Annual Report 2011

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 elfte umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat auch im Jahr 2011 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 2011 trugen wir dazu bei, die Kommunikation zwischen WissenschaftlerInnen und Öffentlichkeit zu fördern. Dazu diente u.a. eine Vernissage, die viele Gäste in das PKI lockte.

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. Diese neuen Kurse bedeuten für das PKI eine deutliche Mehrbelastung auf dem Gebiet der Lehre. 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 21 DoktorandInnen (17 PhD, 4 MD), und 4 DoktorandInnen haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2011 insgesamt 32 Originalarbeiten sowie 17 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >250). MitarbeiterInnen des Instituts wurden

zu insgesamt 27 Vorträgen bzw. Seminaren eingeladen. Mehrere MitarbeiterInnen des PKI wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 8 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) werden in 2012 das „7th Swiss Apoptosis Meeting (SAM)“ organisieren, zu dem wir über 200 TeilnehmerInnen aus dem In- und Ausland erwarten. 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 wurde 2011 als President-elect der International Eosinophil Society (IES) gewählt. Gleichzeitig amtete er 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 2011 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 2012

1.2. Foreword

This is the eleventh 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 2011 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 2011. The organization of art exhibitions within our institute is an example for these efforts.

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, 17 PhD students and 4 MD students work at the PKI, and four students (2 PhD, 2 MD) successfully finished their doctoral and Master studies, respectively, in 2011.

In 2011, members of the PKI published 32 original and 17 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 27 lectures or seminars. Several PKI members received research prizes. Eight 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. In 2012, Prof. Simon and Prof. Brunner (Univ. of Konstanz, Germany) will organize an international congress (7th Swiss Apoptosis Meeting, SAM), which usually attracts more than 200 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 was appointed as President-elect of the International Eosinophil Society (IES) and 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 2011. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, January 2012

2. Staff 2011

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
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

Poorya Amini, visiting scientist* (since November 2011)
Carla Aeberhard, M.Sc. student* (January – June 2011)
Daniel Bachmann, research assistant*
Monika Bodnar, technician* (January - July 2011)
Dr. Sébastien Conus, PhD
Nicole Drewes, M.Sc. student* (January – June 2011)
Nohemy Echeverry, PhD student
Daniel Fallegger, PhD student
Iuliia Filipenko, PhD student (since August 2011)
Kayluz Frias Boligan, PhD student* (since August 2011)
Dr. Barbara Geering, PhD
Andy Gerber, M.Sc. student* (January – June 2011)
Ursina Gurzeler, PhD student*
Zhaoyue He, PhD student
Dr. Susanne Hoesli, MD-PhD student*
Faik Imeri, PhD student
Fabiana Jakob, B.Sc. student* (April – June 2011)
Fabiana Jakob, technician (since July 2011)
Dr. Camilla Jandus, MD, PhD*
Dr. Nataliya Kotelevets, PhD
Evelyne Kozlowski, technician
He Liu, PhD student*
Morshed Mahbubul, PhD student*
Marianne Maillard-van Laer, technician
Livia Mangold, M.Sc. student* (January – June 2011)
Jennifer Mildenberger, M.Sc. student* (April 2011)

Dipak Maskey, PhD student
Dr. Christina Merz - Stöckle, PhD*
Cristina Mihalache, PhD student
Vitalii Mutsenko, ESKAS student M.Sc.* (since September 2011)
Kevin Oberson, technician
Olexsandr Pastukhov, PhD student
Dr. Tatiana Rabachini de Almeida, PhD* (since March 2011)
Laetitia Roh, M.Sc. student* (January – June 2011)
Saša Rožman, PhD student
Inès Schmid, head technician
Matthias Schindler, M.Sc. student* (Mai 2011)
Manuel Simon, PhD student*
Simon Städler, MD student* (until April 2011)
Darko Stojkov, ERASMUS student (since September 2011)
Matthias Stuck, MD student*
Xiaoliang Wang, PhD student* (since October 2011)
Dr. Marc Wehrli, MD-PhD student*

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
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

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

Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT): Progress in Pharmacology - Pharmacology of Pain; Bern, Jan. 27, 2011

Members of the Institute of Pharmacology of the University of Bern together with participants of an international summer school in Sigriswil; August 23, 2011. Our guest speakers from the USA (Prof. A. Haczku), Germany (Prof. M. Schneider and Prof. T. Brunner) and Slovenia (Prof. I. Mlinaric-Rascan) are seen.

