Annual Report 2012

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 zwölfte umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat auch im Jahr 2012 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 2012 trugen wir dazu bei, die Kommunikation zwischen WissenschaftlerInnen und Öffentlichkeit zu fördern.

Neben unserer regulären Lehrtätigkeit im 3. Studienjahr Medizin sowie der Ausbildung der ZahnmedizinerInnen sind einige DozentInnen des Instituts zusätzlich in die Immunologie-Ausbildung von StudentInnen der Biologie (Naturwissenschaftliche Fakultät der Universität Bern) einbezogen. Weiterhin sind wir auch für die Pharmakologie-Ausbildung in B.Sc.- und M.Sc.-Kursen für Biomedizin der Universitäten Fribourg und Bern verantwortlich. Die DozentInnen des PKI sind ausserdem innerhalb der interfakultären Graduate School for Cellular and Biomedical Sciences aktiv tätig. Prof. Kaufmann ist Mitglied einer Betreuungskommission 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 22 DoktorandInnen (19 PhD, 3 MD), und 4 DoktorandInnen haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2012 insgesamt 23 Originalarbeiten sowie 25 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >250). MitarbeiterInnen des Instituts wurden zu insgesamt 31 Vorträgen bzw. Seminaren eingeladen. Mehrere MitarbeiterInnen des PKI wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 9 MitarbeiterInnen 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. Prof. Simon und Prof. Brunner (Universität Konstanz, Deutschland) organisierten das „7th Swiss Apoptosis Meeting (SAM)“ (30.-31.08.2012), zu dem wir über 150 TeilnehmerInnen aus dem In- und Ausland begrüssen durften. Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Prof. Simon ist seit 01.08.2012 als Vize-Dekan Forschung der Medizinischen Fakultät der Universität Bern tätig. Daneben nimmt das PKI auch ausserhalb der Universität wissenschaftspolitische Verantwortung für die Medizin und die Biowissenschaften wahr. Prof. Simon wurde 2012 als Vice-Chair der Immunopharmacology Section der International Union of Basic and Clinical Pharmacology (IUPHAR) gewählt. Ebenso wurde er zum Vorsitzenden des Wissenschaftlichen Beirats des HELMHOLTZ-Zentrums für Umweltforschung in Leipzig gewählt. Gleichzeitig amtete Prof. Simon als President-elect der International Eosinophil Society (IES) sowie als Past-Präsident der Union der Schweizerischen Gesellschaften für Experimentelle Biologie (USGEB) und der European Cell Death Organization (ECDO).

Ich danke allen Mitarbeiterinnen und Mitarbeitern für ihren Einsatz, welcher auch im Jahr 2012 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, Januar 2013

1.2. Foreword

This is the twelfth 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 2012 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 2012.

In addition to regular teaching within the third study year of medical students and our teaching of dental students, some principal investigators of the PKI are additionally involved in Immunology M.Sc. programmes within the Natural Sciences Faculty of our university. Furthermore, we are responsible for teaching Pharmacology in both B.Sc. and M.Sc. courses in Biomedicine at the Universities of Fribourg and Bern. In addition, we are actively involved within the graduation program for MD/PhD students of the University of Bern (Graduate School for Cellular and Biomedical Sciences). Prof. Kaufmann is a member of the tutoring committee “Cell 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, 19 PhD students and 3 MD students work at the PKI, and four students (4 PhD) successfully finished their doctoral studies in 2012.

In 2012, members of the PKI published 23 original and 25 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 31 lectures or seminars. Several PKI members received research prizes. Nine 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. Prof. Simon and Prof. Brunner (Univ. of Konstanz, Germany) organized an

international congress (7th Swiss Apoptosis Meeting; August 30-31, 2012), which attracted more than 150 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.

Prof. Simon serves as Vice-Dean of Research at Medical Faculty of the University of Bern (since August 1, 2012). Moreover, the PKI also takes over responsibilities outside of the university. For instance, Prof. Simon was appointed as Vice-Chair of the Immunopharmacology Section of the International Union of Basic and Clinical Pharmacology (IUPHAR) in 2012. He is also chairman of the Scientific Advisory Board of the HELMHOLTZ center for Environmental Research in Leipzig and President-elect of the International Eosinophil Society (IES). In addition, he served as Past-President of the Union of the Swiss Societies for Experimental Biology (USSEB) and European Cell Death Organization (ECDO).

I thank all co-workers for their hard work that contributed to the success of the PKI in 2012. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, January 2013

2. Staff 2012

Director

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

Deputy Director

Prof. Dr. Andrea Huwiler, PhD

Principal Investigators

Prof. Dr. Andrea Huwiler, PhD
Prof. Dr. Thomas Kaufmann, PhD*
Prof. Dr. Hans-Uwe Simon, MD, PhD
PD Dr. Stephan von Gunten, MD, PhD, MME
Prof. Dr. Shida Yousefi, PhD
Prof. Dr. Uwe Zangemeister-Wittke, PhD
PD Dr. Peter Späth, PhD*
Prof. Dr. Robert Friis, PhD*

Scientific Staff

Dr. Poorya Amini, visiting scientist* (November 2011 – April 2012)
Dr. Poorya Amini, PhD student (since May 2012)
Daniel Bachmann, research assistant*
Lulzime Bullazhi, PhD student, guest scientist* (July – August 2012)
Nathalie Borgeaud, M.Sc. student* (April - May 2012)
Dr. Elisabeth Louisa de Graauw, PhD student* (since July 2012)
Nohemy Echeverry, PhD student
Daniel Fallegger, PhD student
Iuliia Filipenko, PhD student
Kayluz Frias Boligan, PhD student*
Nathalie Friedli, M.Sc. student* (October 2012 – February 2013)
Katharina Fuchs, MD student* (July – August 2012)
Dr. Barbara Geering, PhD (until March 2012)
Ramona Graf, M.Sc. student* (April – May 2012)
Ursina Gurzeler, PhD student*
Pasal Häflinger, M.Sc. student* (May 2012)
Veronika Hanusova, guest PhD student* (February – August 2012)
Zhaoyue He, PhD student (until April 2012)
Dr. Zhaoyue He, PhD (since May 2012)
Dr. Susanne Radonjic-Hösli, MD-PhD student*
Sibylle Horat, M.Sc. student* (May 2012)
Faik Imeri, PhD student
Fabiana Jakob, technician
Dr. Camilla Jandus, MD, PhD* (until March 2012)
Eveline Krajnec, ERASMUS student* (October 2012 – February 2013)
Dr. Nataliya Kotelevets, PhD
Evelyne Kozlowski, technician

He Liu, PhD student (until March 2012)
Dr. He Liu, PhD (since April 2012)
Morshed Mahbubul, PhD student*
Marianne Maillard-van Laer, technician
Dr. Christina Merz - Stöckle, PhD*
Vitalii Mutsenko, ESKAS student* (until June 2012)
Kevin Oberson, technician
Olexsandr Pastukhov, PhD student
Andrea Plüss, M.Sc. student* (January – June 2012)
Dr. Tatiana Rabachini de Almeida, PhD*
Saša Rožman, PhD student
Monica Schillizzi, M.Sc. student* (January – June 2012)
Inès Schmid, head technician
Christoph Schneider, M.Sc. student* (May 2012, August 2012 – Februar 2013)
Myriam Fabiola Schorrer, PhD student*
Manuel Simon, PhD student* (until September 2012)
Dr. Manuel Simon, PhD* (October – December 2012)
Darko Stojkov, ERASMUS student* (January 2012)
Darko Stojkov, IAESTE trainee* (July – October 2012)
Darko Stojkov, PhD student* (since November 2012)
Jennifer Theiler, M.Sc. student* (April – May 2012)
Angela Thomet, M.Sc. student* (January – June 2012)
Tankica Timcheva, PhD student* (since December 2012)
Nicole Tochtermann, MMed student* (August – September 2012)
Mirijam Tschanz, M.Sc. student* (January – June 2012)
Xiaoliang Wang, PhD student*
Dr. Marc Wehrli, MD-PhD student*
Isabelle Wey, M.Sc. student* (April - May 2012)
Simone Wicki, M.Sc. student* (April – May 2012, July 2012 – January 2013)

External University Teachers

Dr. Sibylle Bürgi, PhD*
PD Dr. Armand Cachelin, MD, PhD*
Dr. David Spirk, MD*
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

Prof. Dr. Dagmar Simon, MD*, Dept. of Dermatology, Inselspital, University of Bern
Dr. Alice Soragni, PhD*, UCLA-DOE, Los Angeles, USA
Prof. Dr. Alex Straumann, MD*, Dept. of Gastroenterology, University of Basel
PD Dr. Mario Tschan, PhD*, Dept. of Clinical Research, University of Bern
Dr. Thomas Demoulin, PhD*, Inst. of Virology and Immunoprophylaxis (IVI), Mittelhäusern
Dr. Doriano Fabbro, PhD*

External Computer Support

Dominik Wyss* and Anne Simon**

Office

Sandra Suter, head secretary
Anita Dähler, secretary
Prof. Dr. Shida Yousefi*, Editorial Assistant, ALLERGY
Cornelia Pfister*, Pfizer AG, Zürich (support of the "Progress in Pharmacology" - Meeting)

Workshop

Hans Andres

House Keeping

Isa Conforti and Elisa Piccirilli

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

Symposium: Pharmacology in academia: Today and tomorrow. Bern, May 8, 2012

7th Swiss Apoptosis Meeting (SAM). Bern, Aug. 30 – Aug. 31, 2012

3. Teaching Activities
3.1. Lectures

Lectures for Medical Students

Date	Lecturer	Titel of the lecture
March 12, 2012	PD Dr. Stephan von Gunten	Antidiabetika
March 14, 2012	PD Dr. Stephan von Gunten	Lipidsenker, Behandlung der Gicht
April 2, 2012	Prof. Andrea Huwiler	Antiepileptika
April 2, 2012	Prof. Andrea Huwiler	Therapie von M.Parkinson und Demenz
April 4, 2012	Prof. Andrea Huwiler	Lokalanästhetika
April 23, 2012	PD Dr. Stephan von Gunten	Hormone aus pharmakologischer Sicht (Teil 1)
April 23, 2012	PD Dr. Stephan von Gunten	Hormone aus pharmakologischer Sicht (Teil 2)
April 25, 2012	Prof. Andrea Huwiler	Pharmakologie der Narkotika / Anästhesie 1
April 25, 2012	Prof. Andrea Huwiler	Pharmakologie der Narkotika / Anästhesie 2
May 2, 2012	Prof. Andrea Huwiler	Psychopharmakologie
May 7, 2012	Prof. Andrea Huwiler	Antidepressiva, Anxiolythika und Stimmungsstabilisatoren
May 9, 2012	Prof. Andrea Huwiler	Antipsychotika
May 16, 2012	Prof. Andrea Huwiler	Schmerz und Analgesiologie 1
May 16, 2012	Prof. Andrea Huwiler	Schmerz und Analgesiologie 2
June 6, 2012	Prof. Hans-Uwe Simon	Immunmodulation
Sept. 19, 2012	Prof. Hans-Uwe Simon	Pharmacodynamics I
Sept. 19, 2012	Prof. Hans-Uwe Simon	Pharmacodynamics II
Sept. 19, 2012	Prof. Thomas Kaufmann	Adaptation und Zellschäden
Sept. 26, 2012	Prof. Hans-Uwe Simon	Entzündungshemmung
Sept. 26, 2012	Prof. Hans-Uwe Simon	Einführung in die Toxikologie

