Annual Report 2008

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 achte umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat auch im Jahr 2008 seine Aufgaben in Lehre und Forschung innerhalb der Medizinischen Fakultät vorbildlich erfüllt. 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 translationale 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 2008 trugen wir dazu bei, die Kommunikation zwischen Wissenschaftlern und Öffentlichkeit zu fördern. Dazu dienten u.a. drei Vernissagen, die viele Gäste in das PKI lockte.

Wir freuen uns, dass sich im Jahr 2008 eine neue Forschungsgruppe unter Leitung von Herrn Prof. Thomas Kaufmann im Institut etablieren konnte und eine erfolgreiche Forschung durchführt. Herr Kaufmann erhielt eine Professur des Schweizerischen Nationalfonds und startete nach einem Forschungsaufenthalt in Melbourne (Australien) am 1.5.2008 in unserem Institut.

Neben unserer regulären Lehrtätigkeit im 3. Studienjahr Medizin sowie neben der Ausbildung der ZahnmedizinerInnen sind Prof. Simon, Prof. Huwiler und Prof. Yousefi zusätzlich auch in die Immunologie-Ausbildung von Studenten der Biologie (Naturwissenschaftliche Fakultät der Universität Bern) einbezogen. Weiterhin sind Prof. Simon und Prof. Dr. Zangemeister-Wittke neu in einem B.Sc.-Kurs für Biomedizin der Universität Fribourg tätig (Ausbildung in „Allgemeiner Pharmakologie“). Dieser Kurs mündet im Studienjahr 2009/2010 in einen M.Sc.-Kurs der Universität Bern, wobei die Dozenten des PKI für die spezielle Pharmakologie-Ausbildung zusätzlich verpflichtet worden sind. Diese neuen Kurse bedeuten für das PKI eine deutliche Mehrbelastung auf dem Gebiet der Lehre. Die Dozenten des PKI sind ausserdem innerhalb der interfakultären Graduate School for Cellular and Biomedical Sciences aktiv tätig. Prof. Simon ist Mitglied der Betreuungs-kommission „Medizinische Biologie“ innerhalb dieses Ausbildungsprogramms für Doktorandinnen und Doktoranden. Dazu kommen zusätzliche Bildungsangebote in Form

von Seminaren (Fortschritte in der Pharmakologie), praktischen Kursen (Prof. Yousefi) und einer Summer School (Prof. Simon). Diese Bildungsangebote werden weitgehend aus eigenen finanziellen Mitteln und Sponsorengeldern bestritten. Im Institut arbeiten gegenwärtig 17 DoktorandInnen (13 PhD, 4 MD), und drei DoktorandInnen haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2008 insgesamt 17 Originalarbeiten sowie 11 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >300). MitarbeiterInnen des Instituts wurden zu insgesamt 45 Vorträgen bzw. Seminaren eingeladen. Mehrere Mitarbeiter des PKI wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 5 Mitarbeiter mit namhaften Beiträgen des Schweizerischen Nationalfonds unterstützt. Zahlreiche Persönlichkeiten besuchten das Institut und hielten Forschungsseminare. Der Berner Immunologie-Club erfreut sich, auch durch die aktive Hilfe aus dem PKI, einer grossen Beliebtheit. Eine von Prof. Simon und Prof. Brunner (Institut für Pathologie) organisierte „Euroconference on Apoptosis“ zog ca. 350 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 wissenschaftspolitische Verantwortung für die Medizin und die Biowissenschaften wahr. Prof. Simon amtet gegenwärtig als Präsident der Union der Schweizerischen Gesellschaften für Experimentelle Biologie (USGEB). Er ist gegenwärtig auch Präsident der European Cell Death Organization (ECDO).

Ich danke allen Mitarbeitern und Mitarbeiterinnen für ihren Einsatz, welcher auch im Jahr 2008 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 2009

1.2. Foreword

This is the eighth 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 2008 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 2008. The organization of three art exhibitions within our institute is an example for these efforts.

In 2008, we recruited Prof. Thomas Kaufmann, who established a new research group at the PKI. Prof. Kaufmann received a professorship of the Swiss National Science Foundation and started after a research stay in Melbourne (Australia) on May 1, 2008, in our institute.

In addition to regular teaching within the third study year of medical students and our teaching of dental students, Prof. Simon, Prof. Huwiler, and Prof. Yousefi are additionally involved in Immunology M.Sc. programmes within the Natural Sciences Faculty of our university. Furthermore, Prof. Simon and Prof. Zangemeister-Wittke are active within a new B.Sc. course in Biomedicine at the University of Fribourg (teaching of “General Pharmacology”). The students of this course will have the opportunity to enter into a new M.Sc. program at the University of Bern beginning in the study year 2009/2010. Here, the PKI will be responsible for teaching “Organ-specific Pharmacology”. We are also actively involved within the graduation program for MD/PhD students of the University of Bern (Graduate School for Cellular and Biomedical Sciences). 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 (Prof. Yousefi), and a summer school (Prof. Simon) were provided. Importantly, these additional events were financed exclusively by external sponsors. Currently, 13 PhD students and 4 MD students work at the PKI, and three students (1 PhD, 2 MD) successfully finished their doctoral studies in 2008.

In 2008, members of the Institute of Pharmacology published 17 original and 11 review articles in international peer-reviewed journals (the sum of the “impact factors” is more than 300). Co-workers of the institute were invited to 45 lectures or seminars. Several PKI members received research prizes. Five co-workers are currently supported by grants of the Swiss National Science Foundation. Several prominent researchers visited the institute and presented seminars. The Bern Immunology Club (BIC) is also thanks to our contribution highly active and successful. An international congress (16th Euroconference of Apoptosis) was organized by Prof. Simon and Prof. Brunner (Institute of Pathology, Univ. of Bern) and attracted approximately 350 individuals interested in the field of “Cell Death”. In summary, research plays an important role at the PKI and is performed at a high level.

The PKI also takes over responsibilities outside of the university. For instance, Prof. Simon served as President of the Swiss Society of Experimental Pharmacology (SSEP) until August 2008. He is currently President of the Union of the Swiss Societies for Experimental Biology (USSEB) as well as President of the European Cell Death Organization (ECDO).

I thank all co-workers for their hard work that contributed to the success of the PKI in 2008. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, February 2009

2. Staff 2008

Director

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

Deputy Director

Prof. Dr. Andrea Huwiler, PhD

Permanent Members

Prof. Dr. Andrea Huwiler, PhD
Prof. Dr. Thomas Kaufmann, PhD* (since May 2008)
Prof. Dr. Hans-Uwe Simon, MD, PhD
Prof. Dr. Shida Yousefi, PhD
Prof. Dr. Uwe Zangemeister-Wittke, PhD
PD Dr. Peter Späth, PhD*
Prof. Dr. Robert Friis, PhD* (since April 2008)

Scientific Staff

Dr. Nicola Andina, MD, PhD student
Daniel Bachmann, research assistant* (since July 2008)
Karima Berard Ettoli, research fellow* (until February 2008)
Dr. Sébastien Conus, PhD
Nohemy Echeverry, PhD student (since August 2008)
Hansjürg Engel, M.Sc.* (June – September 2008)
Elena Federzoni, PhD student
Dr. Barbara Geering, PhD
Grace Gordon, technician (until February 2008)
Anna Greening, PhD student* (until June 2008)
Anouk Grünert, MD student* (since November 2008)
Zhaouye He, PhD student
Simone Hildbrand, technician (until May 2008)
Lotte Petra Hofmann, PhD student* (until June 2008)
Dr. Sajid Hussain, PhD* (until January 2008)
Mirjam Kummer, M.Sc. student* (January - June 2008)
Dr. Nataliya Kotelevets, PhD* (since September 2008)
Evelyne Kozlowski, technician
He Liu, PhD student*
Marianne Maillard-Van Laer, technician (since August 2008)
Dipak Maskey, PhD student
Cristina Mihalache, PhD student
Susanne Probst, technician
Annika Quast, PhD student (until November 2008)
Dr. Shuyu Ren, PhD
Dr. Benjamin Sakem, PhD* (until July 2008)
Dr. Souzan Salemi, PhD
Inès Schmid, head technician

Dr. Jan Schmidt-Mende, MD, PhD
Stephanie Schwalm, PhD student* (until June 2008)
Manuel Simon, PhD student
Simon Städler, MD student* (since December 2008)
David Troi, MD student*
Dr. Stephan von Gunten, MD, PhD, MME (since November 2008)
Thomas von Rütte, MD student*
Dr. Johannes Winkler, PhD* (until June 2008)
Dr. Cuiyan Xin, PhD* (since February 2008)
Dr. Xu Xu, PhD* (until April 2008)

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*, Dept. of Dermatology, Inselspital, University of Bern
PD Dr. Alex Straumann, MD*, Dept. of Gastroenterology, University of Basel
PD Dr. Mario Tschan, PhD*, Dept. of Clinical Research, University of Bern
Prof. Dr. Arum M. Dharmarajan, PhD,* School of Anatomy and Human Biology, University of Western Australia, Crawley, Perth (Australia)

External Computer Support

Dominik Wyss*

Office

Sandra Suter, head secretary
Anita Dähler, secretary

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

Workshop

Hans Andres

House Keeping

Isa Conforti
Elisa Piccirilli

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

Members of the Institute of Pharmacology of the University of Bern together with participants of an international summer school in Bönigen (Aug. 2008). In the first raw, our guests from Philadelphia (Prof. Angela Haczku) and Rome (Prof. Gerry Melino) are seen.