3. Teaching Activities
3.1. Lectures

Lectures for medical students

Date	Lecturer	Titel of the lecture
March 14, 2011	Dr. Stephan von Gunten	Antidiabetika
March 16, 2011	Dr. Stephan von Gunten	Fett-Lipidsenker, Behandlung der Gicht
April 4, 2011	Prof. Andrea Huwiler	Antiepileptika
April 4, 2011	Prof. Andrea Huwiler	Therapie von M.Parkinson und Demenz
April 6, 2011	Prof. Andrea Huwiler	Lokalanästhetika
April 18, 2011	Dr. Stephan von Gunten	Hormone aus pharmakologischer Sicht 1
April 18, 2011	Dr. Stephan von Gunten	Hormone aus pharmakologischer Sicht 2
April 20, 2011	Prof. Andrea Huwiler	Pharmakologie der Narkotika / Anästhesie 1
April 20, 2011	Prof. Andrea Huwiler	Pharmakologie der Narkotika / Anästhesie 2
May 4, 2011	Prof. Andrea Huwiler	Psychopharmakologie
May 9, 2011	Prof. Andrea Huwiler	Antidepressiva, Anxiolythika und Stimmungsstabilisatoren
May 9, 2011	Prof. Andrea Huwiler	Antipsychotika
May 18, 2011	Prof. Andrea Huwiler	Schmerz und Analgesiologie 1
May 18, 2011	Prof. Andrea Huwiler	Schmerz und Analgesiologie 2
June 6, 2011	Prof. Hans-Uwe Simon	Immunmodulation
Sept. 12, 2011	Prof. Thomas Kaufmann	Adaptation und Zellschäden
Sept. 19, 2011	Prof. Hans-Uwe Simon	Pharmakodynamik 1
Sept. 19, 2011	Prof. Hans-Uwe Simon	Pharmakodynamik 2
Sept. 21, 2011	Prof. Hans-Uwe Simon	Entzündungshemmung
Sept. 21, 2011	Prof. Hans-Uwe Simon	Einführung in die Toxikologie

Oct. 24, 2011	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Nov. 1, 2011	Prof. Uwe Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Nov. 1, 2011	Prof. Uwe Zangemeister-Wittke	Antihypertensiva
Nov. 1, 2011	Dr. David Spirk	Antithrombotische Therapie & Antikoagulantien
Nov. 9, 2011	Prof. Uwe Zangemeister-Wittke	Antiarrhythmika
Nov. 16, 2011	Dr. David Spirk	Behandlung der Herzinsuffizienz und Angina Pectoris
Dec. 5, 2011	Prof. Uwe Zangemeister-Wittke	Diuretika

Clinical Microbiology for Pharmacy students (together with students of dental medicine)

Date	Lecturer	Title of the lecture
Dec. 2, 2011	Dr. Sibylle Bürgi	Antibiotika I
Dec. 2, 2011	Dr. Sibylle Bürgi	Antibiotika II

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

Date	Lecturer	Title of the lecture
Febr. 7, 2011	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Einführung, Rezeptoren
Febr. 7, 2011	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Dosis-Wirkungskurven
Febr. 9, 2011	Prof. Hans-Uwe Simon	Antagonisten / Applikation
Febr. 21, 2011	Prof. Uwe Zangemeister-Wittke	Aufnahme / Verteilung

Febr. 21, 2011	Prof. Uwe Zangemeister-Wittke	Arzneimittelmetabolismus / Elimination
March 9, 2011	Prof. Uwe Zangemeister-Wittke	Gesamtkinetik / Dosierung
March 9, 2011	Prof. Andrea Huwiler	Interaktionen / Pharmakogenetik, allg.
March 16, 2011	Dr. Stephan von Gunten	Psychopharmaka
March 21, 2011	Prof. Uwe Zangemeister-Wittke	Vegetatives Nervensystem
March 21, 2011	Prof. Uwe Zangemeister-Wittke	Herz-Kreislaufpräparate
March 30, 2011	PD Dr. Armand Cachelin	Immunsuppression
April 6, 2011	Dr. Sibylle Bürgi	Lokalanästhetika
April 13, 2011	Dr. Sibylle Bürgi	Insulin, orale Antidiabetika
April 18, 2011	PD Dr. Armand Cachelin	Schwache Analgetika
April 18, 2011	PD Dr. Armand Cachelin	Starke Analgetika
April 20, 2011	Dr. Stephan von Gunten	Magensäurehemmung
May 4, 2011	Prof. Andrea Huwiler	Narkose-/Beruhigungsmittel
May 9, 2011	PD Dr. Peter Späth	Orale Antikoag./Plättchenhemmer
Oct. 17, 2011	Prof. Thomas Kaufmann	Zellschäden (allg. Pathologie-Vorlesung)