Oct. 29, 2012	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Nov. 1, 2012	Dr. David Spirk	Antithrombotische Therapie & Antikoagulantien
Nov. 7, 2012	Prof. Uwe Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Nov. 7, 2012	Prof. Uwe Zangemeister-Wittke	Antihypertensiva
Nov. 7, 2012	Dr. David Spirk	Pharmakologie der Hämostase
Nov. 13, 2012	Prof. Uwe Zangemeister-Wittke	Antiarrhythmika
Nov. 21, 2012	Dr. David Spirk	Behandlung der Herzinsuffizienz und Angina Pectoris
Dec. 10, 2012	Prof. Uwe Zangemeister-Wittke	Diuretika

Lectures for Pharmacy Students (together with Dental Medicine Students): Clinical Microbiology

Date	**Lecturer**	**Title of the lecture**
Nov. 2, 2012	Dr. Sibylle Bürgi	Antibiotika I
Nov. 2, 2012	Dr. Sibylle Bürgi	Antibiotika II

Lectures for Dental Medicine Students (Coordinator: Prof. Uwe Zangemeister-Wittke)

Date	**Lecturer**	**Title of the lecture**
Febr. 1, 2012	Prof. Andrea Huwiler	Narkose-/Beruhigungsmittel
Febr. 8, 2012	Prof. Hans-Uwe Simon	Rezeptoren, Dosis-Wirkungskurven
Febr. 15, 2012	Prof. Hans-Uwe Simon	Antagonisten, Applikationsarten
Febr. 22, 2012	Dr. Sibylle Bürgi	Antidiabetika
Febr. 29, 2012	Prof. Andrea Huwiler	Pharmakologie der Atemwege

March 19, 2012	Prof. Uwe Zangemeister-Wittke	Einführung in die Pharmakogenetik
Mach 21, 2012	Prof. Thomas Kaufmann	Pharmakogenetik, Interaktionen
March 28, 2012	PD Dr. Stephan von Gunten	Psychopharmaka
April 2, 2012	Dr. David Spirk	Antikoagulantien und Herz-Kreislauf Medikamente
April 23, 2012	PD Dr. Armand Cachelin	Schwache Analgetika, Starke Analgetika
April 25, 2012	Prof. Uwe Zangemeister-Wittke	Phamakologie des vegetativen Nervensystems
April 30, 2012	PD Dr. Parham Sendi	Mechanismen der Antibiotika und der antiviralen Therapie
May 2, 2012	Dr. Sibylle Bürgi	Lokalanästhetika
May 9, 2012	PD Dr. Stephan von Gunten	Magensäurehemmung

Oral examinations: Prof. Zangemeister-Wittke, Prof. Huwiler, Prof. Simon

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

Date	**Lecturer**	**Title of the lecture**
Febr. 23, 2012	Prof. Hans-Uwe Simon	Introduction
Febr. 23, 2012	Prof. Hans-Uwe Simon	Immunopharmacology
May 31, 2012	Prof. Hans-Uwe Simon	Eosinophilic diseases

Written examination and oral tests: Prof. Simon

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

Date	Lecturer	Title of the lecture
Nov. 22, 2012	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
March 22, 2012	Prof. Andrea Huwiler	Lipid mediators in tissue trafficking
May 10, 2012	Prof. Shida Yousefi	Inflammation – good or bad? Resolution of inflammation - apoptosis

Practical work for Natural Science Faculty: Immunology II (Coordinator: PD Dr. Nadia Corazza)

Date	Lecturer	Title of the lecture
Oct. 9, 2012	Prof. Thomas Kaufmann	Isolation of leukocytes (4 h)
Nov. 20, 2012	Prof. Thomas Kaufmann	Isolation of leukocytes (4 h)

Lectures for Biomedical Sciences Students (B.Sc. program, Fribourg): General Pharmacology (Coordinator: Prof. Hans-Uwe Simon)

Date	Lecturer	Title of the lecture
Febr. 27, 2012	Prof. Hans-Uwe Simon	Pharmacodynamics I
Febr. 27, 2012	Prof. Hans-Uwe Simon	Pharmacodynamics II
March 26, 2012	Prof. Uwe Zangemeister-Wittke	Pharmacokinetics I
March 26, 2012	Prof. Uwe Zangemeister-Wittke	Pharmacokinetics II

March 12, 2012	Prof. Hans-Uwe Simon	Toxicology
March 12, 2012	Prof. Hans-Uwe Simon	Pharmacology of inflammation
April 16, 2012	Dr. Christina Merz-Stöckle	Pharmacogenetics
April 30, 2012 (total 1h)	Prof. Uwe Zangemeister-Wittke	Tumorpharmacology

Written examination and oral tests: Prof. Simon

Lectures for Biomedical Sciences Students (M.Sc. program, Bern): Pharmacology of major organ systems (Coordinator: Prof. Thomas Kaufmann)

Date	**Lecturer**	**Title of the lecture**
Sept. 28, 2012	Prof. Uwe Zangemeister-Wittke	Heart and vascular system
Oct 5, 2012	Prof. Thomas Kaufmann	Immune system
Oct. 12, 2012	Prof. Shida Yousefi	Antiinfectious therapy
Oct. 19, 2012	PD Dr. Stephan von Gunten	Pharmacology of the gastrointestinal system
Oct. 26, 2012	PD Dr. Stephan von Gunten	Endocrine and reproductive system
Nov. 2, 2011	Prof. Shida Yousefi	Lungs and kidneys
Nov 6, 2012	Prof. Andrea Huwiler	Nervous system
Nov. 16, 2012	Dr. David Spirk	Haemopoietic system and haemostasis

Lectures for Natural Sciences Faculty and Biomedical Sciences students (M.Sc. program, Bern): General Pathology (Coordinator: Prof. Christoph Müller)

Date	**Lecturer**	**Title of the lecture**
Sept. 19, 2012	Prof. Thomas Kaufmann	Cell damage

Lectures for Biomedical Sciences students (M.Sc. program, Bern): Cutting Edge Microscopy (Coordinator: Prof. Britta Engelhardt)

Date	Lecturer	Title of the lecture
Oct. 19, 2012	Prof. Shida Yousefi	Laser scanning microscopy and applications

External teaching activities: University of Zurich (Molecular Medicine)

Date	Lecturer	Title of the lecture
May 2012 (total 6h)	Prof. Uwe Zangemeister-Wittke	Molecular Cell Biology for students of human and dental medicine

3.2. Coordination PBL Medical Students, 3rd year (2012/2013)

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

3.3. Tutorials (study year 2012/2013)

Medical students 3rd year:
Dr. Marc Wehrli
Prof. Thomas Kaufmann
Dr. Christina Merz-Stöckle
Dr. Susanne Radonjic-Hösli

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

3.4. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan. 18, 2012	Prof. Sanjiv Luther Department of Biochemistry, University of Lausanne (CH)	Lymph node fibroblasts as key players in adaptive immunity
Febr. 15, 2012	Prof. Andreas Strasser, The Walter and Eliza Hall Institute of Medical Research, Parkville, VIC (AUS)	Which pro-survival Bcl-2 protein should be targeted for killing of which cancer cells?
March 7, 2012	Prof. D. Meyer zu Heringdorf Pharmazentrum, University of Frankfurt/M (D)	Regulation of calcium homeostasis by sphingosine-1- phosphate
March 26, 2012	Dr. Hamsa Puthalakath La Trobe University Bundoora, VIC (AUS)	c-AMP: The second messenger of death
April 4, 2012	Dr. Dagmar Kulms Dept. of Dermatology University of Dresden (D)	Three dimensional melanoma treatment
May 2, 2012	Dr. Giovanni Solinas Division of Physiology University of Fribourg (CH)	Obesity-induced metabolic inflammation: A gold mine for pharmaceuticals and nutraceuticals
June 12, 2012	Dr. Donia Moujalled The Walter & Eliza Hall Institute of Medical Research Parkville, VIC (AUS)	Mechanisms of receptor interacting protein kinase 3 (RIPK3)-induced cell death by TNF
June 13, 2012	Prof. Ehud Razin Institute for Medical Research The Hebrew University of Jerusalem (ISR)	Ap4A as a second messenger in a novel gene regulation pathway in immunologically activated mast cells
June 20, 2012	Prof. Burkhard Kleuser Insitut für Ernährungs- Wissenschaften Universität Potsdam (D)	Sphingosine-1-phosphate and the pathophysiological role of the S1P2 receptor
Sept. 5, 2012	Dr. S. Armaz Aschrafi Donders Institute for Brain Cognition and Behaviour Centre for Neuroscience; Dep. of Cognitive Neuroscience Radboud University Nijmegen, (NL)	The mircoRNA pathway in neuronal development and plasticity

Sept. 19, 2012	PD Dr. Eva Tolosa Institut für Immunologie Universitätsklinikum Hamburg-Eppendorf (D)	Split blame in brain inflammation: IFN-γ, IL-17 or both?
Oct. 4, 2012	Prof. Michael S. Goligorsky Goodman Chair in Nephrology Med. College, New York (USA)	Premature vascular aging and the kidney
Oct. 10, 2012	Prof. Richard W. James Lipoprotein Laboratory Dept. of Internal Medicine, University of Geneva (CH)	Expanding and exploiting the cardio-vascular impact of high density lipo-proteins
Oct. 29, 2012	Dr. Francine Ke The Walter & Eliza Hall Institute of Medical Research Parkville, VIC (AUS)	Investigating the physiological functions of the Bcl-2 family member BOK
Nov. 28, 2012	Dr. Stefan Kuchen Dept. of Rheumatology, Clinical Immunology and Allergology Inselspital, Bern (CH)	Regulation of immune homeostasis by a small nucleolar RNA 104 derived microRNA

3.5. Inaugural Lectures (Venia Docendi)

Date	Lecturer	Title
Oct. 2, 2012	PD Dr. Stephan von Gunten Institute of Pharmacology, University of Bern (CH)	Sweets for the immune system: mischievous or innocent