Members of the Institute of Pharmacology of the University of Bern together with participants of the 16th Euroconference on Apoptosis in the Auditorium ETTORE ROSSI of the University Hospital Bern (Sept. 2008).

3. Teaching Activities
3.1. Lectures

Lectures for medical students

Date	Lecturer	Titel of the lecture
March 17, 2008	Dr. Jan Schmidt-Mende	Antidiabetika
March 19, 2008	Dr. Jan Schmidt-Mende	Fett-Lipidsenker, Gicht
April 14, 2008	Prof. Andrea Huwiler	Antiepileptika
April 16, 2008	Prof. Andrea Huwiler	Therapie von Morbus Parkinson und Demenz
April 21, 2008	Dr. Jan Schmidt-Mende	Nebenniere und Hypophyse
April 23, 2008	Dr. Jan Schmidt-Mende	Pharmakologie der Schilddrüse und Nebenschilddrüse
April 28, 2008	Prof. Andrea Huwiler	Lokalanästhetika
May 5, 2008	Prof. Andrea Huwiler	Pharmakologie der Narkotika / Anästhesie 1
May 7, 2008	Prof. Andrea Huwiler	Psychopharmakologie
May 19, 2008	Prof. Andrea Huwiler	Antidepressiva, Anxiolythika und Stimmungsstabilisatoren
May 20, 2008	Prof. Andrea Huwiler	Antipsychotika
May 28, 2008	Prof. Andrea Huwiler	Schmerz und Analgesiologie 1
May 28, 2008	Prof. Andrea Huwiler	Schmerz und Analgesiologie 2
May 28, 2008	Prof. Andrea Huwiler	Pharmakologie im Alter
June 3, 2008	Prof. Robert Friis	Immunmodulation
Sept. 17, 2008	Prof. Hans-Uwe Simon	Pharmakodynamik 1
Sept. 22, 2008	Prof. Hans-Uwe Simon	Pharmakodynamik 2
Sept. 24, 2008	Prof. Hans-Uwe Simon	Einführung in die Toxikologie
Oct. 1, 2008	Prof. Hans-Uwe Simon	Entzündungshemmung
Oct. 27, 2008	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten

Nov. 3, 2008	PD Dr. Peter Späth Prof. Uwe Zangemeister-Wittke	Antithrombotische Therapie II & Antikoagulantien
Nov. 3, 2008	Prof. Uwe Zangemeister-Wittke	Wirkprinzipien der Antihypertensiva
Nov. 4, 2008	Prof. Uwe Zangemeister-Wittke	Behandlung der Herzinsuffizienz und Angina Pectoris
Nov. 12, 2008	Prof. Uwe Zangemeister-Wittke	Antiarrhythmika
Nov. 19, 2008	Prof. Uwe Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Dec. 8, 2008	Prof. Uwe Zangemeister-Wittke	Diuretika

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

Date	**Lecturer**	**Title of the lecture**
Febr. 11, 2008	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Einführung, Rezeptoren
Febr. 13, 2008	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Dosis-Wirkungskurven
Febr. 18, 2008	Prof. Hans-Uwe Simon	Antagonisten / Applikation
Febr. 20, 2008	Prof. Uwe Zangemeister-Wittke	Aufnahme / Verteilung
Febr. 25, 2008	Prof. Uwe Zangemeister-Wittke	Arzneimittelmetabolismus / Elimination
Febr. 27, 2008	Prof. Uwe Zangemeister-Wittke	Gesamtkinetik / Dosierung
March 3, 2008	Prof. Andrea Huwiler	Interaktionen / Pharmakogenetik, allg.
March 5, 2008	Prof. Uwe Zangemeister-Wittke	Vegetatives Nervensystem
March 10, 2008	Prof. Uwe Zangemeister-Wittke	Herz-Kreislaufpräparate

March 12, 2008	Prof. Andrea Huwiler	Narkose-/Beruhigungsmittel
March 17, 2008	PD Dr. Armand Cachelin	Immunsuppression
March 19, 2008	PD Dr. Armand Cachelin	Schwache Analgetika
March 26, 2008	PD Dr. Armand Cachelin	Starke Analgetika
March 31, 2008	Dr. Sibylle Bürgi	Lokalanästhetika
April 2, 2008	Dr. Sibylle Bürgi	Lokalanästhetika
April 7, 2008	Dr. Sibylle Bürgi	Antibiotika I
April 7, 2008	Dr. Sibylle Bürgi	Antibiotika II
April 9, 2008	Dr. Sibylle Bürgi	Insulin, orale Antidiabetika
April 14, 2008	PD Dr. Peter Späth	Orale Antikoag./Plättchenhemmer
April 16, 2008	Dr. Jan Schmidt-Mende	Magensäurehemmung
April 21, 2008	Dr. Jan Schmidt-Mende	Psychopharmaka
April 23, 2008	Prof. Uwe Zangemeister-Wittke	Examensvorbereitung

Lectures for Natural Sciences Faculty: Clinical Immunology (Coordinator: Prof. Hans-Uwe Simon)

Date	**Lecturer**	**Title of the lecture**
May 8, 2008	Prof. Hans-Uwe Simon	Eosinophilic diseases
May 15, 2008	Prof. Hans-Uwe Simon	Pharmacological immunomodulation

Lectures for Natural Sciences Faculty: Cellular and Molecular Immunology (Coordinator: Prof. Beda Stadler)

Date	**Lecturer**	**Title of the lecture**
Nov. 13, 2008	Prof. Hans-Uwe Simon	Immunomodulators and immune response modifiers

Lectures for Natural Sciences Faculty: Molecular Biology of Inflammation (Coordinator: Prof. Britta Engelhardt)

Date	Lecturer	Title of the lecture
April 3, 2008	Prof. Andrea Huwiler	Lipid mediators involved in inflammation
May 22, 2008	Prof. Shida Yousefi	Resolution of inflammation - apoptosis

External teaching activities: University of Zurich (Molecular Medicine)

Date	Lecturer	Title of the lecture
April 14-15, 2008	Prof. Uwe Zangemeister-Wittke	Introduction into tumor biology

3.2. Coordination PBL Medical Students, 3rd year (2008/2009)

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. Stephan von Gunten (block V)
Prof. Andrea Huwiler (blocks VI and VII)

3.3. Tutorials (study year 2008/2009)

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

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

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

3.4. Inaugural Lectures

Date	Lecturer	Title
June 25, 2008	Prof. Thomas Kaufmann, Institute of Pharmacology University of Bern	Role of apoptosis in experimental hepatitis
Febr. 25, 2009	Prof. Shida Yousefi, Institute of Pharmacology University of Bern	DNA release by granulocytes: Anti-bacterial catapults

3.5. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan. 16, 2008	Prof. Heinried Radeke Institute of Pharmacology and Toxicology, University of Frankfurt Frankfurt/M. (D)	Multiple functions of dendritic cells: gatekeeper and peacemaker
Jan. 30, 2008	Dr. Isabelle Décosterd, Dept. of Anesthesiology CHUV, Lausanne	Persistent pain: a shift toward hyperexcitability of the nervous system
Febr. 14, 2008	Dr. Kantari Chahrazade Research Center, Hôpital Necker, Paris (F)	Externalization of proteinase 3 during neutrophil apoptosis
April 2, 2008	Prof. Peter Krammer Deutsches Krebs-Forschungszentrum Heidelberg (D)	Life and death of a T cell
April 16, 2008	Prof. Daniel Hoessli Dept. of Pathology CMU, Geneva	Signaling proliferation and apoptosis in lymphomas

May 16, 2008	Prof. Peter Mertens Nephrology and Clin. Immunology University of Aachen Aachen (D)	Y-box protein-1 as molecular target to prevent atherogenesis
May 21, 2008	Dr. Remo Perozzo School of Pharmaceutical Sciences, University of Geneva	From hit to novel targets against human African trypanosomiasis
June 18, 2008	Prof. J.-C. Martinou Dept. of Cell Biology, University of Geneva	Mechanisms of mitochondrial membrane permeabilization during apoptosis
Sept. 3, 2008	Prof. A.M. Dharmarajan School of Anatomy and Human Biology, University of Western Australia, Crawley, Perth (Australia)	sFRP4: Role in cancer
Oct. 1, 2008	Dr. Christina Stöckle Hertie Institute for Clinical Brain Research, University of Tübingen (D)	Antigen processing in health and autoimmunity
Oct. 8, 2008	Dr. Janine Reichenbach University Children's Hospital, Zurich	Gene therapy for X-CGD: Follow-up of the clinical phase I/II trial
Oct. 28, 2008	Dr. Stephan von Gunten Institute of Pathology University of Basel	Siglecs, a novel family of inhibitory receptors on hematopoietic cells
Nov. 19, 2008	Dr. Marco Idzko Dept. of Pneumology, University of Freiburg (D)	P2 receptors on dendritic cells and eosinophils: role in asthma
Dec. 3, 2008	Dr. Alexandre Arcaro University Children's Hospital, Zurich	Development of targeted therapies for medulloblastoma