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. 24, 2011	Prof. Hans-Uwe Simon	Introduction
Febr. 24, 2011	Prof. Hans-Uwe Simon	Immunopharmacology
May 26, 2011	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. 10, 2011	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 24, 2011	Prof. Andrea Huwiler	Lipid mediators in tissue trafficking
May 12, 2011	Prof. Shida Yousefi	Resolution of inflammation - apoptosis

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

Date	Lecturer	Title of the lecture
Oct. 11, 2011	Prof. Thomas Kaufmann	Isolation of leukocytes (4 h)
Nov. 22, 2011	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. 28, 2011	Prof. Hans-Uwe Simon	Pharmacodynamics I
Febr. 28, 2011	Prof. Hans-Uwe Simon	Pharmacodynamics II
March 7, 2011	Prof. Uwe Zangemeister-Wittke	Pharmacokinetics I
March 7, 2011	Prof. Uwe Zangemeister-Wittke	Pharmacokinetics II
March 14, 2011	Prof. Hans-Uwe Simon	Toxicology
March 14, 2011	Prof. Hans-Uwe Simon	Pharmacology of inflammation

March 28, 2011	Dr. Christina Merz-Stöckle	Pharmacogenetics
May 2, 2011 (total 1h)	Prof. Uwe Zangemeister-Wittke	Tumorpharmacology

Written examination and oral tests: Prof. Simon

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

Date	Lecturer	Title of the lecture
Sept. 23, 2011	Prof. Thomas Kaufmann	Immune system
Sept. 30, 2011	Prof. Uwe Zangemeister-Wittke	Heart and vascular system
Oct. 7, 2011	Prof. Shida Yousefi	Antiinfectious therapy
Oct. 14, 2011	Dr. Stephan von Gunten	Pharmacology of the gastrointestinal system
Oct. 21, 2011	Prof. Andrea Huwiler	Nervous system
Oct. 28, 2011	Dr. Stephan von Gunten	Endocrine and reproductive system
Nov. 4, 2011	Prof. Shida Yousefi	Lungs and kidneys
Nov. 11, 2011	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
Oct. 31, 2011	Prof. Thomas Kaufmann	Cell damage

External teaching activities: University of Zurich (Molecular Medicine)

Date	Lecturer	Title of the lecture
March 14-15, 2011	Prof. Uwe Zangemeister-Wittke	Introduction into tumor biology
May 2011 (total 6h)	Prof. Uwe Zangemeister-Wittke	Human and dental medicine students: Molecular Cell Biology

3.2. Coordination PBL Medical Students, 3rd year (2011/2012)

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 2011/2012)

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

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. 12, 2011	Prof. Nicola Harris Swiss Vaccine Res. Institute, Lausanne (CH)	Antibody-mediated immunity against gastro-intestinal helminths
Jan. 17, 2011	Prof. David Smith Dept. of Biochemistry, Atlanta, Georgia (USA)	From glycan microarrays to shotgun glycomics
Jan. 18, 2011	Dr. Irina Lehmann Zentrum für Umweltforschung (UFZ), Helmholtz Centre, Leipzig (D)	Impact of indoor air pollutants on immune regulation and allergy development
Febr. 23, 2011	Prof. Christoph Thiemermann The William Harvey Res. Inst., London (UK)	Beneficial effects of PPAR-beta agonists in shock
March 2, 2011	Prof. Matthias Schwab Dr. M. Fischer-Bosch-Institut für Klinische Pharmakologie, Stuttgart (D)	Pharmacogenomics of ADME genes
March 7, 2011	Prof. Hajime Karasuyama Dept. of Immune Regulation, Medical and Dental University, Tokyo (J)	Emerging roles of basophils in allergy and protective immunity: a neglected minority gains new respect
April 6, 2011	Prof. Christian Münz Inst. of Exp. Immunology, University of Zurich	Human NK cell compartments and their activation by dendritic cells
June 17, 2011	Prof. Beat Schwaller Department of Anatomy, University of Fribourg (CH)	Calcium-binding proteins are part of a cell's calcium homeostasome: implications for signaling and remodeling
July 14, 2011	Prof. Bruce S. Bochner Div. Allergy & Clin. Immunol. Johns Hopkins Asthma & Allergy Center Baltimore, MD, USA	Alteration of eosinophil survival by targeting Siglec-8 and Siglec-F and their sialylated pulmonary glycan ligands
July 27, 2011	Dr. R. Lukowski Institute of Pharmacy, University of Tübingen (D)	Modulating cGMP kinase I signaling in mouse models of hypertrophic cardio-myopathy
Sept. 7, 2011	Dr. David Spirk Sanofi-Aventis (Schweiz) AG	Antithrombotic Therapy and Anticoagulation