3.6. Bern Immunology Club (BIC)

Date	Teacher	Title of the seminar
Jan. 25, 2012	Prof. Christian Münz Inst. of Exp. Immunol. University of Zürich (CH)	Regulation of macroautophagy by pathogens
Febr. 29, 2012	Prof. Hanno Würbel Abteilung Tierschutz DCR-VPHI Vetsuisse Fakultät University of Bern (CH)	Enrichment, animal welfare and the validity of animal experiments
April 4, 2012	Prof. Dr. S. C. Bischoff Institut für Ernährungsmedizin und Immunologie Universität Hohenheim (D)	Understanding the intestinal microbiota: A new era in mucosal immunology
April 25, 2012	Dr. Markus Geuking Universitätsklinik für Viszerale Chirurgie & Medizin Inselspital & DKF, Bern (CH)	The role of the intestinal CD4 T cell compartment in mutualism with the intestinal microbiota
May 30, 2012	Prof. Britta Engelhardt Theodor Kocher Institut University of Bern (CH)	Clinical Immunological Conference on Multiple Sclerosis
June 27, 2012	Prof. Karl-Heinz Krause Dept. of Pathol. & Immunol. University of Geneva (CH)	NADPH oxidase inhibitors: drugs for the future?
Sept. 26, 2012	Prof. Andrew Macpherson Viszerale Chirurgie & Medizin Gastroenterologie Inselspital, Bern (CH)	Mutualism between commensal intestinal bacteria and the immune system
Oct. 31, 2012	Prof. Pieter Hiemstra Dept. of Pulmonology Leiden University (NL)	Novel mechanisms for epithelial cell activation in chronic lung disease
Nov. 26, 2012	Dr. Thorsten R. Mempel Center for Immunology and Inflammatory Diseases, Mass. Gen. Hosp., Boston (USA)	T cell migration and activation during the anti-tumor response
Nov. 28, 2012	PD Dr. Stephan von Gunten (organizer)	Highlights of the Year

For the current program of the Bern Immunology Club (BIC), please consult the following website: http://www.bic.unibe.ch/content/teaching/bic_lectures_13/index_eng.html

3.7. Academic Degrees

Stephan von Gunten, PD Dr. med. (Habilitation), University of Bern

He Liu, PhD, University of Bern
Thesis: Down-regulation of autophagy-related gene 5 (ATG5) in cutaneous malignant melanoma and its role in melanoma tumorigenesis (March 2012)
Supervisors: Prof. Hans-Uwe Simon and Prof. Shida Yousefi

Zhaoyue He, PhD, University of Bern
Thesis: Transcriptional regulation of autophagy-related protein 5 (ATG5) (April 2012)
Supervisor: Prof. Hans-Uwe Simon

Manuel Simon, PhD, University of Bern
Thesis: Engineering and preclinical investigation of designed ankyrin repeat proteins as a versatile platform of binding proteins for tumor targeting (August 2012)
Supervisor: Prof. Uwe Zangemeister-Wittke

Nohemy Echeverry, PhD, University of Bern
Thesis: Investigation of the subcellular localization and molecular functions of the Bcl-2 family member BOK (September 2012)
Supervisor: Prof. Thomas Kaufmann

Andrea Plüss, M.Sc. pharm., University of Basel
Thesis: Characterization of the inflammatory infiltrate and cytokine expression in cutaneous and oral lichen planus (June 2012)
Supervisors: Prof. Dagmar Simon and Prof. Hans-Uwe Simon

Monica Schillizzi, M.Sc. pharm, University of Basel
Thesis: Expression of novel cytokines in eosinophilic esophagitis (June 2012)
Supervisors: Prof. Dagmar Simon and Prof. Hans-Uwe Simon

Angela Thomet, M.Sc. pharm, University of Basel
Thesis: Functional basophil responses upon stimulation with damage associated molecular patterns (June 2012)
Supervisors: Dr. Christina Merz-Stöckle and Prof. Hans-Uwe Simon

Mirjam Tschanz, M.Sc. pharm, University of Basel
Thesis: Eosinophilic esophagitis without eosinophils (June 2012)
Supervisors: Dr. Susanne Hösli and Prof. Hans-Uwe Simon

Darko Stojkov, M.Sc. pharm, University of Ljubljana
Thesis: The role of Ca^{2+} and ROS in the activation of neutrophils with physiological agonists (September 2012)
Supervisors: Prof. Shida Yousefi and Prof. Hans-Uwe Simon

Simone Wicki, M.Sc., University of Bern
Thesis: The role of XIAP in survival and cytokine production of neutrophils (December 2012)
Supervisor: Prof. Thomas Kaufmann

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

Group members: Dr. Nataliya Kotelevets, Postdoc[1]
Daniel Fallegger, PhD student[1]
Iuliia Filipenko, PhD student[1]
Faik Imeri, PhD student[1]
Oleksandr Pastukhov, PhD student[1]
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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 (ceramidases, sphingosine kinases, ceramide kinase) are investigated to understand under which conditions a certain sphingolipid is accumulating in the cell to exert a function. The major goal is it to identify novel therapeutic targets within the sphingolipid cascades which may turn useful in the treatment of diseases characterized by abnormal cell growth and/or death.

The ω3-polyunsaturated fatty acid derivatives AVX001 and AVX002 directly inhibit cytosolic phospholipase A(2) and suppress PGE(2) formation in mesangial cells
A. Huwiler, A.J. Feuerherm, B. Sakem, O. Pastukhov, J. Filipenko, T. Nguyen, B. Johansen
BACKGROUND AND PURPOSE: ω3-polyunsaturated fatty acids (ω3-PUFAs) are known to exert anti-inflammatory effects in various disease models although their direct targets are only poorly characterized. **EXPERIMENTAL APPROACH:** Here we report on two new cPLA(2) inhibitors, the ω3-derivatives AVX001 and AVX002, and their effects on inflammatory PGE(2) production in cultures of renal mesangial cells. **KEY RESULTS:**

AVX001 and AVX002 dose-dependently inhibited the group IVA cytosolic phospholipase A(2) (cPLA(2)) in an in vitro activity assay with similar IC(50) values for AVX001 and AVX002, whereas the known cPLA(2) inhibitor AACOCF(3) was less potent and docosahexaenoic acid (DHA) was inactive. In renal mesangial cells, AVX001 and AVX002 suppressed IL-1β-induced PGE(2) synthesis. Mechanistically, this effect occurred by a down-regulation of IL-1β-induced group IIA-sPLA(2) protein expression, mRNA expression and promoter activity. A similar but less potent effect was seen with AACOCF(3) and no effect was seen with DHA. As gene expression of sPLA(2) is known to be regulated by the transcription factor NF-κB, we further investigated NF-κB activation. Both compounds prevented NF-κB activation by blocking degradation of the inhibitor of κB. **CONCLUSIONS AND IMPLICATIONS:** These data show for the first time that the novel cPLA(2) inhibitors AVX001 and AVX002 exert an anti-inflammatory effect in cultures of renal mesangial cells and reduce the pro-inflammatory mediator PGE(2) through an inhibitory effect on NF-κB activation. Therefore, these compounds may represent promising novel drugs for the treatment of inflammatory disorders.
See original publication No. 1

Targeting sphingosine kinase 1 in carcinoma cells decreases proliferation and survival by compromising PKC activity and cytokinesis

N. Kotelevets, D. Fabbro, A. Huwiler, U. Zangemeister-Wittke

Sphingosine kinases (SK) catalyze the phosphorylation of proapoptotic sphingosine to the prosurvival factor sphingosine 1-phosphate (S1P), thereby promoting oncogenic processes. Breast (MDA-MB-231), lung (NCI-H358), and colon (HCT 116) carcinoma cells were transduced with shRNA to downregulate SK-1 expression or treated with a pharmacologic SK-1 inhibitor. The effects of SK-1 targeting were investigated by measuring the level of intracellular sphingosine, the activity of protein kinase C (PKC) and cell cycle regulators, and the mitotic index. Functional assays included measurement of cell proliferation, colony formation, apoptosis, and cell cycle analysis. Downregulation of SK-1 or its pharmacologic inhibition increased intracellular sphingosine and decreased PKC activity as shown by reduced phosphorylation of PKC substrates. In MDA-MB-231 cells this effect was most pronounced and reduced cell proliferation and colony formation, which could be mimicked using exogenous sphingosine or the PKC inhibitor RO 31-8220. SK-1 downregulation in MDA-MB-231 cells increased the number of cells with 4N and 8N DNA content, and similar effects were observed upon treatment with sphingosine or inhibitors of SK-1 or PKC. Examination of cell cycle regulators unveiled decreased cdc2 activity and expression of Chk1, which may compromise spindle checkpoint function and cytokinesis. Indeed, SK-1 kd cells entered mitosis but failed to divide, and in the presence of taxol also failed to sustain mitotic arrest, resulting in further increased endoreduplication and apoptosis. Our findings delineate an intriguing link between SK-1, PKC and components of the cell cycle machinery, which underlines the significance of SK-1 as a target for cancer therapy.
See original publication No. 2

Thiazolidinedione-dependent activation of sphingosine kinase 1 causes an anti-fibrotic effect in renal mesangial cells

A. Koch, A. Völzke, C. Wünsche, D. Meyer zu Heringdorf, A. Huwiler, J. Pfeilschifter

BACKGROUND AND PURPOSE: PPARγ agonists [thiazolidinediones (TZDs)] are known to exert anti-fibrotic effects in the kidney. In addition, we previously demonstrated that sphingosine kinase 1 (SK-1) and intracellular sphingosine-1-phosphate (S1P), by reducing the expression of connective tissue growth factor (CTGF), have a protective role in the fibrotic process. **EXPERIMENTAL APPROACH:** Here, we investigated the effect of TZDs on

intracellular sphingolipid levels and the transcriptional regulation of SK-1 in mesangial cells to evaluate potential novel aspects of the anti-fibrotic capacity of TZDs.
KEY RESULTS: Stimulation with the TZDs, troglitazone and rosiglitazone, led to increased S1P levels in rat mesangial cells. This was paralleled by increased SK-1 activity as a consequence of direct effects of the TZDs on SK-1 expression. GW-9662, a PPARγ antagonist, inhibited the stimulating effect of TZDs on SK-1 mRNA and activity levels and intracellular S1P concentrations. Furthermore, SK-1 up-regulation by TZDs was functionally coupled with lower amounts of pro-fibrotic CTGF. SK-1 inhibition with SKI II almost completely abolished this effect in a dose-dependent manner. Moreover, the CTGF lowering effect of TZDs was fully blocked in MC isolated from SK-1 deficient mice (SK-1(-/-)) as well as in glomeruli of SK-1(-/-) mice compared with wild-type mice treated with TRO and RSG.
CONCLUSION AND IMPLICATIONS: These data show that TZD-induced SK-1 up-regulation results in lower amounts of CTGF, demonstrating novel facets for the anti-fibrotic effects of this class of drugs.
See original publication No. 3

Original publications

1. **A. Huwiler**, AJ Feuerherm, B. Sakem, O. Pastukhov, J. Filipenko, T. Nguyen, B. Johansen: The ω3-polyunsaturated fatty acid derivatives AVX001 and AVX002 directly inhibit cytosolic phospholipase A(2) and suppress prostaglandin E(2) formation in mesangial cells.
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Our group is interested in the molecular mechanisms of apoptosis, also called programmed cell death. Apoptosis is recognised to be crucial for sculpting the developing embryo, for maintaining tissue homeostasis in the adult, for shaping the immune repertoire, for terminating immune responses and in host responses to infections. Abnormalities in the control of apoptosis have been implicated in a variety of diseases, including cancer, autoimmune and neurodegenerative disorders, AIDS, stroke and sepsis. A deeper understanding of the regulation of apoptosis will thus not only help to clarify significant questions about normal development and physiology but may also provide insight into a number of pathological states.