3.6. Bern Immunology Club (BIC)

Date	Teacher	Title of the seminar
Jan. 30, 2008	Prof. Reinhard Fässler Max-Planck-Institut für Biochemie, Martinsried (D)	Genetic analysis of integrin signalling
Febr. 27, 2008	Dr. Sébastien Conus PKI, Univ. Bern	Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation
	Dr. Jens Stein TKI, Univ. Bern	In vivo imaging of the roles of endothelial ICAM-1 and ICAM-2 in lymphocyte trafficking to the lymph nodes.
March 26, 2008	Prof. Cem Gabay Div. of Rheumatology, University of Geneva	IL-1 family of cytokines in the control of inflammation
April 30, 2008	Prof. B. Schraven O.v.Guericke-University, Magdeburg (D)	Regulation of T-cell activation by adapter and effector molecules
May 28, 2008	Prof. Walter Reith, Dept. of Pathology and Immunology, University of Geneva	Maintenance of thymic self-tolerance is sustained by autoreactive CD4+ thymocytes
Aug. 10-12, 2008	Prof. Hans-Uwe Simon and Faculty	7th International Summer School, Bönigen (CH)
Aug. 27, 2008	Prof. Steffen Gay, Dept. of Rheumatology, University Hospital Zurich	Epigenetics in the pathogenesis of RA
Sept. 24, 2008	Dr. Martina Ulrich Med. Mikrobio. & Hygiene Univ. Tübingen (D)	Mechanisms and marker of lung inflammation in cystic fibrosis
Oct. 29, 2008	Prof. Luca Borradori Universitätsklinik für Dermatologie, Inselspital	Pemphigoid: paradigm of an organ-specific autoimmune disease of immunology
Nov. 26, 2008	Prof. Christoph Müller Institut of Pathology University of Bern	Highlights of immunology in 2008

For the current program of the Bern Immunology Club (BIC), please consult the following website:
http://www.bic.unibe.ch/content/teaching/bic_lectures_09/index_eng.html

3.7. Academic Degrees

Shida Yousefi, Prof., University of Bern
Assoziierte Professorin / Associate Professor
February 2009

Nicola Andina, Dr. phil. (PhD), University of Bern
Thesis: The role of Bim and Pim-1 in granulocyte survival
Institute of Pharmacology, Bern, December 2008
Supervisor: Prof. Hans-Uwe Simon

Susanne Hösli, Dr. med. (MD), University of Bern
Thesis: Anti-CD20 treatment for atopic eczema
Institute of Pharmacology, Bern, May 2008
Supervisors: Prof. Hans-Uwe Simon, PD Dr. Dagmar Simon

Jennifer Wittwer, Dr. med. (MD), University of Bern
Thesis: Alefasept (lymphocyte function-associated molecule 3/ IgG fusion protein) treatment for atopic eczema
Institute of Pharmacology, Bern, August 2008
Supervisors: Prof. Hans-Uwe Simon, PD Dr. Dagmar Simon

Mirjam Kummer, M.Sc. pharm, University of Basel
Master Thesis: Remodelling and apoptosis in eosinophilic esophagitis: effects of budesonide
Institute of Pharmacology, Bern, June 2008
Supervisors: Prof. Hans-Uwe Simon, Dr. Sébastien Conus

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

Group members: Marianne Maillard – Van Laer, technician[1]
Dr. Shuyu Ren, PhD[1]
Dr. Cuiyan Xin, PhD[1]
Dr. Xu Xu, PhD[1]
Dr. Benjamin Sakem, PhD[1]
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.

Sphingosine kinase-1 is a hypoxia-regulated gene that stimulates migration of human endothelial cells

S. Schwalm, F. Döll, I. Römer, S. Bubnova, J. Pfeilschifter, A. Huwiler

Sphingosine kinases (SK) catalyze the production of sphingosine-1-phosphate which in turn regulates cell responses such as proliferation and migration. Here, we show that exposure of the human endothelial cell line EA.hy 926 to hypoxia stimulates a increased SK-1, but not SK-2, mRNA, protein expression, and activity. This effect was due to stimulated SK-1 promoter activity which contains two putative hypoxia-inducible factor-responsive-elements (HRE). By deletion of one of the two HREs, hypoxia-induced promoter activation was abrogated. Furthermore, hypoxia upregulated the expression of HIF-1alpha and HIF-2alpha,

and both contributed to SK-1 gene transcription as shown by selective depletion of HIF-1alpha or HIF-2alpha by siRNA. The hypoxia-stimulated SK-1 upregulation was functionally coupled to increased migration since the selective depletion of SK-1, but not of SK-2, by siRNAs abolished the migratory response. In summary, these data show that hypoxia upregulates SK-1 activity and results in an accelerated migratory capacity of endothelial cells. SK-1 may thus serve as an attractive therapeutic target to treat diseases associated with increased endothelial migration and angiogenesis such as cancer growth and progression.
See original publication No. 1

Sphingosine kinase 1 and 2 regulate the capacity of mesangial cells to resist apoptotic stimuli in an opposing manner
L.P. Hofmann, S. Ren, S.Schwalm, J. Pfeilschifter, A. Huwiler
Sphingosine kinases (SKs) are key enzymes regulating the production of sphingosine-1-phosphate (S1P), which determines important cell responses including cell growth and death. Here we show that renal mesangial cells isolated from wild-type, SK-1(-/-), and SK-2(-/-) mice show a differential response to apoptotic stimuli. Wild-type mesangial cells responded to staurosporine with increased DNA fragmentation and caspase-3 processing, which was enhanced in SK-1(-/-) cells. In contrast, SK-2(-/-) cells were highly resistant to staurosporine-induced apoptosis. Furthermore, the basal phosphorylation and activity of the anti-apoptotic protein kinase B (PKB) and of its substrate Bad were decreased in SK-1(-/-) but not in SK-2(-/-) cells. Upon staurosporine treatment, phosphorylation of PKB and Bad decreased in wild-type and SK-1(-/-) cells, but remained high in SK-2(-/-) cells. In addition, the anti-apoptotic Bcl-X(L) was significantly upregulated in SK-2(-/-) cells, which may further contribute to the protective state of these cells. In summary, our data show that SK-1 and SK-2 have opposite effects on the capacity of mesangial cells to resist apoptotic stimuli. This is due to differential modulation of the PKB/Bad pathway and of Bcl-X(L) expression. Thus, subtype-selective targeting of SKs will be critical when considering these enzymes as therapeutic targets for the treatment of inflammation or cancer.
See original publication No. 2

Original publications

1. S. Schwalm, F. Döll, I. Römer, S. Bubnova, J. Pfeilschifter, **A. Huwiler:** Sphingosine kinase-1 is a hypoxia-regulated gene that stimulates migration of human endothelial cells.
Biochim. Biophys. Res. Commun. 368 (2008), 1020-1025.

2. L.P. Hofmann, S. Ren, S. Schwalm, J. Pfeilschifter, **A. Huwiler**: Sphingosine kinase 1 and 2 regulate the capacity of mesangial cells to resist apoptotic stimuli in an opposing manner.
Biol. Chem. 389 (2008), 1399-1407.

3. A. Doller, E.S. Akool, **A. Huwiler**, R. Müller, H. Radeke, J. Pfeilschifter, W. Eberhardt: Posttranslational modification of the AU-rich element binding protein HuR by PKCδ-elicits angiotensin II-induced stabilization and nuclear export of COX-2 mRNA.
Mol. Cell. Biol. 28 (2008), 2608-2625.

Review article

1. **A. Huwiler,** J. Pfeilschifter: Sphingolipids take the center stage: Sphingosine 1-phosphate and its receptors as new drug targets.
   Biochem. Pharmacol. 75 (2008), 1893-1900.

Book chapter

1. **A. Huwiler**: Drug Discovery and Evaluation: Pharmacological Assays, Vol 1 and 2, 3rd ed, Vogel HG (Ed), Springer, Berlin - Heidelberg - New York, 2008.

Group Prof. Thomas Kaufmann

Group members: Daniel Bachmann
Nohemy Echeverry, PhD student

Our group is interested in the molecular mechanisms of apoptosis, also called programmed cell death. A particular interest of our research lies in the members of the Bcl-2 protein family, which are crucial regulators of apoptosis. Besides cell death regulation in haematopoietic cells, we are interested in apoptosis pathways in hepatocytes. Abnormal hepatocyte apoptosis is a cause or contributing factor in many chronic as well as acute liver diseases in humans, including viral and autoimmune hepatitis, alcoholic liver disease, fat liver and endotoxin-induced liver failure. The generation and use of genetically modified mice allows analysis of the regulation of apoptosis in organs/tissues of the developing and mature organism as well as the development of tumours and autoimmunity in case of a de-regulated apoptotic program. We are using mouse strains lacking important apoptosis regulators, such as pro- and anti-apoptotic members of the Bcl-2 family. Members of the BH3-only subgroup, which acts as sensors of apoptotic stress signals, are of particular interest and there are now mice available lacking one or several BH3-only proteins. On the other hand, we have shown that anti-apoptotic proteins of the 'inhibitor of apoptosis' family (IAP) are crucial in preventing death receptor-induced hepatocyte apoptosis. Using both *in vitro* as well as *in vivo* approaches, we aim to further characterise the role of those regulators.

