennial Congress of the International Eosinophil Society (IES); Session: Eosinophil effector functions"; Snowbird, Utah (USA), July 19-22, 2007.

Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Onkologie; Symposium: Regulation der normalen und leukämischen Myelopoese; Basel (CH), Oct. 5-9, 2007.

Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Onkologie; Session: Grundlagenforschung; Basel (CH), Oct. 5-9, 2007.

International Workshop: Naturally occurring antibodies in health and disease; Session: Natural occurring antibodies as modulators; Bern (CH), Oct. 19-20, 2007.

15th Euroconference on Apoptosis (ECDO); Session: Autophagy in health and disease; Portoroz (SL), Oct. 26-31, 2007.

PD Dr. Peter Späth

International Workshop: Naturally occurring antibodies in health and disease; Session: Naturally occurring antibodies with homeostatic properties in clearance of tumor cells; Bern (CH), Oct. 19-20, 2007.

International Workshop: Naturally occurring antibodies in health and disease; Session: Naturally occurring antibodies and the adaptive immune response; Bern (CH), Oct. 19-20, 2007.

Prof. Uwe Zangemeister-Wittke

Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerischen

Gesellschaften für Hämatologie und Onkologie; Session: Postersession Basic Research II; Basel (CH), Oct. 5-9, 2007.

Annual Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT); Session: Tumorpharmacology: from bench to bedside; Bern, September 27 - 28, 2007.

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
Arch Biochem Biophys
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
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

Prof. Uwe Zangemeister-Wittke

Clin Cancer Res
Science
Int J Cancer
Cell Death Differ
Anti Cancer Drugs
Lung Cancer
Mol Cancer Ther
Breast Cancer Res

4.7. Referee Work for Grant Bodies

Prof. Andrea Huwiler

Deutsche Forschungsgemeinschaft (DFG)
Norwegian Research Council

Prof. Hans-Uwe Simon

Swiss National Science Foundation (SNF)
Deutsche Forschungsgemeinschaft (DFG)
Deutsches Krebsforschungszentrum (DKFZ), Israelkooperation (V200)
Science Foundation Irland (SFI)
The Wellcome Trust, London, UK
Medical Research Council (MRC), London
Italian Association for Cancer Research (AIRC)
Institut Pasteur, Paris

Prof. Uwe Zangemeister-Wittke

Swiss Cancer League/OncoSwiss)
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

PD Dr. Shida Yousefi

Spirig Pharma AG (2nd Prize)
Annual Congress of the Swiss Society of Allergology and Immunology (SSAI)
(Basel, April 19 – 20, 2007)

Dr. Sebastien Conus

Novartis Poster Prize (1st Prize)
Annual Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT)
(Bern, September 27 – 28, 2007)

Prof. Harald Reuter

Honorary Member of the Swiss Society of Experimental Pharmacology (SSEP)
Annual Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT)
(Bern, September 27 – 28, 2007)

5. Administrative, Advisory, and Honorary Posts

Dr. Sebastien Conus

Webmaster of the PKI

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 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

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, Foundation pour la recherche et le traitement des maladies respiratoires, Lausanne, since 2006

Member of the Standardization Committee, European Cell Death Organization (ECDO), since 2007

President, European Cell Death Society (ECDO), since 2007

President, Union of the Swiss Societies for Experimental Biology (USSEB), since 2007

Associate Editor, Allergy

Section Editor, Apoptosis

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

Member of the Scientific Board, Allergologie

Member of the Editorial Board, Clinical and Experimental Allergy

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

Member of the Advisory Board, Allergo-Journal

Member of the 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

Invitation to EU expert and reviewer panel meetings.
Expert of the FP7 Call HEALTH 2007 of the European Commission consensus groups on the topics -Improving targeted drug delivery to cancer- and -Inflammation and cancer-; expert in the final consensus panel meeting on -Cancer-