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 apoptosis. We have addtionally estalished a system to differentiate *ex vivo* immortalised myeloid progenitor cells (derived from any given genetically modified mouse strain) into mature granulocytes (neutrophils or basophils) or macrophages in near unlimited numbers.

BCL-2 family member BOK is widely expressed but its loss has only minimal impact in mice

F. Ke, A. Voss, J.B. Kerr, L.A. O'Reilly, L. Tai, N. Echeverry, P. Bouillet, A. Strasser, T. Kaufmann

BOK/MTD was discovered as a protein that binds to the anti-apoptotic Bcl-2 family member MCL-1 and shares extensive aminoacid sequence similarity to BAX and BAK, which are essential for the effector phase of apoptosis. Therefore, and on the basis of its reported

expression pattern, BOK is thought to function in a BAX/BAK-like pro-apoptotic manner in female reproductive tissues. In order to determine the function of BOK, we examined its expression in diverse tissues and investigated the consequences of its loss in Bok-/- mice. We confirmed that Bok mRNA is prominently expressed in the ovaries and uterus, but also observed that it is present at readily detectable levels in several other tissues such as the brain and myeloid cells. Bok-/- mice were produced at the expected Mendelian ratio, appeared outwardly normal and proved fertile. Histological examination revealed that major organs in Bok-/- mice displayed no morphological aberrations. Although several human cancers have somatically acquired copy number loss of the Bok gene and BOK is expressed in B lymphoid cells, we found that its deficiency did not accelerate lymphoma development in El-Myc transgenic mice. Collectively, these results indicate that Bok may have a role that largely overlaps with that of other members of the Bcl-2 family, or may have a function restricted to specific stress stimuli and/or tissues.

See original publication No. 1

Intracellular localization of the BCL-2 family member BOK and functional implications

N. Echeverry, D. Bachmann, F. Ke, A. Strasser, H.-U. Simon and T. Kaufmann

The pro-apoptotic BCL-2 family member BOK is widely expressed and resembles the multi-BH domain proteins BAX and BAK based on its amino acid sequence. The genomic region encoding BOK was reported to be frequently deleted in human cancer and it has therefore been hypothesized that BOK functions as a tumor suppressor. However, little is known about the molecular functions of BOK. We show that enforced expression of BOK activates the intrinsic (mitochondrial) apoptotic pathway in BAX/BAK-proficient cells but fails to kill cells lacking both BAX and BAK or sensitize them to cytotoxic insults. Interestingly, major portions of endogenous BOK are localized to and partially inserted into the membranes of the Golgi apparatus as well as the endoplasmic reticulum (ER) and associated membranes. The C-terminal transmembrane domain of BOK thereby constitutes a 'tail-anchor' specific for targeting to the Golgi and ER. Over-expression of full-length BOK causes early fragmentation of ER and Golgi compartments. A role for BOK on the Golgi apparatus and the ER is supported by an abnormal response of *Bok*-deficient cells to the Golgi/ER stressor brefeldin A. Based on these results, we propose that major functions of BOK are exerted at the Golgi and ER membranes and that BOK induces apoptosis in a manner dependent on BAX and BAK.

See original publication No. 2

TRAIL enhances paracetamol-induced liver sinusoidal endothelial cell death in a Bim- and Bid-dependent manner

A. Badmann, S. Langsch, A. Keough, T. Brunner, T. Kaufmann, N. Corazza

Paracetamol (acetaminophen, APAP) is a universally used analgesic and antipyretic agent. Considered safe at therapeutic doses, overdoses cause acute liver damage characterized by centrilobular hepatic necrosis. One of the major clinical problems of paracetamol-induced liver disease is the development of hemorrhagic alterations. Although hepatocytes represent the main target of the cytotoxic effect of paracetamol overdose, perturbations within the endothelium involving morphological changes of liver sinusoidal endothelial cells (LSECs) have also been described in paracetamol-induced liver disease. Recently, we have shown that paracetamol-induced liver damage is synergistically enhanced by the TRAIL signaling pathway. As LSECs are constantly exposed to activated immune cells expressing death ligands, including TRAIL, we investigated the effect of TRAIL on paracetamol-induced LSEC death. We here demonstrate for the first time that TRAIL strongly enhances paracetamol-mediated LSEC death with typical features of apoptosis. Inhibition of caspases using specific inhibitors resulted in a strong reduction of cell death. TRAIL appears to enhance

paracetamol-induced LSEC death via the activation of the pro-apoptotic BH3-only proteins Bid and Bim, which initiate the mitochondrial apoptotic pathway. Taken together, this study shows that the liver endothelial layer, mainly LSECs, represent a direct target of the cytotoxic effect of paracetamol and that activation of TRAIL receptor synergistically enhances paracetamol-induced LSEC death via the mitochondrial apoptotic pathway. TRAIL-mediated acceleration of paracetamol-induced cell death may thus contribute to the pathogenesis of paracetamol-induced liver damage.
See original publication No. 3

Original publications

1. F. Ke, A. Voss, J.B. Kerr, L.A. O'Reilly, L. Tai, N. Echeverry, P. Bouillet, A. Strasser, **T. Kaufmann**: BCL-2 family member BOK is widely expressed but its loss has only minimal impact in mice.
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**Joint supervision together with Prof. D. Simon.

We are interested in the role of apoptosis and autophagy in inflammatory diseases and cancer. 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 malignant melanoma. 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 2012.

Autophagy is required for self-renewal and differentiation of adult human stem cells

S. Salemi, S. Yousefi, M.A. Constantinescu, M.F. Fey, H.-U. Simon

In the human body, skin and blood cells must constantly be renewed during normal homeostasis. This process is disturbed during anticancer therapies resulting in unwanted side effects, such as hair loss, epithelial barrier defects, and immunodeficiency. Tissue homeostasis is maintained by stem cell reservoirs that persist for life. Here, we report that autophagy of adult stem cells from skin and blood is required for both their self-renewal and differentiation. Autophagy also protected these cells from undergoing anticancer drug-induced death and it maintained their self-renewal and differentiation capacities after anticancer drug withdrawal. Moreover, differentiation of stem cells was associated with reduced autophagic activity and increased drug sensitivity. Thus, we could show that adult skin and blood stem cells exhibit high autophagic activity that seems to ensure survival and functionality even under conditions of cell stress.

See original publication No. 1

Cathepsin D primes caspase-8 activation by multiple intra-chain proteolysis

S. Conus, C. Pop, S.J. Schnipas, G.S. Salvesen, H.-U. Simon

During the resolution of inflammatory responses, neutrophils rapidly undergo apoptosis. A direct and fast activation of caspase-8 by cathepsin D was shown to be crucial in the initial steps of neutrophil apoptosis. Nevertheless, the activation mechanism of caspase-8 remains unclear. Here, by using site-specific mutants of caspase-8, we show that both cathepsin D-mediated proteolysis and dimerization of caspase-8 are necessary to generate an active caspase-8. At acidic pH, cathepsin D specifically cleaved caspase-8, but not the initiator caspase-9 or -10, and significantly increased caspase-8 activity in dimerizing conditions. These events were completely abolished by pepstatin A, a pharmacological inhibitor of cathepsin D. The cathepsin D intra-chain proteolysis greatly stabilized the active site of caspase-8. Moreover, the main caspase-8 fragment generated by cathepsin D cleavage could be affinity-labelled with the active site probe biotin-VAD-FMK, suggesting that this fragment is enzymatically active. Importantly, in an *in vitro* cell-free assay, the addition of recombinant human caspase-8 protein, pre-cleaved by cathepsin D, was followed by caspase-3 activation. Our data, therefore, indicate that cathepsin D is able to initiate the caspase cascade by direct activation of caspase-8. As cathepsin D is ubiquitously expressed, this may represent a general mechanism to induce apoptosis in a variety of immune and non-immune cells.

See original publication No. 2

Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis

A. Straumann, S. Hoesli, C. Bussmann, M. Stuck, M. Perkins, L.P. Collins, M. Payton, R. Pettipher, M. Hunter, J. Steiner, H.-U. Simon

Background: Eosinophilic esophagitis (EoE) is a chronic, Th2-type inflammatory disease. CRTH2 (chemoattractant receptor-homologous molecule on Th2 cells) is a prostaglandin D_2 (PGD_2) receptor, expressed by Th2 cells and other inflammatory cells, including eosinophils and basophils, that mediates chemotaxis and activation. OC000459 is a selective CRTH2 antagonist and would be expected to suppress eosinophilic tissue inflammation. **Objective:** The purpose of this study was to evaluate the efficacy and safety of an OC000459 monotherapy in adult patients with active, corticosteroid-dependent or corticosteroid-refractory EoE. **Methods:** In this randomized, double-blind, placebo-controlled trial, 26 adult patients (m/f = 22/4; mean age 41 yrs, range 22-69 yrs) with active EoE, dependent or resistant to corticosteroids, were treated either with 100 mg OC000459 (n=14) or placebo (n=12) twice daily. Pre- and post-treatment disease activity was assessed clinically,

endoscopically, histologically and via biomarkers. The primary endpoint was the reduction of esophageal eosinophil infiltration. **Results:** After an 8-week OC000459 treatment, the esophageal eosinophil load decreased significantly, from 114.83 to 73.26 eosinophils per high power field (eos/hpf), p=0.0256), whereas no reduction was observed with placebo (102.80 to 99.47 eos/hpf, p=0.870). With OC000459, the physician's global assessment of disease activity improved from 7.13 to 5.18 (p=0.035). OC000459 likewise reduced extracellular deposits of eosinophil peroxidase and tenascin C, effects not seen with placebo. No serious adverse events were observed. **Conclusions:** An 8-week treatment with the CRTH2-antagonist, OC000459, exerts modest, but significant anti-eosinophil and beneficial clinical effects in adult patients with active, corticosteroid-dependent or corticosteroid-refractory EoE, and is well tolerated.
See original publication No. 3

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Adv. Exp. Med. Biol. 750 (2012), 157-172.

2. S. Yousefi, **H.-U. Simon**: Mitochondrial DNA released by eosinophils contributes to innate immunity. In: Translational Science: from Basic to Clinical Immunology and Allergy (Eds. G. Marone, M. Triggiani and A. Genovese); Pacini Editore S.p.A., Pisa, 2012, p. 129-131.

3. D. Simon, **H.-U. Simon**: Biologics targeting T and B cells improve atopic eczema. In: Translational Science: from Basic to Clinical Immunology and Allergy (Eds. G. Marone, M. Triggiani and A. Genovese); Pacini Editore S.p.A., Pisa, 2012, p. 329-331.