Fatal hepatitis mediated by tumor necrosis factor-α requires caspase-8 and involves the BH3-only proteins Bid and Bim

T. Kaufmann, P.J. Jost, M. Pellegrini, H. Puthalakath, R. Gugasyan, S. Gerondakis, E. Cretney, M.J. Smyth, J. Silke, R. Hakem, P. Bouillet, T.W. Mak, V.M. Dixit, A. Strasser

Apoptotic death of hepatocytes, a feature and contributing factor of many chronic and acute liver diseases, can be a consequence of over-activation of the immune system. Injection with lipopolysaccharide (LPS) plus the transcriptional inhibitor D(+)-galactosamine (GalN) or mitogenic T cell activation cause fatal hepatocyte apoptosis in mice. In both settings hepatocyte killing is mediated by TNFa/TNF-R signaling but the effector mechanisms remain unclear. Our analysis of gene-targeted mice showed that caspase-8 is essential for hepatocyte killing in both settings. Loss of Bid, the pro-apoptotic BH3-only protein activated by caspase-8, and essential for Fas ligand-induced hepatocyte killing, resulted only in a minor reduction of liver damage. However, combined loss of Bid and another BH3-only protein, Bim, activated by JNK, protected mice from LPS+GalN-induced hepatitis. These observations identify caspase-8 and the BH3-only proteins Bid and Bim as potential therapeutic targets for treatment of inflammatory liver diseases.

See original publication No. 1

XIAP loss converts Fas-induced apoptosis signaling in hepatocytes from type II into type I

P.J. Jost, J. Silke, S. Grabow, U. Nachbur, D.C.S. Huang, P. Bouillet, C. Borner, A. Strasser, T. Kaufmann

Distinct cell types differ in the mechanisms by which the 'death receptor' Fas (APO-1/CD95) triggers their apoptosis. In lymphocytes (type I cells) activation of effector caspases by caspase-8 suffices for cell killing, whereas in hepatocytes (type II), amplification of the caspase cascade through caspase-8 mediated activation of the pro-apoptotic Bcl-2 family member Bid is essential. Our experiments revealed that gene targeting-mediated loss of the caspase inhibitor XIAP or treatment with Smac/Diablo mimetic IAP inhibitory drugs rendered hepatocytes independent of Bid for Fas-induced apoptosis signaling. These results show that XIAP is the critical discriminator between type I versus type II apoptosis signaling and suggest that IAP inhibitors should be used with caution in cancer patients with underlying liver conditions.

See original publication No. 2

Original publications

1. **T. Kaufmann**, P. Jost, M. Pellegrini, H. Puthalakath, R. Gugasyan, S. Gerondakis, E. Cretney, M.J. Smyth, J. Silke, R. Hakem, P. Bouillet, T.W. Mak, V.M. Dixit, A. Strasser: Fatal hepatitis mediated by TNF-α requires caspase-8 and involves the BH3-only proteins Bid and Bim.
   Immunity 30 (2009), 56-66.

2. P. Jost, J. Silke, S. Grabow, P. Bouillet, DC Huang, CB Borner, J. Tschopp, DL Vaux, A. Strasser, **T. Kaufmann**: XIAP loss converts Fas-induced apoptosis signaling in hepatocytes from type II into type I. *submitted.*

3. D. Walter, S. Vogel, **T. Kaufmann**, S. McNelly, A. Haber, K. Neubert, R. Pick, JG Hengstler, T. Dandekar, J. Silke, A. Strasser, F. von Weizsäcker, C. Borner: Switching of Fas/CD95 signalling from type II to type I upon in vitro plating of mouse hepatocytes.
   Hepatology 48 (2008), 1942-1953.

4. A. Jabbour, J.E. Heraud, C.P. Daunt, **T. Kaufmann**, J. Sandow, L. O'Reilly, B. Callus, A. Lopez, A. Strasser, D.L. Vaux, P.G. Ekert: Puma indirectly activates Bax to cause apoptosis in the absence of Bid or Bim.
   Cell Death Differ. 16 (2009), in press. doi:10.1038/cdd.2008.179.

5. MD McKenzie, EM Carrington, **T. Kaufmann**, A. Strasser, DCS Huang, TWH Kay, J. Allison, HE Thomas: Pro-apoptotic BH3-only protein Bid is essential for death receptor-induced apoptosis of pancreatic β cells.
   Diabetes 57 (2008), 1284-1292.

Group Prof. Hans-Uwe Simon

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**Joint supervision together with PD Dr. D. Simon.

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 2008.

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

S. Yousefi, J.A. Gold, N. Andina, J.J. Lee, A.M. Kelly, E. Kozlowski, I. Schmid, A. Straumann, J. Reichenbach, G.J. Gleich, H.-U. Simon
(Collaboration with the Division of Pulmonary and Critical Care, Oregon Health and Sciences University, Portland, USA; Dept. of Biochemistry and Molecular Biology, Mayo Clinic Arizona, Arizona, USA; Dept. of Dermatology, University of Utah, Salt Lake City, USA; and University Children's Hospital, Zurich, Switzerland)

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 better understand the role of eosinophils within the gastrointestinal immune system. We show here that lipopolysaccharide (LPS) from gram-negative bacteria activates interleukin (IL)-5 or interferon (IFN)-γ 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. Moreover, following cecal ligation and puncture, IL-5 transgenic but not wild-type mice demonstrated intestinal eosinophil infiltration and extracellular DNA deposition in association with protection against microbial sepsis. 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.

See original publication No. 1

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, University of Geneva; and Institute of Molecular Medicine and Cell Research, University of Freiburg, 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. 2

Pim-1 but not PI3K is essential in the anti-apoptotic signalling cascade initiated by IL-5 in eosinophils

N. Andina, S. Didichenko, J. Schmidt-Mende, C.A. Dahinden, H.-U. Simon
(Collaboration with the Department of Immunology, University of Bern)

Background: Eosinophil differentiation, activation, and survival are largely regulated by interleukin-5 (IL-5). IL-5 – mediated transmembrane signal transduction involves both Lyn - mitogen-activated protein kinases (MAPK) and Janus kinase 2 (Jak2) – signal transduction and activator of transcription (STAT) pathways. Objective: We asked whether additional

signalling molecules/pathways are critically involved in IL-5 – mediated eosinophil survival. Methods: Eosinophil survival and apoptosis was measured in the presence and absence of IL-5 and defined pharmacological inhibitors in vitro. The specific role of the serine/threonine kinase Pim-1 was tested using HIV-TAT fusion proteins containing wild-type Pim-1 or a dominant-negative form of Pim-1. The expression of Pim-1 in eosinophils was analyzed by immunoblotting and immunofluorescence. Results: Although pharmacological inhibition of phosphatidylinositol-3 kinase (PI3K) by LY294002, wortmannin, or the selective PI3K p110δ isoform inhibitor IC87114 was successful in each case, only LY294002, but not the other two PI3K inhibitors, blocked increased IL-5 – mediated eosinophil survival. This suggested that LY294002 inhibited, besides PI3K, another kinase, which is critically involved in this process. Indeed, Pim-1 was rapidly and strongly expressed in eosinophils following IL-5 stimulation in vitro and readily detected in eosinophils under inflammatory conditions in vivo. Moreover, by using specific protein transfer, we identified Pim-1 as a critical element in IL-5 – mediated anti-apoptotic signalling in eosinophils. Conclusions: Pim-1 but not PI3K plays a major role in IL-5 – mediated anti-apoptotic signalling in eosinophils. Clinical implication: Pim-1 represents a potential new anti-eosinophil drug target.

See original publication No. 3

Anti-CD20 (rituximab) treatment improves atopic eczema

D. Simon, S. Hösli, G. Kostylina, N. Yawalkar, H.-U. Simon
(Collaboration with the Department of Dermatology, Inselspital, 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. 4

Anti-IL-5 (mepolizumab) treatment in active eosinophilic esophagitis

A. Straumann, S. Conus, P. Grzonka, H. Kita, G. Kephart, C. Bussmann, C. Beglinger, D.A. Smith, J. Patel, M. Byrne, H.-U. Simon
(Collaboration with the Department of Gastroenterology, University of Basel; Mayo Clinic, Rochester, MN, USA; Institute of Clinical Pathology Viollier, Basel; and GlaxoSmithKline, Greenford, UK)

Backgound & Aims: Eosinophilic esophagitis (EoE) is a clinico-pathological condition defined by proton-pump-inhibitor refractory esophagus-related symptoms in combination with a

dense esophageal eosinophilia. The aim of this study was to evaluate the efficacy and safety of mepolizumab (a humanized anti-interleukin-5 monoclonal antibody), an agent designed to target eosinophils, in EoE. Methods: Eleven adults with active EoE (>20 peak eosinophil number/hpf and dysphagia) were randomized to 750 mg mepolizumab (n=5) or placebo (n=6) and received two intravenous applications, one week apart. Those patients not in complete remission (<5 peak eosinophil number/hpf) received two further doses four weeks apart, 1500 mg mepolizumab or placebo according to their original randomization. Patients did not obtain any other anti-eosinophil therapy. The effect of mepolizumab was assessed clinically, endoscopically, histologically, and via blood and tissue biomarkers. Results: As assessed by immunofluorescence, a marked reduction of mean esophageal eosinophilia (p=0.03) was seen in the mepolizumab group (-54%) compared with the placebo group (-5%) four weeks after initiation of treatment. Blood eosinophil numbers also significantly declined in the mepolizumab but not in the placebo group (p=0.006). No further reduction of eosinophil numbers was observed in response to the two additional infusions in either group. Mepolizumab reduced tenascin C (p=0.033) and TGF-β1 (p=0.05) expression in the esophageal epithelial layer 13 weeks after initiation of treatment. Clinically, no impressive improvement of symptoms was seen, although a trend to an improvement was seen between 4 and 13 weeks after initiation of mepolizumab therapy. Treatment with mepolizumab was well tolerated and no relevant adverse events occurred. Conclusions: Mepolizumab significantly reduced eosinophil numbers in both blood and esophageal tissues in patients with active EoE. Changes in the expression of molecules associated with esophageal remodeling were reversed by the antibody treatment. Minimal clinical improvement was achieved in a subgroup of EoE patients. Mepolizumab had an acceptable safety profile, even at the high 1500 mg dose level.