Oct. 19, 2011	Dr. Bertrand Huard Pathology-Immunology Med. University Centre & Hematology, University Hospitals Geneva	Myelopoiesis controls antibody-producing cell survival
Nov. 2, 2011	Prof. Benjamin Gantenbein ARTORG Center for Biomedical Engineering Res., Institute for Surgical Technology and Biomechanics, University of Bern	The intervertebral disc - can we regenerate or repair ?
Dec. 7, 2011	Dr. Yitzhak Zimmer Dep. of Clin. Research, University of Bern	Targeting MET - impact on DDR signaling and the relevance of Ras mutations for tumor cell response to anti MET treatment
Dec. 15, 2011	Prof. Nobuhiro Yuki Dep. of Microbiology and Medicine, Nat. University of Singapore	Gangliosides – their role in pathogenesis and treatment of immune-neuropathies

3.5. Inaugural Lectures **(Venia Docendi)**

Date	**Lecturer**	**Title**
Oct. 4, 2011	Prof. Thomas Kaufmann Institute of Pharmacology, University of Bern	Fascination cell death: Many ways and reasons for a cell to die

3.6. Bern Immunology Club (BIC)

Date	Teacher	Title of the seminar
Jan. 26, 2011	Dr. Isabelle Schepens Universitätsklinik für Dermatologie Inselspital, Bern	Paraneoplastic pemphigus: Identification of the p170 antigen
Febr. 23, 2011	Prof. Klaus Peter Rippe Ethik im Diskurs, Zürich	Ethik des Lebens vs. Ethik des Todes – Die zwei Gesichter der modernen Bioethik
April 6, 2011	Dr. Kathy McCoy Dept. Clinical Research, University of Bern	Hygiene-mediated immune dysregulation
April 27, 2011	Dr. Mariagrazia Uguccioni Institute for Research in Biomedicine, Bellinzona (CH)	Synergy-inducing chemokines: a new model for chemokine interactions
May 25, 2011	PD Dr. Artur Summerfield Institute of Virology and Immunoprophylaxis (IVI), Mittelhaeusern (CH)	Plasmacytoid dendritic cells at the frontline of pathogen attack: lessons from pigs
June 29, 2011	Prof. Burkhard Möller & Prof. Clemens Dahinden University of Bern	Clinical Immunology Conference
Sept. 28, 2011	Prof. Jörg Seebach Dept. Internal Medicine, Immunology and Allergy, University of Geneva	Effect of immunosuppressive drugs on the function of NK and T regulatory cells
Oct. 26, 2011	Dr. Philippe Krebs Dept. of Genetics, The Scripps Res. Institute, La Jolla (USA)	Cross-talk of innate and adaptive immunity in sterile and infectious conditions
Nov. 30, 2011	Dr. Charaf Benarafa & Dr. Christophe von Garnier University of Bern	Best of 2011: 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_12/index_eng.html

3.7. Academic Degrees

Cristina Claudia Mihalache, PhD, University of Bern
Thesis: A novel CD44-mediated death pathway in human neutrophils
Institute of Pharmacology, Bern, May 2011
Supervisor: Prof. Hans-Uwe Simon

Dipak Maskey, PhD, University of Bern
Thesis: Nuclear localization and function of autophagy-related gene 5 (Atg5) during chemotherapy
Institute of Pharmacology, Bern, November 2011
Supervisors: Prof. Hans-Uwe Simon and Prof. Shida Yousefi

Stephanie Felder, Dr. med. (MD), University of Bern
Thesis: Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis
Institute of Pharmacology, Bern, July 2011
Supervisor: Prof. Hans-Uwe Simon