4. **H.-U. Simon**, S. Yousefi: Eosinophil-mediated antibacterial host defense. In: Eosinophils in Health and Disease (Eds. J.J. Lee and H.F. Rosenberg); Elsevier Inc., London – Waltham, MA – San Diego, CA, 2013, p. 279-281.

5. S.Radonjic-Hoesli, **H.-U. Simon:** History of Eosinophils. In: History of Allergy (Series: Chemical Immunology and Allergy). Karger, in press.

Group PD Dr. Stephan von Gunten

Group members: Kayluz Frias Boligan, PhD student
Dr. Thomas Demoulin, PhD*
Dr. Camilla Jandus, Postdoc
Christoph Schneider, M.Sc. student
Fabiola Schorer, PhD student
Dr. Marc Wehrli, MD-PhD student

* Visiting scientist; research group of PD Dr. Kenneth McCullough, Institute of Virology and Immunoprophylaxis (IVI), Mittelhäusern, Switzerland

Our laboratory is interested in molecular mechanisms that control inflammation and cancer. In particular, we focus on protein-carbohydrate interactions in the immune system and on anti-inflammatory effects mediated by Siglec receptors. Siglecs are carbohydrate-binding receptors (lectins) that have recently received particular attention in light of the capacity to mediate cell death, anti-proliferative effects, and inhibition of cellular activities. We recently identified natural autoantibodies within human intravenous immunoglobulin (IVIG) as endogenous Siglec receptor ligands. PD Dr. S. von Gunten is a participating investigator at the Consortium of Functional Glycomics (www.functionalglycomics.org) that aims at defining paradigms by which protein-carbohydrate interactions mediate cell communication. Our group has collaborations with scientists and clinicians from many international and local academic institutions, companies and hospitals.

Glycomic analysis of human mast cells, eosinophils and basophils
S.J. North, S. von Gunten, A. Antonopoulos, A. Trollope, D.W. MacGlashan, J. Jr Jang-Lee, A. Dell, D.D. Metcalfe, S. Kirshenbaum, B.S. Bochner, S.M. Haslam
In allergic diseases such as asthma, eosinophils, basophils and mast cells, through release of preformed and newly generated mediators, granule proteins and cytokines, are recognized as key effector cells. While their surface protein phenotypes, mediator release profiles, ontogeny, cell trafficking and genomes have been generally explored and compared, there has yet to be any thorough analysis and comparison of their glycomes. We report here the application of high-sensitivity mass spectrometric-based glycomics methodologies to the analysis of N-linked glycans derived from isolated populations of human mast cells, eosinophils and basophils. The samples were subjected to matrix-assisted laser desorption ionization (MALDI) time-of-flight (TOF) screening analyses and MALDI-TOF/TOF sequencing studies. Results reveal substantive quantities of terminal N-acetylglucosamine containing structures in both the eosinophil and the basophil samples, whereas mast cells display greater relative quantities of sialylated terminal epitopes. For the first time, we characterize the cell surface glycan structures of principal allergic effector cells, which by interaction with glycan-binding proteins (e.g. lectins) have the possibility to dictate cellular functions, and might thus have important implications for the pathogenesis of inflammatory and allergic diseases.
See original publication No. 1

Siglec-7/-9 ligands dampen NK cell immunity in human cancer
C. Jandus, O. Chijioke, H. Liu, M. Dahlhaus, T. Démoulins, K. Frias Boligan, C. Schneider, M. Wehrli, R.E. Hunger, G.M. Baerlocher, H.-U. Simon, P. Romero, C. Münz, S. von Gunten
Altered surface glycosylation on malignant cells may directly affect NK cell responses in tumor immunity. Siglec-7 and -9 are MHC class I-independent inhibitory receptors on human NK cells. Given their sialic-acid binding capacity they may participate in sialoglycan-mediated interactions during natural anti-tumor immunity. We show that engagement of these receptors inhibits NK-cell mediated degranulation, IFNγ-secretion and cytolysis of target cells. In contrast to ubiquitous expression of Siglec-7 on NKs, Siglec-9 defines a subset of CD56dim NK cells with higher frequency in cord than in adult blood, exhibiting a more mature phenotype, yet similar telomere length, and enhanced CXCR1 expression with concomitantly augmented chemotaxis towards IL-8 compared to Siglec-9- CD56dim NK cells. The frequency of Siglec-9+ CD56dim NK cells was significantly reduced in cancer patients. Siglec-7 and -9 ligands are significantly overexpressed on human tumor cell lines of different histological types and tumor biopsies from melanoma patients. Enzymatic removal of Siglec-7 and -9 ligands on NK cell-susceptible tumor cells resulted in their increased killing in vitro, and in vivo in a mouse model with a reconstituted human NK-cell compartment. Altogether, our data highlight the potential of therapeutically targeting Siglec-7 and -9, and their ligands, to efficiently enhance NK cell-mediated anti-tumor immunity.

Original publication

1. S.J. North, **S. von Gunten**, A. Antonopoulos, A. Trollope, D.W. MacGlashan, J. Jr Jang-Lee, A. Dell, D.D. Metcalfe, S. Kirshenbaum, B.S. Bochner, S.M. Haslam: Glycomic analysis of human mast cells, eosinophils and basophils. Glycobiology 22 (2012), 12 - 22.

Review articles/Editorials

1. **S. von Gunten**, T. Kaufmann
Glucocorticoids 'on air'.
Allergy 67 (2012), 144 - 146.

2. **S. von Gunten**, Marsland BJ, C. von Garnier, D. Simon
Update in clinical allergy and immunology.
Allergy 67 (2012), 1491 - 1500.

Book chapter

1. **S. von Gunten**, H.-U. Simon: Granulocyte death regulation by naturally occurring autoantibodies. In: Naturally occurring antibodies (NAbs) (Ed. H.U. Lutz); Landes Bioscience and Springer, Austin, TX, 2012, p. 157-172.
Adv. Exp. Med. Biol. 750 (2012), 157-172.

Patent

Co-inventors M. Wehrli, A.W. Zuercher, S.M. Miescher, **S. von Gunten**
Pub. No.: WO/2012/080306, International Application No.: PCT/EP2011/072711, International Filing Date: 14.12.2011, Publication Date: 21.06.2012.
“CD89 activation in therapy.”

Group Prof. Shida Yousefi

Group members: Poorya Amini, PhD student*
Fabiana Jakob, technician*
Eveline Krajnec, M.Sc. student*
Evelyne Kozlowski, technician*
Morshed Mahbubul, PhD student*
Kevin Oberson, technician (70%)*
Inès Schmid, head technician*
Darko Stojkov, PhD student*
Ramona Graf, M.Sc. student

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

We are interested in molecular mechanisms regulating granulocyte functions, such as the release of inflammatory mediators. This includes cell signaling and death pathways. 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. Moreover, we are specialized in using confocal microscopy and imaging analysis. Recently, we became interested in an exciting new field of granulocyte biology that is the investigation of both mechanism and function of mitochondrial DNA release by eosinophils, neutrophils, and basophils.

Formation of extracellular mitochondrial DNA traps by viable basophils
M. Morshed, D. Simon, R. Hlushchk, T. Kaufmann, A.F. Walls, K. Obata-Ninomiya, H. Karasuyama, V. Djonov, H.-U. Simon, S. Yousefi
Studies have shown that basophils are able to bind bacteria. We recently observed that activated human and mouse basophils generate reactive oxygen species (ROS) and subsequently form extracellular DNA traps containing mitochondrial DNA and basogranulin that are able to bind and kill bacteria extracellularly. Basophil extracellular traps are present under pathological conditions in both human and mouse tissues. The newly identified function of basophils is performed in the absence of basophil death and represents a significant step forward in our understanding of the biological function of basophils.

Original publications

1. S. Salemi, **S. Yousefi**, M.A. Constantinescu, M.F. Fey, H.-U. Simon: Autophagy is required for self-renewal and differentiation of adult human stem cells. Cell Res. 22 (2012), 432-435.

2. M. Morshed, **S. Yousefi**, C. Stöckle, H.-U. Simon, D. Simon: Thymic stromal lymphopoietin stimulates the formation of eosinophil extracellular traps. Allergy 67 (2012), 1127-1137.

3. A. Kerstan, H.-U. Simon, **S. Yousefi**, M. Leverkus: Extensive accumulation of eosinophil extracellular traps in bullous delayed pressure urticaria: a pathophysiological link?
   Br. J. Dermatol. 166 (2012), 1151-1152.

Review articles/Editorials

1. **S. Yousefi**, D. Simon, H.-U. Simon: Eosinophil extracellular DNA traps: molecular mechanisms and potential roles in disease.
   Curr. Opin. Immunol. 24 (2012), 736-739.

2. D. Simon, H.-U. Simon, **S. Yousefi**: Extracellular DNA traps in allergic, infectious, and autoimmune diseases.
   Allergy 68 (2013), in press.

Book chapters

1. **S. Yousefi**, H.-U. Simon: Mitochondrial DNA released by eosinophils contributes to innate immunity. In: Translational Science: from Basic to Clinical Immunology and Allergy (Eds. G. Marone, M. Triggiani and A. Genovese); Pacini Editore S.p.A., Pisa, 2012, p. 129-131.

2. H.-U. Simon, **S. Yousefi**: Eosinophil-mediated antibacterial host defense. In: Eosinophils in Health and Disease (Eds. J.J. Lee and H.F. Rosenberg); Elsevier Inc., London – Waltham, MA – San Diego, CA, 2013, p. 279-281.

Group Prof. Uwe Zangemeister-Wittke

Group members: Dr. Nataliya Kotelevets, Postdoc[1]
Iuliia Filipenko, PhD student[1]
Tankica Timcheva, PhD student[1]
Vitalij Muzenko, M.Sc. ESKAS fellowship student[1]
Veronica Hanusova, guest PhD student[1]
Dr. Manuel Simon, Postdoc[2]
Nikolas Stefan, PhD student
Kevin Oberson, technician (30%)
Linda Vorak, M.Sc. student[2]

[1]Institute of Pharmacology, University of Bern
[2]Institute of Biochemistry, University of Zürich

We are interested in translational aspects of tumor targeting and molecular oncology.

1) We investigate mechanisms of drug resistance in solid tumors and identify targets in the sphingolipid signaling pathway for molecular intervention to facilitate tumor cell death. These include sphingosine kinase 1 and its prosurvival product sphingosine-1-phosphate (S1P). As a new approach to counteract the oncogenic potential of the sphingosine signaling cascade we have developed a recombinant enzyme, S1P lyase/Espilase, which depletes the pool of circulating S1P. Beyond cancer, this enzyme has implication for the treatment of other hyperproliferative diseases associated with aberrant S1P signaling, including fibrosis and aberrant angiogenesis (PCT/EP2011/071446). Espilase has been subjected to rational protein engineering, e.g. site-specific PEGylation, to increase its stability and circulation half-life in vivo.