Original publications

1. S. Yousefi, J.A. Gold, N. Andina, J.J. Lee, A.M. Kelly, E. Kozlowski, I. Schmid, A. Straumann, J. Reichenbach, G.J. Gleich, **H.-U. Simon**: Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense.
   Nat. Med. 14 (2008), 949-953.
   Comment in: Nature Medicine 14 (2008), 910-912 (Nizet V & Rothenberg ME)
   Comment in: Nature Reviews Immunology 8 (2008), 658 (Leavy O)
   Comment in: Science 321 (2008), 1021 (PAK)
   Comment in: J. Allergy Clin. Immunol. 122 (2008), 661 (Gabbert S)

2. S. Conus, R. Perozzo, T. Reinheckel, C. Peters, L. Scapozza, S. Yousefi, **H.-U. Simon**: Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation.
   J. Exp. Med. 205 (2008), 685-698.
   Comment in: Nature Reviews Immunology 8 (2008), 244 (Tufet M)
   Comment in: J. Exp. Med. 205 (2008), 505 (Bashyam H)

3. N. Andina, S. Didichenko, J. Schmidt-Mende, C.A. Dahinden, **H.-U. Simon**: Pim-1 but not PI3K is essential in the anti-apoptotic signalling cascade initiated by IL-5 in eosinophils.
   J. Allergy Clin. Immunol. 123 (2009), in press. DOI: 10.1016/j.jaci.2008.12.004

4. D. Simon, S. Hösli, G. Kostylina, N. Yawalkar, **H.-U. Simon**: Anti-CD20 (rituximab) treatment improves atopic eczema.
   J. Allergy Clin. Immunol. 121 (2008), 122-128.

5. 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.

6. D. Simon, S. Salami, S. Yousefi, **H.-U. Simon**: Primary resistance to imatinib in Fip1-like 1-platelet-derived growth factor receptor α-positive eosinophilic leukemia.
J. Allergy Clin. Immunol. 121 (2008), 1054-1056.

7. A. Straumann, C. Bussmann, S. Conus, C. Beglinger, **H.-U. Simon**: Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis.
J. Allergy Clin. Immunol. 122 (2008), 425-427.

8. S. Conus, A. Straumann, **H.-U. Simon**: Anti-IL-5 (mepolizumab) therapy does not alter IL-5 receptor α levels in patients with eosinophilic esophagitis.
J. Allergy Clin. Immunol. 123 (2009), 269.

9. S. Salemi, S. Yousefi, D. Simon, I. Schmid, L. Moretti, L. Scapozza, **H.-U. Simon**: A novel FIP1L1-PDGFRA mutant destabilizing the inactive conformation of the kinase domain in chronic eosinophilic leukemia/hypereosinophilic syndrome.
Allergy 64 (2009), in press. DOI: 10.1111/j.1398-9995.2009.01943.x

10. **H.-U. Simon**, B. Malhotra: The pharmacokinetic profile of fesoterodine: Similarities and differences to tolterodine.
Swiss Med. Wkly. 139 (2009), in press.

11. S. von Gunten, S.M. Jakob, B. Geering, J. Takala, **H.-U. Simon**: Different patterns of Siglec-9-mediated neutrophil death in septic shock.
Shock 31 (2009), in press.

12. 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.
Allergy 63 (2008), 333-340.

13. M.E. Rothenberg, A.D. Klion, F.E. Roufosse, J.E. Kahn, P.F. Weller, **H.-U. Simon**, L.B. Schwartz, L.J. Rosenwasser, J. Ring, A.E. Haig, P.I.H. Frewer, J.M. Parkin, G.J. Gleich: Treatment of patients with the hypereosinophilic syndrome with mepolizumab.
N. Engl. J. Med. 358 (2008), 1215-1228.

14. 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.
Lung Cancer 60 (2008), 355-365.

15. 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. 117 (2008), 45-49.

16. A. Straumann, C. Bussmann, M. Zuber, S. Vannini, **H.-U. Simon**, A. Schoepfer: Eosinophilic esophagitis: Analysis of food impaction and perforation in 251 adolescent and adult patients.
Clin. Gastroenterol. Hepatol. 6 (2008), 598-600.

17. M. Ulrich, A. Petre, ……..**H.-U. Simon**, ……G. Döring: Post-translational tyrosine nitration of eosinophil granule toxins mediated by eosinophil peroxidase.
J. Biol. Chem. 283 (2008), 28629-28640.

18. D. Simon, J. Wittwer, G. Kostylina, U. Buettiker, **H.-U. Simon**, N. Yawalkar: Alefacept (lymphocyte function-asscoiated molecule 3/IgG fusion protein) treatment for atopic eczema.
J. Allergy Clin. Immunol. 122 (2008), 423-424.

19. D. Kassahn, U. Nachbur, S. Conus, O. Micheau, P. Schneider, **H.-U. Simon**, T. Brunner: Distinct requirements for activation-induced cell surface expression of preformed Fas/CD95 ligand and cytolytic granule markers in T cells.
Cell Death Differ. 16 (2009), 115-124.

20. S. Aits, L. Gustafsson, O. Hallgren, P. Brest, M. Gustafsson, M. Trulsson, A.-K. Mossberg, **H.-U. Simon**, B. Mograbi, C. Svanborg: HAMLET (human α-lactalbumin made lethal to tumor cells) triggers autophagic tumor cell death.
Int. J. Cancer 124 (2009), 1008-1019.

Review articles

1. S. von Gunten, **H.-U. Simon**: Natural anti-Siglec autoantibodies mediate potential immunoregulatory mechanisms: Implications for the clinical use of intravenous immunoglobulins (IVIg).
Autoimmun. Rev. 7 (2008), 453-456.

2. S. Conus, **H.-U. Simon**: General laboratory diagnostics of eosinophilic GI diseases.
Best Pract. Res. Clin. Gastroenterol. 22 (2008), 441-453.

3. S. Conus, **H.-U. Simon**: Cathepsins: Key modulators of cell death and inflammatory responses.
Biochem. Pharmacol. 76 (2008), 1374-1382.

4. S. Yousefi, **H.-U. Simon**: Autophagy in cancer and chemotherapy.
Results Probl. Cell Differ., 2009, in press. DOI: 10.1007/400_2008_25

5. **H.-U. Simon**: Cell death in allergic diseases.
Apoptosis 14 (2009), in press. DOI: 10.1007/s10495-008-0299-1

6. S. Yousefi, **H.-U. Simon**: Autophagy in cells of the blood.
Biochim. Biophys. Acta (BBA), 2009, in press. DOI: 10.1016/j.bbamcr.2008.12.023

7. D. Simon, **H.-U. Simon**: Reply – Anti-CD20 (rituximab) treatment for atopic eczema.
J. Allergy Clin. Immunol. 121 (2008), 1515-1516.

8. D.J. Klionsky, …, **H.-U. Simon**, ...R.L. Deter: Guidelines for the use and interpretation of assays for monitoring autophagy in higher eukaryotes.
Autophagy 4 (2008), 151-175.

9. J. Bousquet, T. Bieber, W. Fokkens, M. Humbert, M.L. Kowalski, B. Niggemann, **H.-U. Simon**, H. Schünemann: Consensus statements, evidence-based medicine and guidelines in allergic diseases.
Allergy 63 (2008), 1-4.

10. J. Bousquet, T. Bieber, W. Fokkens, M.L. Kowalski, M. Humbert, B. Niggemann, **H.-U. Simon**, P. Burney, P. van Cauwenberge, T. Zuberbier, C.A. Akdis, P. Demoly: Important questions in allergy: novel research areas.
Allergy 63 (2008), 143-147.

11. J. Bousquet, T. Bieber, W. Fokkens, M. Kowalski, M. Humbert, B. Niggemann, **H.-U. Simon**, A.A. Cruz, T. Haahtela: In allergy, "a new day has begun".
Allergy 63 (2008), 631-633.

12. J. Bousquet, …, **H.-U. Simon**, ...J.P. Zock: Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper.
Allergy 63 (2008), 842-853.