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

Member of the Editorial Board of the journal Lung Cancer

Quality coach of the PKI

Biosafety Coordinator PKI

Information Technology Coordinator at the PKI

6. Services

6.1. Confocal Microscopy

The facility belongs to the **Department of Clinical Research (DKF)** of the University of Bern. It hosts a new laser scanning microscope (LSM 5 Excitor, Carl Zeiss Microimaging GmbH, Jena), which was obtained in 2007 and may be used by members of the Medical Faculty at a small charge (CHF 50 per h). It replaced the earlier LSM410 instrument. Together with the Image analysis station, this facility (LSM410 and LSM 5 Excitor) was in operation in 2007 for approximately 445 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 20 different research groups. In 2007, the operator and her team spent for the facility more than 500 hours. In general, the usage of this facility increased as soon as the new LSM 5 Excitor had been obtained. PD Dr. S. Yousefi organizes practical courses for confocal microscopy and image analysis twice per year.

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, FAMH Clinical Immunology), 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 Exhibition

Silvan Schwager, Bern, Switzerland
Vernissage: November 8, 2007

8. Sponsors

8.1. Research Grants

Dr. Sébastien Conus

Jubiläumsstiftung der Schweizerischen Lebensversicherungs- und Rentenanstalt für Volksgesundheit und medizinische Forschung (SwissLife), Zurich

Dr. Barbara Geering

Roche Research Foundation

Prof. Andrea Huwiler

Swiss National Science Foundation (grant No. 3100AO-111806/1)
Deutsche Forschungsgemeinschaft
Norwegian Research Council and Avexxin AS
Wilhelm Sander-Stiftung
Novartis Stiftung
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)
AstraZeneca AG, Zug (CH)
Jubiläumsstiftung der Schweizerischen Lebensversicherungs- und Rentenanstalt für Volksgesundheit und medizinische Forschung (SwissLife), Zurich (together with S. Conus)

PD Dr. Shida Yousefi

Swiss National Science Foundation (grant No. 310000-112078)
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

6th III-International Summer School, Heiligenschwendi (CH), August 12-14, 2007

ABBOTT, Baar
Allexis Corporation, Lausen
Allergomed, Therwil
AstraZeneca AG, Zug
Becton Dickinson Biosciences, Allschwil
GlaxoSmithKline AG, Münchenbuchsee
Pfizer AG, Zürich
UCB-Pharma AG, Bulle
Programm für die Interfakultäre Ausbildung des Forschungsnachwuchses der Univ. Bern
USGEB

Annual Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT), Bern (CH), September 27 – 28, 2007

Max and Elsa Beer-Brawand-Fonds, Bern
USGEB
and
ALEXIS Corporation, Lausen
ANAWA Trading SA, Wangen/Zurich
AstraZeneca AG, Zug
BD Biosciences, Allschwil
BioConcept, Allschwil
Carl Zeiss AG, Feldbach
CSL Behring AG, Bern
GlaxoSmithKline AG, Münchenbuchsee
Kontaktgruppe für Forschungsfragen (KGF), Basel
Mundipharma Medical Company, Basel
Novartis Pharma (Schweiz) AG, Bern
Pfizer AG, Zurich
UCB-Pharma AG, Bulle

8.3. Seminars „Progress in Pharmacology“

2007:
AstraZeneca AG, Zug
CSL Behring AG, Bern
Pfizer AG, Zürich
Vifor AG, Villars-sur-Glâne

2008:
Mepha Pharma AG, Aesch
Pfizer AG, Zürich
Wyeth Pharmaceuticals AG, Zug
Vifor AG, Villars-sur-Glâne

8.4. Seminars „Bern Immunology Club“

2008:
CSL Behring AG, Bern

8.5. Travel Support

Swiss Society of Pharmacology and Toxicology (SSPT)
Support of Dr. Barbara Geering
Support of Dr. Jan Schmidt-Mende
Support of Dr. Nicola Andina

European Cell Death Organization (ECDO)
Support of Dr. Barbara Geering
Support of Dr. Jan Schmidt-Mende
Support of Dr. Nicola Andina

UCB-Pharma AG, Bulle
Support of Prof. Hans-Uwe Simon

8.6. Other Support

Bürgi Fonds Seminar series of the institute
Bürgi-Preis 2008