2) We focus on tumor targeting with Designed Ankyrin Repeat Proteins (DARPins) as highly stable non-IgG scaffold proteins for drug delivery. To this end, affinity-maturated DARPins with specificity for the pan-carcinoma antigen EpCAM were developed. Using maleimide and the DARPin compatible bioorthogonal click chemistry for site-specific functionalization, we have generated state-of-the-art nanomedicines equipped with various payloads comprising bacterial biotoxins, chemotherapeutic agents and therapeutic oligonucleotides.

Targeting sphingosine kinase 1 in carcinoma cells decreases proliferation and survival by compromising PKC activity and cytokinesis

N. Kotelevets, D. Fabbro, A. Huwiler, U. Zangemeister-Wittke

Sphingosine kinases (SK) catalyze the phosphorylation of proapoptotic sphingosine to the prosurvival factor sphingosine 1-phosphate (S1P), thereby promoting oncogenic processes. Breast (MDA-MB-231), lung (NCI-H358), and colon (HCT 116) carcinoma cells were transduced with shRNA to downregulate SK-1 expression or treated with a pharmacologic SK-1 inhibitor. The effects of SK-1 targeting were investigated by measuring the level of

intracellular sphingosine, the activity of protein kinase C (PKC) and cell cycle regulators, and the mitotic index. Functional assays included measurement of cell proliferation, colony formation, apoptosis, and cell cycle analysis. Downregulation of SK-1 or its pharmacologic inhibition increased intracellular sphingosine and decreased PKC activity as shown by reduced phosphorylation of PKC substrates. In MDA-MB-231 cells this effect was most pronounced and reduced cell proliferation and colony formation, which could be mimicked using exogenous sphingosine or the PKC inhibitor RO 31-8220. SK-1 downregulation in MDA-MB-231 cells increased the number of cells with 4N and 8N DNA content, and similar effects were observed upon treatment with sphingosine or inhibitors of SK-1 or PKC. Examination of cell cycle regulators unveiled decreased cdc2 activity and expression of Chk1, which may compromise spindle checkpoint function and cytokinesis. Indeed, SK-1 kd cells entered mitosis but failed to divide, and in the presence of taxol also failed to sustain mitotic arrest, resulting in further increased endoreduplication and apoptosis. Our findings delineate an intriguing link between SK-1, PKC and components of the cell cycle machinery, which underlines the significance of SK-1 as a target for cancer therapy.
See original publication No. 1

Facile double-functionalization of designed ankyrin repeat proteins using click and thiol chemistries

M. Simon M, U. Zangemeister-Wittke, A. Plückthun

Click chemistry is a powerful technology for the functionalization of therapeutic proteins with effector moieties, because of its potential for bio-orthogonal, regio-selective, and high-yielding conjugation under mild conditions. Designed Ankyrin Repeat Proteins (DARPins), a novel class of highly stable binding proteins, are particularly well suited for the introduction of clickable methionine surrogates such as azidohomoalanine (Aha) or homopropargylglycine (Hpg), since the DARPin scaffold can be made methionine-free by an M34L mutation in the N-cap which fully maintains the biophysical properties of the protein. A single N-terminal azidohomoalanine, replacing the initiator Met, is incorporated in high yield, and allows preparation of "clickable" DARPins at about 30 mg per liter E. coli culture, fully retaining stability, specificity, and affinity. For a second modification, we introduced a cysteine at the C-terminus. Such DARPins could be conveniently site-specifically linked to two moieties, polyethylene glycol (PEG) to the N-terminus and the fluorophore Alexa488 to the C-terminus. We present a DARPin selected against the epithelial cell adhesion molecule (EpCAM) with excellent properties for tumor targeting as an example. We used these doubly modified molecules to measure binding kinetics on tumor cells and found that PEGylation has no effect on dissociation rate, but slightly decreases the association rate and the maximal number of cell-bound DARPins, fully consistent with our previous model of PEG action obtained in vitro. Our data demonstrate the benefit of click chemistry for site-specific modification of binding proteins like DARPins to conveniently add several functional moieties simultaneously for various biomedical applications.
See original publication No. 2

Original publications

1. N. Kotelevets, D. Fabbro, A. Huwiler, **U. Zangemeister-Wittke:** Targeting sphingosine kinase 1 in carcinoma cells decreases proliferation and survival by compromising PKC activity and cytokinesis.
PloS ONE 7 (2012):e39209.

2. M. Simon, **U. Zangemeister-Wittke,** A. Plueckthun: Facile double-functionalization of Designed Ankyrin Repeat Proteins using click and thiol chemistries.
Bioconjug. Chem. 23 (2012), 279 – 286.

3. M. Heine, B. Freund, P. Nielsen, J. Heeren, C. Jung, R. Reimer, H. Hohenberg, **U. Zangemeister-Wittke,** J. Wester, G.H. Lüers, U. Schumacher: High interstitial fluid pressure prevents tumour penetration of diagnostic monoclonal antibodies applied for molecular imaging purposes.
PloS ONE 7 (2012):e36258.

4. A. Wojtalla, B. Fischer, N. Kotelevets, F.A. Mauri, J. Sobek, H. Rehrauer, C. Wotzkow, M.P. Tschan, M.J. Seckl, **U. Zangemeister-Wittke,** A. Arcaro: Targeting the phosphoinositide 3-kinase p110a isoform impairs cell proliferation, survival and tumor growth in small cell lung cancer.
Clin. Cancer Res., in press.

Review article

1. M. Simon, N. Stefan, A. Plückthun, **U. Zangemeister-Wittke**: Epithelial cell adhesion molecule-targeted drug delivery for cancer therapy.
Exp. Opin. Drug Delivery, in press.

Additional Publications by PKI Members

PD Dr. Peter Späth

Original article

D. Charignon, **P. Späth**, L. Martin, C. Drouet: Icatibant, the bradykinin B2 receptor antagonist with target to the interconnected kinin systems.
Exp. Opin. Pharmacother. 13 (2012), 2233-2247.

Review articles

V. Wahn, W. Aberer, W. Eberl,M. Fasshauer, T. Kühne, K. Kurnik, M. Magerl, D. Meyer-Olson, I. Martinez-Saguer, **P. Späth**, P. Staubach-Renz, W. Kreuz: Hereditary angioedema (HAE) in children and adolescents - a consensus on therapeutic strategies.
Eur. J. Pediatr. 171 (2012), 1339-1348 and
Monatsschr. Kinderheilkd. 160 (2012), 774-781 [*Deutsche Version*].

J. Krudewig, U. Baumann, H. von Bernuth, M. Borte, U. Burkhard-Meier, G. Dueckers, E. Foerster-Waldl, K. Franke, P. Habermehl, M. Hönig, W. Kern, K. Kösters, K. Kugel, T. Lehrnbecher, J. Liese, R. Marks, G.A. Müller, R. Müller, D. Nadal, HH Peter, D. Pfeiffer-Kascha, M. Schneider, H. Sitter, **P. Späth**, V. Wahn, T. Welte, T. Niehues: Interdisziplinäre AWMF-Leitlinie zur Therapie primärer Antikörpermangelerkrankungen.
Klin. Pädiatr. 224 (2012), 404-415.

Book chapter

P.J. Späth, H.U. Lutz: Naturally occurring antibodies/autoantibodies in polyclonal immunoglobulin concentrates. In: Naturally occurring antibodies (NAbs) (Ed. H.U. Lutz); Landes Bioscience and Springer, Austin, TX, 2012, p. 239-261.
Adv. Exp. Med. Biol. 750 (2012), 239-261.

Dr. Camilla Jandus

Original articles

M. Braun, **C. Jandus**, P. Maurer, A. Hammann-Haenni, K. Schwarz, M.F. Bachmann, D.E. Speiser, P. Romero: Virus-like particles induce robust human T-helper cell responses.
Eur. J. Immunol. 42 (2012), 330-340.

P. Baumgaertner, **C. Jandus**, J.P. Rivals, L. Derré, T. Lövgren, L. Baitsch, P. Guillaume, I.F. Luescher, G. Berthod, M. Matter, N. Rufer, O. Michielin, D.E. Speiser: Vaccination-induced functional competence of circulating human tumor-specific CD8 T-cells.
Int. J. Cancer 130 (2012), 2607-2617.

L. Bron, **C. Jandus**, S. Andrejevic-Blant, D.E. Speiser, P. Monnier, P. Romero, J.P. Rivals: Prognostic value of arginase-II expression and regulatory T-cell infiltration in head and neck squamous cell carcinoma.
Int. J. Cancer 132 (2013), in press. doi: 10.1002/ijc.27728

Dr. Christina Merz - Stöckle

Original article

C. Stoeckle, P. Quecke, T. Rückrich, T. Burster, M. Reich, E. Weber, H. Kalbacher, C. Driessen, A. Melms, E. Tolosa: Cathepsin S dominates autoantigen processing in human thymic dendritic cells.
J. Autoimmun. 38 (2012), 332-343.

4.2. Congress Invitations

Dr. Susanne Radonjic-Hösli

European Academy of Dermatology and Venereology (EADV)-Workshop: Immune response in chronic inflammatory and autoimmune diseases, Bellinzona (CH), Nov. 8, 2012;
Cytosolic vacuolization of eosinophils.

Prof. Thomas Kaufmann

EMBRN-COST International Mast Cell and Basophil Meeting (IMCBM)
Berlin (D), November 26-27, 2012;
In vitro differentiation of unlimited numbes of functional mouse basophils.

Prof. Hans-Uwe Simon

Conference on Programmed Cell Death in Biology and Medicine, Medical Centre, Moscow State University, Moscow (Russia), June 4-5, 2012;
Programmed cell death pathways in neutrophils.

Conference on Therapeutic Targets in Cell Death, St. Petersburg State Institute of Technology, St. Petersburg (Russia), June 6-7, 2012;
A dual role for ATG5 upon anticancer drug treatment.

International Symposium: The Neutrophil in Immunity. Québec, QC (Canada), June 9-12, 2012;
Apoptosis and other forms of neutrophil cell death.

Annual Meeting of the European Allergy and Clinical Immunology (EAACI), Geneva (CH), June 16-20, 2012;
Plenary lecture: A come-back for the eosinophil?

Annual Meeting of the European Allergy and Clinical Immunology (EAACI), Geneva (CH), June 16-20, 2012;
Targeting the right journal with your manuscript.

Annual Meeting of the European Allergy and Clinical Immunology (EAACI), Geneva (CH), June 16-20, 2012;
Differential diagnosis of eosinophilic conditions.

Eicosanoids, aspirin and asthma 2012; Symposium in memory of Professor Andrew Szczeklik, Cracow (Poland), June 21-22, 2012;
New insights into eosinophil biology.

Workshop on Cell Death, Villa Vigoni, Loveno di Menaggio, Como (I), July 20-23, 2012;
ATG5 regulates lipid metabolism and oncogene-induced senescence.