13. S. Bialik, A. Eisenberg, **H.-U. Simon**, A. Kimchi: Life and death partners: Apoptosis, autophagy and the cross-talk between them.
Cell Death Differ. 16 (2009), in press.

Book chapters

1. **H.-U. Simon**: Hypereosinophilic syndromes. In: Allergy and Allergic Diseases, 2nd edition (Eds. A.B. Kay, A.P. Kaplan, J. Bousquet, P.G. Holt); Blackwell Publishing, Oxford, 2008, p. 1802-1809.

2. U. Zangemeister, **H.-U. Simon**: Myelosuppression. In: Encyclopedia of Cancer, 2nd edition, Springer-Verlag, Heidelberg, 2008, p. 2008-2010.

3. **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, 2009, p. 413-421.

4. Simon D, **H.-U. Simon**: Eosinophils. In: Asthma and COPD, 2nd edition (Eds. P.J. Barnes, J.M. Drazen, S.I. Rennard, N.C. Thomson); Academic Press, Elsevier Ltd., 2009, p. 145-156.

5. S. Yousefi, **H.-U. Simon**: Autophagy in cancer and chemotherapy. In: Death receptors and cognate ligands in cancer (Ed. H. Kalthoff); Springer, Berlin – Heidelberg, 2009, in press.

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*Joint supervision together with Prof. 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. 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. Specifically, we investigate both mechanism and function of DNA release by eosinophils and neutrophils.

Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense
S. Yousefi, J.A. Gold, N. Andina, J.J. Lee, A.M. Kelly, E. Kozlowski, I. Schmid, A. Straumann, J. Reichenbach, G.J. Gleich, H.-U. Simon
(Collaboration with the Division of Pulmonary and Critical Care, Oregon Health and Sciences University, Portland, USA; Dept. of Biochemistry and Molecular Biology, Mayo Clinic Arizona, Arizona, USA; Dept. of Dermatology, University of Utah, Salt Lake City, USA; and University Children's Hospital, Zurich, Switzerland)
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 better understand the role of eosinophils within the gastrointestinal immune system. We show here that lipopolysaccharide (LPS) from gram-negative bacteria activates interleukin (IL)-5 or interferon (IFN)-γ 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. Moreover, following cecal ligation and puncture, IL-5 transgenic but not wild-type mice demonstrated intestinal eosinophil infiltration and extracellular DNA deposition in association with protection against microbial sepsis. 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.
See original publication No. 1

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. 2

Original publications

1. **S. Yousefi**, J.A. Gold, N. Andina, J.J. Lee, A.M. Kelly, E. Kozlowski, I. Schmid, A. Straumann, J. Reichenbach, G.J. Gleich, H.-U. Simon: Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense.
   Nat. Med. 14 (2008), 949-953.
   Comment in: Nature Medicine 14 (2008), 910-912 (Nizet V & Rothenberg ME)
   Comment in: Nature Reviews Immunology 8 (2008), 658 (Leavy O)
   Comment in: Science 321 (2008), 1021 (PAK)
   Comment in: J. Allergy Clin. Immunol. 122 (2008), 661 (Gabbert S)

2. 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. 117 (2008), 45-49.

3. S. Conus, R. Perozzo, T. Reinheckel, C. Peters, L. Scapozza, **S. Yousefi**, H.-U. Simon: Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation.
   J. Exp. Med. 205 (2008), 685-698.
   Comment in: Nature Reviews Immunology 8 (2008), 244 (Tufet M)
   Comment in: J. Exp. Med. 205 (2008), 505 (Bashyam H)

4. 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.

5. D. Simon, S. Salami, **S. Yousefi**, H.-U. Simon: Primary resistance to imatinib in Fip1-like 1-platelet-derived growth factor receptor α-positive eosinophilic leukemia.
   J. Allergy Clin. Immunol. 121 (2008), 1054-1056.

6. S. Salemi, **S. Yousefi**, D. Simon, I. Schmid, L. Moretti, L. Scapozza, H.-U. Simon: A novel FIP1L1-PDGFRA mutant destabilizing the inactive conformation of the kinase domain in chronic eosinophilic leukemia/hypereosinophilic syndrome.
Allergy 64 (2009), in press.
DOI: 10.1111/j.1398-9995.2009.01943.x

Review articles

1. **S. Yousefi**, H.-U. Simon: Autophagy in cancer and chemotherapy.
Results Probl. Cell Differ., 2009, in press. DOI: 10.1007/400_2008_25

2. **S. Yousefi**, H.-U. Simon: Autophagy in cells of the blood.
Biochim. Biophys. Acta (BBA), 2009, in press. DOI: 10.1016/j.bbamcr.2008.12.023

Book chapter

1. **S. Yousefi**, H.-U. Simon: Autophagy in cancer and chemotherapy. In: Death receptors and cognate ligands in cancer (Ed. H. Kalthoff); Springer, Berlin – Heidelberg, 2009, in press.

Group Prof. Uwe Zangemeister-Wittke

Group members: Manuel Simon, PhD student
Nataliya Kotelevets, PhD ESKAS fellowship student
Johannes Winkler, PhD (until July)
Annika Quast, PhD student
Susanne Probst, technician
Sajid Hussain, PhD (until Feb)
Patricia Martin-Killias, PhD student[1]
Nikolas Stefan, PhD student[1]

[1] Institute of Biochemistry, University of Zürich

Our research is focused on translational aspects in molecular oncology. A major goal is to investigate mechanisms of drug resistance in solid tumors and to identify survival pathways and their regulators for molecular intervention to facilitate tumor cell apoptosis. One major target in this program is sphingosine kinase 1 and we are evaluating its ability to regulate tumor cell survival, proliferation and migration.

In addition, we are interested in improving tumor-targeted drug delivery using rationally engineered protein-based delivery systems. For this purpose, we have developed affinity-maturated Designed Ankyrin Repeat Proteins (DARPins) as novel binding proteins with specificity for the epithelial cell adhesion molecule (EpCAM). Various nanomedicines including tumor-targeted nanovesicles incl. pH-sensitive DARPinosomes encapsulating protein toxins as well as protamin fusion proteins for intracellular siRNA delivery are under investigation.

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, and 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. 1

Original publications

1. LL. 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 60 (2008), 355-365.

2. M. Marinov, A. Ziogas, O.E. Pardo., LT Tan, T. Dhillon, F.A. Mauri, H.A. Lane, L.R. Lemoine, **U. Zangemeister-Wittke**, M.J. Seckl, A. Arcaro: AKT/mTOR pathway activation and bcl-2 family proteins modulate the sensitivity of human small cell cancer cancer cells to RAD001 (Everolimus).
   Clin. Cancer Res., in press.

Book chapter

U. Zangemeister-Wittke, H.-U. Simon: Myelosuppression in Encyclopedia of Cancer, Second Edition, Springer Verlag, 2008.

Additional Publications of PKI Members

Prof. Robert Friis

Original publications

1. T. Constantinou, F. Baumann, M. D. Lacher, S. Saurer, **R. Friis**, A. Dharmarajan: SFRP-4 abrogates Wnt-3a-induced beta-catenin and Akt/PKB signalling and reverses a Wnt-3a-imposed inhibition of in vitro mammary differentiation. J. Mol. Signal. 3 (2008), 10. DOI: 10.1186/1750-2187-3-10.

2. L. White, S. Ganapathipillai, **R. Friis**, A. Dharmarajan, A. Charles: Expression of secreted frizzled-related protein 4 in the primate placenta. Reproductive BioMedicine Online, in press.

Dr. Stephan von Gunten

Original publication

1. H. Yokoi, O.H. Choi, ……. , **S. von Gunten**, …… B.S. Bochner: Inhibition of FcεRI-dependent mediator release and calcium flux from human mast cells by sialic acid-binding immunoglobulin-like lectin 8 engagement. J. Allergy Clin. Immunology 121 (2008), 499-505.

Review article

1. **S. von Gunten,** B.S. Bochner: Basic and Clinical Immunology of Siglecs. Ann. N. Y. Acad. Sci. 1143 (2008), 61–82.

PD Dr. Peter Späth

Review article

1. V. Wahn, **P. Späth**: Komplementdefekte, Kinder und Jugendmedizin. Kinder- und Jugendmedizin 3 (2008), 179-184.

Book chapter

1. **P. Späth**, RW van Holten: Pathogen safety of immunoglobulin preparations. In: Wahn, V. and Orange, J. (eds) Clinical Use of Immunoglobulins, 1st edn. UNI-MED Verlag, Bremen - London - Boston, p. 29-50.

4.2. Congress Invitations

Dr. Sébastien Conus

Annual Meeting of the Swiss Society of Experimental Pharmacology (SSEP),
Zurich (CH), Aug. 29, 2008;
Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation.

Prof. Andrea Huwiler

Tagung Schwerpunktprogramm DFG “Sphingolipids: signalling and disease”,
Frankfurt am Main (D), Sept. 3–4, 2008;
Antiinflammatory and profibrotic actions of S1P and SPC in renal mesangial cells.

Leopoldina Symposium of Lipid Signalling,
Frankfurt am Main (D), Sept. 4 – 9, 2008;
Antiinflammatory actions of sphingolipids.

Sphingolipid Club Meeting,
Leiden (The Netherlands), Nov. 14 – 16, 2008;
Transcriptional regulation of sphingosine kinase 1 by hypoxia and other factors.

Prof. Thomas Kaufmann

16th Euroconference on Apoptosis - 5th Swiss Conference on Apoptosis
Bern (CH), Sept. 4 – 9, 2008;
Fatal hepatitis mediated by secreted TNF-alpha requires caspase-8 and the two BH3-only proteins Bid and Bim.

EMBO Workshop “Cytotoxicity, cell death & the immune system”
Zaragoza (E), Sept. 17-20, 2008;
The role of pro-apoptotic BH3-only proteins in death receptor-induced apoptosis.

Prof. Hans-Uwe Simon

Apoptosis World 2008: From mechanisms to applications; Luxembourg (L), Jan. 23-26, 2008;
Caspase-8 activation by cathepsin D – a novel pro-apoptotic signalling pathway operating in neutrophils.

20. Mainzer Allergie-Workshop, German Society for Allergology and Clinical Immunology; Mainz (D), March 7-8, 2008;
Eosinophils release mitochondrial DNA to trap and kill bacteria extracellularly.

49. Jahrestagung der Deutschen Gesellschaft für Pharmakologie und Toxikologie (DGPT);
Mainz (D), March 11-13, 2008;
Depletion of B cells and eosinophils in Th2 cells disorders.

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI);
Philadelphia (PA, USA), March 14-18, 2008;
Anti – IL-5 for non-HES diseases.

74. Jahrestagung der Deutschen Gesellschaft für Kardiologie; Mannheim (D),
March 27-29, 2008;
Kardiovaskuläre Medizin: Antiinflammatorische Therapie.

9th World Congress of the World Organization for specialized studies on diseases of the esophagus (OESO); Monaco, April 6-9, 2008;
Immunopathogenesis of eosinophilic esophagitis.

Annual Joint Meeting of the Swiss Societies for Pneumology, Paediatric Pneumology, Allergology and Immunology, Thoracic Surgery; Fribourg (CH), April 17-18, 2008;
Lung and eosinophilia.

XXVII. Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Barcelona (Spain), June 7-11, 2008;
Novel cell communication mechanisms in granulocytes.

Workshop on “Programmed cell death in cancer and immunology”, Loveno di Menaggio (I), June 28 – July 2, 2008;
Bacteria and eosinophil interactions in the intestinal mucosa.

PD Dr. Peter Späth

Winter School of the European Society of Artificial Organs (ESAO) – Inflammation and Artificial Organs, Cortina d’Ampezzo (I), March 6-8, 2008;
Artificial organs/surfaces and the complement system.

Annual Meeting of the Romanian Society of Allergology and Immunology, Baja Mare (Rom), May 2 – 4, 2008;
Immunologic background, diagnosis and treatment of selected autoimmune diseases & C1-esterase inhibitor – Physiology and pathophysiology.

Expert Meeting – Guidelines for the use of intravenous immunoglobulins – Organised by the Belgian Superior Health Council, Brussels (B), May 9, 2008;
Preparation & Mechanism of action of immunoglobulins.

7. Summer School der Charité, Berlin (D), Aug. 29-30, 2008;
Complement.

Joined Annual Congress of ÖGHO/DGHO/SGMO, Satellite symposium, Vienna (A), Oct. 10-14, 2008;
Intravenous immunoglobulins – new developments.

Prof. Uwe Zangemeister-Wittke

World Immune Regulation Meeting-II, Davos (CH), Febr. 29, 2008;
EpCAM-specific nanomedicines and designed ankyrin repeat proteins for tumor targeting.

25th International Conference on Advances in the Application of Monoclonal Antibodies in Clinical Oncology - Monoclonal Antibodies and Cancer Stem Cells in Clinical Oncology, Amathus Beach (Rhodes, GR), June 17, 2008;
EpCAM-specific nanomedicines and designed ankyrin repeat proteins for tumor targeting.

2nd International Symposium on EpCAM and Cancer Stem Cell Markers, Evangelische Akademie Tutzing, Munich (D), Oct. 9, 2008;
EpCAM-targeted nanomedicine delivery using designed ankyrin repeat proteins.

4.3. Seminar Invitations

Prof. Andrea Huwiler

University of Trondheim (N); Jun. 6, 2008; guest of Prof. Johansen:
Sphingosine kinases as a suitable target for cancer therapy?

Novartis Basel, Basel (CH); Jun. 10, 2008; guest of Dr. K. Seuwen:
The yin and yang of sphingolipids: a regulatory role of sphingosine kinases?

University of Geneva, Pharmacology, Geneva (CH), Dec. 5, 2008; guest of Prof. U. Rüegg:
Regulation of phospholipases A2 in renal mesangial cells.

University Mainz, Institute of Pharmacology , Mainz (D), Dec. 12, 2008; guest of Prof. U. Förstermann:
Transcriptional regulation of sphingosine kinase 1 and functional implications.

Prof. Thomas Kaufmann

Department of Gynecology, University Hospital Zürich, Zürich (CH), Oct. 21, 2008;
guest of PD Dr. A. Fedier:
Regulation of apoptosis by the Bcl-2 protein family.

Institute of Virology, Vetsuisse-Faculty, University of Zürich, Zürich (CH), Nov. 14, 2008;
guest of Prof. Dr. M. Ackermann:
Regulation of apoptosis by Bcl-2 family members.

Prof. Hans-Uwe Simon

Rheumaklinik und Institut für Physikalische Medizin, Center for Experimental Rheumatology, University of Zurich, Zurich (CH), Jan. 8, 2008; guest of Prof. Dr. Renate Gay:
Identification of novel pro-apoptotic pathways in neutrophils.

Biochemische Pharmakologie, International Research Training Group (IRTG) Konstanz-Zürich, Universität Konstanz, Konstanz (D), Jan. 17, 2008; guest of Prof. Dr. Albrecht Wendel:
A novel mechanism of caspase-8 activation and its critical role in neutrophilic inflammation.

Institut für Pharmakologie, Universität Mainz, Mainz (D), Febr. 22, 2008;
guest of Prof. Dr. Ulrich Förstermann:
Non-caspase proteases in neutrophil apoptosis.

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI); Philadelphia (PA, USA), March 17, 2008:
Targeting eosinophils in disease.

Pulmonary, Allergy and Critical Care Division, Department of Medicine, University of Pennsylvania, Philadelphia (PA, USA), March 18, 2008; guest of Prof. Dr. Angela Haczku:
New roles for caspase-8 and mitochondria in granulocytes.

Nycomed GmbH, Konstanz (D), June 20, 2008; guest of Dr. Angelika Hoffmeyer:
Identification of a novel function of eosinophils in innate immunity.

Medizinische Klinik II, Universitätsklinikum Aachen, SFB542, Colloquium Molekulare Medizin, Aachen (D), Oct. 22, 2008; guest of Prof. Dr. Peter R. Mertens:
New insights into the role of eosinophils in the gastrointestinal tract.

Institut für Pathologie, Universität Basel (CH), Dec. 12, 2008; guest of Dr. Stephan Frank:
Ein eosinophiles antibakterielles Katapult.

PD Dr. Peter Späth

University of Tirgu Mures, Medical Faculty – Brain storming meeting “2008 Call for Proposals for Projects Programme of Community action in the Field of Health (2008-2013)”, Tirgu Mures (Rom), Febr. 22, 2008;
Ups & downs in Switzerland in communication and networking for some rare diseases.

CSL Behring AG, “R & D Forum”, Berne (CH), May 15 and 22, 2008;
IgM – Known molecule? – Known functions? (in humans!)
Part 1 – Host defence
Part 2 – Natural antibodies.

Philipps-University Marburg, Dept. of Neurology, Marburg a.d. Lahn (D), March 28, 2008;
Naturally occurring antibodies – Immunmodulation and tissue homeostasis.

Teaching course for CSL-Behring GmbH, Vienna (A), June 9, 2008;
Evidence-based medicine and the use of IVIG.

Klinikum der Johann Wolfgang Goethe-Universität, Klinik für Kinderheilkunde III Pädiatrische Hämatologie, Onkologie und Hämostasiologie, Frankfurt (D), August 27, 2008;
Pathophysiology of hereditary angioedema.

Teaching courses in neurology, St. Gilgen (A), Oct. 10-11, & Bruck a.d. Mur (A), Nov. 14-15, 2008;
Principles and mechanism of action of mono- and polyclonal immunglobulins in autoimmune diseases.

Dr. Stephan von Gunten

CSL Behring AG, Bern (CH), Oct. 16, 2008; guest of PD Dr. S. Miescher:
Carbohydrate-specific antibodies contained in IVIg.

Institute of Pharmakologie, University of Bern, Bern (CH), Oct. 28, 2008; guest of Prof. Dr. H.-U. Simon:
Siglecs, a novel family of inhibitory receptors.

4.4. Organization of Meetings and Courses

PD Dr. Peter Späth

Teaching courses in neurology “Demyelinating, Inflammatory Peripheral Autoimmune Neuropathies” together with Landeskrankenhaus Linz, Dept. of Neurology (Prof. Ransmayr), St. Gilgen (A), Oct. 10-11, 2008; Kaiser-Franz-Josef-Spital Vienna, Dept. of Neurology (Prof. Grisold), Vienna (A), Oct. 30, 2008; Landeskrankenhaus Bruck a.d. Mur, Dept. of Neurology (Prim. Varosanec), Bruck a.d. Mur (A), Nov. 14-15, 2008.