9. Sommerakademie – Immunvaskulitis 2012: "Rheuma trifft Eosinophile", Bad Bramstedt (D), August 24-25, 2012;
Hypereosinophilie Syndrom.

7th Training Course on "Concepts and Methods in Programmed Cell Death", Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, August 29, 2012;
Autophagy and autophagic cell death.

International Conference "Innate Immunity of the Lung – Improving Pneumonia Outcome", Transregional Collaborative Research Center (SFB-TR 84) and German Academy of Science Leopoldina, Berlin, September 19-22, 2012;
Innate immunity mediated by eosinophils.

XIIIth International Symposium on Proteinases, Inhibitors, and Biological Control, Portoroz, Slovenia, September 22-26, 2012;
p73 regulates hepatocellular lipid metabolism.

29th Symposium of the Collegium Internationale Allergologicum, Jeju Island, Korea, October 14-19, 2012;
Functional aggregation of major basic protein in eosinophil granules and inflamed tissues.

Kick-off Meeting: Platform for Stem Cell Research and Regenerative Medicine, University of Bern, Bern, November 1, 2012;
Autophagy and stem cells.

European Academy of Dermatology and Venereology (EADV)-Workshop: Immune response in chronic inflammatory and autoimmune diseases, Bellinzona (CH), Nov. 8, 2012;
Epigenetic silencing of ATG5 in melanoma – role in tumorigenesis.

32. Symposium der Walter-Siegenthaler-Gesellschaft für Fortschritte in der Inneren Medizin, Köln (D), Nov. 15-17, 2012;
Biopharmaceuticals – Arzneimittel der Zukunft?

PD Dr. Peter Späth

1st HAE Global Conference, Copenhagen, (DK), May 17-20, 2012;
How to identify HAE patients in developed and less developed countries.

PD Dr. Stephan von Gunten

4th ICIS Expert Meeting on Changes in ITP, Montreux (CH), Sept. 13 -15, 2012;
Immune thrombocytopenia (ITP): Cell death.

Prof. Shida Yousefi
16th Biennial meeting of Society for Free Radical Research Internatioal (SFRRI), London (UK), Sept. 6-9, 2012;
The mitochondrial angle: viable granulocyte extracellular trap production.

4.3. Seminar Invitations

Prof. Thomas Kaufmann

Vall d'Hebron Research Institute, Cell Signalling and Apoptosis Group, Barcelona (E), Nov. 15, 2012; guest of Prof. Juan Comella Carnice:
Regulation of apoptosis by BCL-2 family members.

Prof. Hans-Uwe Simon

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI), Orlando, FL (USA), March 3, 2012:
Personalized medicine: The importance of biomarkers.

University of Basel, Seminars on drug discovery and development, May 9, 2012;
host of Prof. Stephan Krähenbühl:
Autophagy in tumorigenesis and anticancer drug treatment.

Kantonsspital Baden, Nov. 29, 2012; host of Prof. Jürg H. Beer:
Biopharmaceuticals – Arzneimittel der Zukunft?

Department of Physiology, University of Lausanne, Dec. 10, 2012;
host of Prof. Christian Widmann:
The p73-ATG5 axis in hepatocellular lipid metabolism.

PD Dr. Peter Späth

Workshop: From genetics, through international research to national therapeutic guidelines and public health programs in hereditary angioedema. Romania quo vadis? University of Medicine and Pharmacy, Tirgu Mures (Ro), Aug. 30 – Sept. 1, 2012:
Bradykinin-mediated hereditary angioedema - available drugs and their site of intervention.

Workshop: Pain Relief with Immunoglobulin, Liverpool (UK), Oct. 5 – 6, 2012:
Immunoglobulin supply - factors which may influence availability and costs in the future".

PD Dr. Stephan von Gunten

The Johns Hopkins University, Division of Allergy and Clinical Immunology, Baltimore (MD, USA), March 21, 2012; guest of Prof. M. Kollarik:
Immunoregulatory activities of CD33-like Siglecs.

Emory University School of Medicine, Department of Biochemistry, Atlanta (GA, USA), August 2, 2012; guest of Prof. D. Smith:
Immunoglobulin A (IgA) in inflammation: Novel aspects.

Bulgarian Academy of Sciences, Sofia (BG), Dec. 7, 2012; guest of Prof. T. Vassilev:
Granulocyte death regulation by immunoglobulins.

4.4. Organization of Meetings and Courses

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology (together with task force SSPT): Fortschritte in der Pharmakologie – Kardiovaskuläre Pharmakologie, Bern (CH), Jan. 26, 2012

Mitglied der Programmkommission: 78. Jahrestagung der Deutschen Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie e.V. (DGPT), Dresden (D), March 19-22, 2012

Symposium: Pharmacology in academia: Today and tomorrow (50 years PKI at Friedbühlstrasse 49), Bern (CH), May 8, 2012

Member of the International Scientific Advisory Board: The neutrophil in immunity, Québec (Canada), June 9-12, 2012

Member of the Local Organizing Board: Annual Meeting of the European Allergy and Clinical Immunology (EAACI), Geneva (CH), June 16-20, 2012

11th International Summer School, Bönigen (CH), Aug. 12-14, 2012

7th Swiss Apoptosis Meeting (SAM), Bern (CH), Aug. 30-31, 2012

Member of the International Scientific Advisory Board: 20th Meeting of the European Cell Death Organization (ECDO), Rome (I), Sept. 14-17, 2012

Bern Immunology Club (together with the other founder members); Institute of Pharmacology, University of Bern, one meeting in each month of 2012

Prof. Shida Yousefi

DKF, MIC, GCB - Course in fluorescent staining, confocal microscopy, and image analysis, Bern (CH), April 17-18, 2012.

DKF, MIC, GCB - Course in fluorescent staining, confocal microscopy, and image analysis, Bern (CH), Oct. 30-31, 2012.

Prof. Thomas Kaufmann

7th Training Course on “Concepts and Methods in Programmed Cell Death”, Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, August 29, 2012.

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology (together with task force SSPT): Fortschritte in der Pharmakologie – Cardiovascular Pharmacology, Morning session; Bern (CH), Jan. 26, 2012

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI); Session: "Beyond necrosis and apoptosis: Spectrum of cell death";
Orlando (FL, USA), March 2-6, 2012.

78. Jahrestagung der Deutschen Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie e. V. (DGPT); Poster session: „Respirationstrakt, Gastrointestinaltrakt, Niere/Harnblase, Pharmakokinetik bei Versuchstieren“; Dresden (D), March 19-22, 2012.

Spring meeting of the Swiss Society of Pharmacology and Toxicology (SSPT);
Minisymposium: „Cancer as a consequence of aging“; Bern (CH), April 19, 2012.

Annual Meeting of the European Allergy and Clinical Immunology (EAACI); Poster session: „Mast cells, basophils and eosinophils“; Geneva (CH), June 16-20, 2012.

9. Sommerakademie – Immunvaskulitis 2012: “Rheuma trifft Eosinophile”; Session: “Systemerkrankungen mit Eosinophilie”; Bad Bramstedt (D), August 24-25, 2012.

9. Sommerakademie – Immunvaskulitis 2012: “Rheuma trifft Eosinophile”; Session: “Eosinophile Erkrankungen”; Bad Bramstedt (D), August 24-25, 2012.

7th Swiss Apoptosis Meeting; Session: “Apoptosis/Autophagy and Cancer”;
Bern (D), August 30-31, 2012.

20th Meeting of the European Cell Death Organization (ECDO); Session: “Regulation of Autophagy”; Rome (I), Sept. 14-17, 2012.

29th Symposium of the Collegium Internationale Allergologicum; Session:
“Dendritic cells, mast cells, monocytes and granulocytes”; Jeju Island, Korea,
Oct. 14-19, 2012.

PD Dr. Peter Späth

International Plasma Protein Congress, Session 7: “Established products, new indications, great future”; Madrid (E), March 13-14, 2012.

PD Dr. Stephan von Gunten

USGEB Meeting 2012, Satellite Symposium of the Swiss Society for Pharmacology and Toxicology (SSPT), Lausanne (CH), Feb. 6, 2012.

Spring Meeting 2012 of the Swiss Society of Pharmacology and Toxicology (SSPT), Session: "Young investigator research"; Bern, (CH), April 19, 2012.

4.6. Referee Work for Peer-Reviewed Journals

Dr. Barbara Geering

Cell Death Differ.
FEBS Lett.
Allergy
J. Immunol.

Dr. Zhaoyue He

Allergy
Cell Death Dis.

Dr. Susanne Radonjic-Hösli

Allergy

Prof. Andrea Huwiler

Biochem. Pharmacol.
Biochim. Biophys. Acta
Blood
Br. J. Pharmacol.
Carcinogenesis
Circ. Res.
Clin. Chem. Lab. Med.
Diabetologica
Eur. J. Pharmacol.
Exp. Cell Res.
FEBS Lett.
Hormone 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

Apoptosis
Allergy
Cell Commun. Signal.
Cell Death Differ.
Cell Death Dis.
Eur. J. Immunol.
Frontiers Mol. Cell. Oncol.
Future Oncol.
Hepatology
Immunology and Cell Biology
J. Hepatol.
Methods
Mol. Cancer Therap.
Oncogene
PLoS One

Dr. He Liu

Cell Death Differ.
Cell Death Dis.

Dr. Christina Merz-Stöckle

Allergy
Mini-Rev. Med. Chem.
FEBS Journal

Prof. Hans-Uwe Simon

Allergy
Apoptosis
Autophagy
Biochem. Biophys. Acta
Blood
Cell Biol. Toxicol.
Clin. Exp. Allergy
EMBO Journal
EMBO Reports
Eur. J. Haematol.
Eur. J. Immunol.
FASEB J.
Cell Death Differ.
Cytokine
Gut
J. Allergy Clin. Immunol.
J. Antioxid. Redox Signal.
J. Exp. Med.
J. Immunol.
J. Leukoc. Biol.
Lancet
N. Engl. J. Med.
Int. J. Cancer
Proc. Natl. Acad. Sci. USA
PloS One
Trends Pharmacol. Sci.
Cell Death Dis.
Mitochondrion

PD Dr. Peter Späth

Allergy
Br. J. Medicine Med. Res.