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology (together with task force SSPT): Fortschritte in der Pharmakologie - Pharmacovigilanz, Bern (CH), Jan. 31, 2008.

7th III-Bern International Summer School, Bönigen (CH), Aug. 10.-12., 2008.

16th Euroconference on Apoptosis and 5th Swiss Apoptosis Meeting (together with T. Brunner, Institute of Pathology, University of Bern), Bern (CH), Sept. 6-9, 2008.

Bern Immunology Club (together with the other founder members); Institute of Pharmacology, University of Bern, one meeting in each month of 2008.

Prof. Shida Yousefi

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis. Bern (CH), April 29-30, 2008.

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis. Bern (CH), Oct. 21-22, 2008.

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon

Symposium der Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie - Pharmacovigilanz; Bern (CH), January 31, 2008.

Meeting of the Swiss Society of Experimental Pharmacology (SSEP); Poster session and Bürgi-Prize; Zurich (CH), Aug. 29, 2008.

16th Euroconference on Apoptosis (ECDO); Sessions: “Welcome and ECDO Honorary Lecture” and “Cell death and inflammation”; Bern (CH), Sept. 6-9, 2008.

PD Dr. Peter Späth

Annual Meeting of the Romanian Society of Allergology and Immunology, Session: “Hereditary Angoedema”; Baja Mare (Rom), May 2-4, 2008.

Prof. Uwe Zangemeister-Wittke

2nd International Symposium on EpCAM and Cancer Stem Cell Markers, Evangelische Akademie Tutzing, Session III: Cancer; Munich (D), Oct. 9, 2008.

4.6. Referee Work for Peer-Reviewed Journals

Dr. Sébasien Conus

Cell Death Differ.

Dr. Barbara Geering

Allergy
Cell Death Differ.

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. Thomas Kaufmann

Cell Death Differ.

Prof. Hans-Uwe Simon

Allergy
Am. J. Pathol.
Apoptosis
Arch. Biochem. Biophys.
Blood
Cell Death Differ.
Clin. Exp. Allergy
Clin. Exp. Immunol.
Eur. J. Immunol.
Expert Rev. Clin. Immunol.
Faseb J.
FEBS Letters
Int. Arch. Allergy Immunol.
J. Allergy Clin. Immunol.
J. Exp. Med.
J. Mol. Med.
J. Immunol.
J. Leukoc. Biol.
N. Engl. J. Med.
Oncogene
Proc. Natl. Acad. Sci. USA
Swiss Med. Wkly.
Trends Pharmacol. Sci.

Prof. Shida Yousefi

Arch. Biochem. Biophys.
Cell Death Differ.
Int. J. Hyg. Environ. Health

Dr. Stephan von Gunten

Allergy

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)
Italian Association for Cancer Res. (AIRC)
Deutsche Forschungsgemeinschaft (DFG)
Swiss Cancer League

Prof. Uwe Zangemeister-Wittke

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

4.8. Awards

Dr. Barbara Geering

Novartis Poster Prize (2nd Prize)
Annual Meeting of the Swiss Society of Experimental Pharmacology (SSEP)
(Zürich, Aug. 29, 2008)

Prof. Shida Yousefi

Spirig Pharma AG Poster Prize (1st Prize)
Annual Meeting of the Swiss Society of Allergology and Immunology (SSAI)
(Fribourg, April 17 – 18, 2008)

Dr. Sébastien Conus

Ludwig Heilmeyer Medal (Silver)
German Society for Progress in Internal Medicine
30th Ludwig-Heilmeyer-Symposium
(Cologne (D), Nov. 10, 2008)

Prof. Shida Yousefi

Best original publication in 2008
Prize of the Bern Immunology Club (BIC)
(Bern, Jan. 28, 2009)

Dr. Sébastien Conus

Pfizer Research Prize 2009
Rheumatology and Immunology
(Zurich, Febr. 5, 2009)

PD Dr. Dagmar Simon (guest scientist at PKI)

Prize of the Allergie-Stiftung Ulrich Müller-Gierok
This prize honours a study, which was jointly published with the Institute of Pharmacology: J. Allergy Clin. Immunol. 121 (2008), 1515-1516.
(Geneva, March 19, 2009)

5. Administrative, Advisory, and Honorary Posts

Dr. Sébastien Conus

Webmaster of the PKI

Coordinator for Chemicals at the PKI

Prof. Andrea Huwiler

Member of the Advisory Editorial Board of Naunyn Schmiedeberg's Archives of Pharmacology

Member of the Collegium generale of the University of Bern

Prof. Hans-Uwe Simon

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

Member of the Scientific Advisory Board, Society in Science: The Branco Weiss Fellowship, 2003-2008

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

Member of the Advisory Board, Research Foundation, 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

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

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

Member of the Scientific Committee, Swiss Cancer League, 2008 – 2011

Member of Scientific Advisory Board, HELMHOLTZ Zentrum für Umweltforschung (UFZ), Leipzig (D), since 2008

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

Editorial and Advisory Board, Molecular and Cellular Pharmacology

Prof. 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 Human SwissMedic Expert Committee

Member of the thesis committee for PhD students in Molecular Life Sciences, University of Zürich

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

Quality & Biosafety coach at the PKI

Informatics & Network Coordinator at the PKI

Member of the Editorial Board, Lung Cancer

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). Together with the Image analysis station, this facility was in operation in 2008 for approximately 507 hours. The facility for confocal microscopy and image analysis was operated by Prof. 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 31 different research groups. In 2008, the operator and her team spent for the facility more than 600 hours. In general, the usage of this facility has dramatically increased upon acquisition of the new LSM 5 Excitor instrument. Prof. 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 Exhibitions

Peter Mertens, Aachen, Germany
Vernissage: May 15, 2008

Paola Brunetta Motta, Bern, Switzerland
Vernissage: Nov. 6, 2008

Bernadette Stauffer, Lyss, Switzerland
Vernissage: Nov. 6, 2008

8. Sponsors

8.1. Research Grants

Dr. Sébastien Conus

Support for the preparation of a SNF-grant, University of Bern

Prof. Arum M. Dharmarajan

Hans-Sigrist-Stiftung, Bern

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

Prof. Thomas Kaufmann

Swiss National Science Foundation, SNF-Professorship (grant No. PP00A-119203/1)

Dr. Nataliya Kotelevets

Fellowship, Eidgenössische Stipendienkommission für ausländische Studierende (ESKAS)

Prof. Hans-Uwe Simon

Swiss National Science Foundation (grant No. 310000-107526)
OPO-Foundation, Zurich (CH)
Stanley Thomas Johnson Foundation, Bern (CH)
GlaxoSmithKline, Greenford (UK)
AstraZeneca AG, Zug (CH)
Nycomed GmbH, Konstanz (D)

Prof. Shida Yousefi

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Sassella-Stiftung of the Zürcher Kantonalbank
Werner und Hedy Berger-Janser-Stiftung
Stiftung zur Förderung der wissenschaftlichen Forschung an der Universität Bern

8.2. Meetings

7th III-International Summer School, Bönigen (CH), Aug. 10-12, 2008

Allexis Corporation, Lausen
Allergomed, Therwil
Becton Dickinson Biosciences, Allschwil
Carl Zeiss AG, Feldbach
CSL Behring AG, Bern
Pfizer AG, Zurich
USGEB
Graduate School of Cellular and Biomedical Science, University of Bern

16th Euroconference on Apoptosis - 5th Swiss Apoptosis Meeting Bern (CH), Sept. 4-9, 2008

Regierungsrat des Kantons Bern, Staatskanzlei, Bern
Herrn Stadtpräsident Alexander Tschäppät, Bern
Max and Elsa Beer-Brawand-Fonds, Bern
USGEB
Kontaktgruppe für Forschungsfragen (KGF), Basel
Pfizer AG, Zurich
Carl Zeiss AG, Feldbach
Sigma-Aldrich Chemie GmbH, Buchs
Millipore GmbH, Schalbach (D)
Graduate School of Cellular and Biomedical Science, University of Bern
Institut of Pathology, University of Bern
LI-COR Biosciences GmbH, Bad Homburg (D)
BioConcept, Allschwil
LabForce AG, Nunningen
LubioScience GmbH, Luzern
Pfizer AG, Zurich
LucernaChem AG, Luzern

8.3. Seminars „Progress in Pharmacology“

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

2009:
Pfizer AG, Zurich
AstraZeneca AG, Zug
GlaxoSmithKline AG, Münchenbuchsee
Novartis Pharma AG, Bern
Vifor AG, Villars-sur-Glâne

8.4. Seminars „Bern Immunology Club“

2008:
CSL Behring AG, Bern

2009:
Britta Engelhardt, Thomas Geiser, Christoph Müller, Hans-Uwe Simon, Beda Stadler, Peter Villiger

8.5. Travel Support

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8.6. Other Support

Bürgi Fonds	Seminar series of the institute
	Bürgi-Preis 2008