PD Dr. Stephan von Gunten

Allergy
Am. J. Respir. Cell Mol. Biol.
Front. Mol. Cell. Oncol.
Cell Death Differ.
Cell Death Dis.
Immunol. Lett.
J. Allergy Clin. Immunol.
J. Invest. Dermatol.
J. Immunol
J. Immunotoxicol.
Med. Inflamm.
Respiration
Pathobiology

Prof. Shida Yousefi

Allergy
Cell Biochem. Biophys.
Cell. Mol. Neurobiol.
Int. J. Biochem. Cell Biol.
Arch. Biochem. Biophys.
Cell Death Differ.
Frontiers Immunol.
PloS One

Prof. Uwe Zangemeister-Wittke

Bioconjug. Chem.
J. Biol. Chem.
J. Drug Targeting
Lung Cancer
Mol. Cell. Biol.
PLoS One

4.7. Referee Work for Grant Bodies

Dr. Barbara Geering

Swiss Cancer League

Prof. Andrea Huwiler

Deutsche Forschungsgemeinschaft (DFG)

Prof. Thomas Kaufmann

Swiss Cancer League
Swiss National Science Foundation (SNF)

Prof. Hans-Uwe Simon

Swiss National Science Foundation (SNF)
Italian Association for Cancer Res. (AIRC)
European Research Council (ERC)
Germ.-Isr. Found. for Sci. Res. & Development
Deutsche Forschungsgemeinschaft (DFG)
Swiss Cancer League
HELMHOLTZ-Gemeinschaft

PD Dr. Stephan von Gunten

Israel Science Foundation (ISF)
Swiss Cancer League
Swiss National Science Foundation (SNF)

Prof. Shida Yousefi

National Science Center, Poland

Prof. Uwe Zangemeister-Wittke

Swiss Cancer League
Bernische Krebsliga
Swiss National Science Foundation (SNF)

4.8. Awards

Dr. He Liu

Best Oral Presentation Award
Swiss Society of Pharmacology and Toxicology (SSPT); Bern, April 19, 2012

Dr. Camilla Jandus-Marone

Best Poster Award
Swiss Society of Pharmacology and Toxicology (SSPT); Bern, April 19, 2012

Dr. He Liu

Poster Award (1st)
7th Swiss Apoptosis Meeting (SAM); Bern, Aug. 30-31, 2012

Dr. Nohemy Echeverry

Poster Award (3rd)
7th Swiss Apoptosis Meeting (SAM); Bern, Aug. 30-31, 2012

Dr. Zhaoyue He

Logo-Contest prize
Stem Cell Research and Regenerative Medicine, University of Bern;
Bern, Nov. 1, 2012

5. Administrative, Advisory, and Honorary Posts

Dr. Zhaoyue He

Coordinator for PC work at the PKI

Webmaster at the PKI

Prof. Andrea Huwiler

Member of the Ernennungs- und Habilitationskommission (EHK), Medical Faculty, University Bern

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

Member of the Collegium generale of the University of Bern

Prof. Thomas Kaufmann

Member of the Supervision commission “Cell Biology” within the Graduate School for Cellular and Biomedical Sciences of the University of Bern, since 2009

Member of Review Editorial Board: Frontiers in Molecular and Cellular Oncology

Coordinator for FACS and Chemicals at the PKI

Prof. Hans-Uwe Simon

Vice-Dean of Research, Medical Faculty, University of Bern

Vice-Chair, Immunopharmacology Section, International Union of Basic and Clinical Pharmacology (IUPHAR)

President-elect, International Eosinophil Society (IES)

Member of the German National Academy of Sciences (Deutsche Akademie der Naturforscher Leopoldina)

Member of the Scientific Committee, Swiss Cancer League

Chairman of Scientific Advisory Board, HELMHOLTZ Zentrum für Umweltforschung (UFZ), Leipzig (D)

Member of Council of the Collegium International Allergologicum (CIA)

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

Vice Workshop Representative of the Mechanisms of Allergy/Asthma/ Immunology (MAAI) section of the American Academy of Allergy, Asthma and Immunology (AAAAI)

Member of the Cells and Cytokine Committee (Workshops) of the American Academy of Allergy, Asthma and Immunology (AAAAI)

Member of the Advisory Board, Research Foundation, University of Bern

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

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

Member of the Advisory Board of the Max and Elsa Beer-Brawand-Fonds

Mentor, junior EAACI member program

Past-President, European Cell Death Society (ECDO)

Past-President, Union of the Swiss Societies for Experimental Biology (USSEB)

Past-President, Swiss Society of Pharmacology and Toxicology (SSPT)

Editor-in-Chief, 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, 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

Section Editor, Cell Death and Disease

Associate Editor, Frontiers in Oncology

PD Dr. Peter Späth

Consultant for the 'FindID' project, a project to provide early diagnosis and increase diagnosis rates to patients with primary immunodeficiency diseases.

Representant of the Swiss Society for Allergology and Immunology preparing a "Guideline for the Treatment of Primary Antibody Deficiencies" (German speaking countries)

PD Dr. Stephan von Gunten

Member of the Editorial Board, Allergy

Member of the Council of the Swiss Society of Experimental Pharmacology (SSEP)

Webmaster at the PKI

Coordinator for FACS and library at the PKI

Prof. Shida Yousefi

Editorial Assistant, Editorial Office, Allergy

Coordinator for radioactive work at the PKI

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

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

Prof. Uwe Zangemeister-Wittke

Consultant of the Human SwissMedic Expert Committee

Consultant of the Scientific Committee of the Centro Genética Humana, Facultad de Medicina, Clinica Alemana-Universidad del Desarrollo, Santiago de Chile

Member of the Editorial Board, Lung Cancer

Review Editor, Frontiers in Molecular and Cellular Oncology

All PKI principal investigators served as tutors in graduation committes of the Graduate School for Cellular and Biomedical Sciences of the University of Bern.

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 Exciter, 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). The LSM 5 Exciter was in operation in 2012 for approximately 1373 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 (35 scientists), as well as technical and scientific support. The DKF compensated this work by providing a 50% salary for one Ph.D. student of our institute. During the past year, the confocal microscope has been used by 24 different research groups. In 2012, the operator and her team spent for the facility more than 300 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 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. Sponsors

7.1. Research Grants

Dr. Barbara Geering
L'Oréal fellowship "For Women in Science"

Dr. Susanne Radonjic-Hösli

Swiss National Science Foundation and Swiss Academy of Medical Sciences (SAMW)
Allergie-Stiftung Ulrich Müller-Gierok, Bern (together with Prof. Hans-Uwe Simon)

Prof. Andrea Huwiler

Swiss National Science Foundation (grant No. 310030-135619/1)
Deutsche Forschungsgemeinschaft
Schweizerische Multiple Sklerose Gesellschaft

Dr. Camilla Jandus

Swiss National Science Foundation, Marie Heim-Vögtlin Program (grant No. Pmdp3_129022)

Prof. Thomas Kaufmann

Swiss National Science Foundation, SNF-Professorship (grant No. PP0033_119203)
3R Research Foundation (grant No. 127-11)
Novartis Stiftung für medizinisch-biologische Forschung

Eveline Krajnec

Fellowship, ERASMUS program (Oct. 2012 – Jan. 2013)

Dr. Christina Merz-Stöckle

Deutsche Forschungsgemeinschaft (grant No. Sto 906/1-1)

Vitalii Mutsenko

Fellowship, Eidgenössische Stipendienkommission für ausländische Studierende (ESKAS) (Sept. 2011 – June 2012)

Prof. Hans-Uwe Simon

Swiss National Science Foundation (grant No. 310000-107526)
Stiftung zur Krebsbekämpfung, Zurich
Allergie-Stiftung Ulrich Müller-Gierok, Bern (together with Dr. Susanne Radonjic-Hösli)

PD Dr. Stephan von Gunten

Swiss National Science Foundation (grant No. 310030_135734/1)
Swiss National Science Foundation, Bulgarian-Swiss Research Programme (grant No. IZEBZO_142967/1)
CSL Behring AG, Bern
Novartis Stiftung für medizinisch-biologische Forschung
UniBern Forschungsstiftung

Darko Stojkovo

Fellowship, ERASMUS program (Sept. 2011 – Jan. 2012)
IAESTE trainee (July – October 2012)

Prof. Shida Yousefi

Swiss National Science Foundation (grant No. 310030-127628/1)

Xiaoliang Wang

State Scholarship Fund of China (CSC Scholarship)

Dr. Marc Wehrli

Swiss National Science Foundation and Swiss Academy of Medical Sciences (SAMW)

Prof. Uwe Zangemeister-Wittke

Swiss National Science Foundation (grant No. 310030E_132762/1)
Swiss National Science Foundation (grant No. 310030E_138201/1)
Sasella-Stiftung (Zürcher Kantonalbank)

7.2. Meetings

Swiss Society of Pharmacology and Toxicology (SSPT): Progress in Pharmacology Bern (CH), Jan. 26, 2012
Pfizer AG, Zurich
Bristol-Meyers Squibb SA, Baar
Servier SA, Meyrin

Symposium: Pharmacology in academia: Today and tomorrow Bern (CH), May 8, 2012
Sanofi Aventis (Schweiz) AG

11th III-International Summer School, Bönigen (CH), Aug. 12 – 14, 2012
Allergopharma AG, Therwil
Carl Zeiss AG, Feldbach
CSL Behring AG, Bern
Novartis Pharma AG, Bern
Pfizer AG, Zurich
LS2 - Life Sciences Switzerland (former Union of the Swiss Societies of Experimental Biology (USSEB))
Graduate School of Cellular and Biomedical Science, University of Bern
Supported by the member companies of the KGF (Kontaktgruppe für Forschungsfragen), Novartis, F. Hoffmann-La Roche and Merck Serono

Swiss Apoptosis Meeting (SAM), Bern (CH), Aug. 30 – 31, 2012
Supported by the member companies of the KGF (Kontaktgruppe für Forschungsfragen), Novartis, F. Hoffmann-La Roche and Merck Serono
BD Biosciences, Allschwil
LS2 - Life Sciences Switzerland (former Union of the Swiss Societies of Experimental Biology (USSEB))

7.3. Seminars „Progress in Pharmacology“

2012:
ASTELLAS Pharma AG, Wallisellen
NOVARTIS Pharma Schweiz AG, Bern
CSL Behring AG, Bern

2013:
ASTELLAS Pharma AG, Wallisellen
CSL Behring AG, Bern
PFIZER AG, Zurich

7.4. Seminars „Bern Immunology Club“

Luca Borradori, Britta Engelhardt, Thomas Geiser, Andrew Macpherson, Christoph Müller, Hans-Uwe Simon, Artur Summerfield, Beda Stadler, Peter Villiger

7.5. Travel Support

Ursina Gurzeler
Graduate School for Cellular and Biomedial Sciences, Univ. Bern (8th Eur. Workshop on Cell Death, Serre Chevalier, F, June 3-8, 2012)

Dr. Marc Wehrli
Graduate School for Cellular and Biomedial Sciences, Univ. Bern, and
Swiss Society of Experimental Pharmacology (SSEP) (Glycobiology Symposium, San Diego, CA, USA, March 16-17, 2012)

Dr. Tatiana Rabachini de Almeida
Swiss Society of Experimental Pharmacology (SSEP) (EACR Conference on Cell Death in Cancer, Amsterdam, NL, Jan. 26-28, 2012)

Saša Rožman
European Cell Death Organization (ECDO) (20th Meeting of the European Cell Death Organization, Rome, I, Sept. 14-17, 2012)

PD Dr. Peter Späth
Congress attendance; Organizing Committee 8th International Congress on Autoimmunity, Granada, E, May 9-13, 2012

7.6. Other Support

Bürgi Fonds Seminar series of the institute