Simon Städler, Dr. med. (MD), University of Bern
Thesis: Eosinophil skin diseases: Investigation of eotaxins and TGF-β
Institute of Pharmacology, Bern, April 2011
Supervisor: Prof. Dagmar Simon

Matthias Stuck, MMed, University of Bern
Thesis: A systematic literature review of Foxp3 expression in Th2-mediated inflammatory disorders
Institute of Pharmacology, Bern, Sept. 2011
Supervisor: Prof. Hans-Uwe Simon

Carla Aeberhard, M.Sc. Pharm., University of Basel
Thesis: Th17 cells and remodelling in eczema
Institute of Pharmacology, Bern, June 2011
Supervisors: Prof. Dagmar Simon and Prof. Hans-Uwe Simon

Andy Gerber, M.Sc.pharm, University of Basel
Thesis: The role of ATG5 in myeloid cell differentiation
Institute of Pharmacology, Bern, June 2011
Supervisor: Prof. Hans-Uwe Simon

Nicole Drewes, M.Sc.pharm, University of Basel
Thesis: Pharmacological inactivation of serine proteases in human neutrophils
Institute of Pharmacology, Bern, June 2011
Supervisors: Dr. Sebastien Conus and Prof. Hans-Uwe Simon

Livia Mangold, M.Sc.pharm, University of Basel
Thesis: Role of Atg5 in TNF-death signalling
Institute of Pharmacology, Bern, June 2011
Supervisors: Prof. Shida Yousefi and Prof. Hans-Uwe Simon

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

Group members: Daniel Fallegger, PhD student[1]
Iuliia Filipenko, PhD student[1]
Faik Imeri, PhD student[1]
Oleksandr Pastukhov, PhD student[1]
Marianne Maillard-van Laer, technician[1]
Stephanie Schwalm, Postdoc[2]
Mahsa Ebadi, PhD student[2]
Ankathrin Förster, PhD student[2]
Isolde Römer, technician[2]
Svetlana Bubnova, 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 (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.

Loss of sphingosine kinase-1 in carcinoma cells increases reactive oxygen species formation and sensitizes to drug-induced DNA damage.
A. Huwiler, N. Kotelevets, C. Xin, O. Pastukhov, J. Pfeilschifter, U. Zangemeister-Wittke
BACKGROUND AND PURPOSE: Sphingosine kinases (SK) catalyse the formation of sphingosine 1-phosphate, which is a key lipid mediator regulating cell responses such as proliferation, survival and migration. Here we have investigated the effect of targeted inhibition of SK-1 on cell damage and elucidated the mechanisms involved. EXPERIMENTAL **APPROACH:** Three human carcinoma cell lines (colon HCT-116, breast MDA-MB-231, lung NCI-H358) were used, which were either transduced with shRNA constructs to deplete SK-1, or treated with a SK-1 inhibitor. Cell growth and viability were assayed by [(3) H] thymidine incorporation and colony formation. Reactive oxygen species (ROS) were measured by fluorescence and apoptosis by annexin V with flow cytometry. Proteins were analysed by Western blotting. DNA damage was induced by doxorubicin. **KEY RESULTS**: Knock-down of SK-1 by shRNA strongly inhibited DNA synthesis and colony formation of carcinoma cells.

SK-1 knock-down (SK-1kd) cells revealed dysfunctional extracellular signal-regulated protein kinase and PKB/Akt cascades, and contained increased levels of ROS. After SK-1kd, treatment with doxorubicin increased DNA damage, measured by histone-2AX phosphorylation. Similar effects were found in cells with a SK-1 inhibitor and doxorubicin. The increased damage response in SK-1kd cells was accompanied by greater reduction of DNA synthesis and colony formation, and by more pronounced apoptosis. Addition of a NADPH oxidase inhibitor reduced the increased apoptosis in doxorubicin-treated SK-1kd cells. **CONCLUSIONS AND IMPLICATIONS:** SK-1kd in carcinoma cells triggered oxidative stress by increasing intracellular Ros production. Targeted inhibition of SK-1 represents a promising approach to sensitize cells to DNA damage and facilitate apoptosis upon doxorubicin treatment.
See original publication No. 1

A prokaryotic S1P lyase degrades extracellular S1P in vitro and in vivo: implication for treating hyperproliferative disorders
A. Huwiler, F. Bourquin, N. Kotelevets, O. Pastukhov, G. Capitani, M.G. Grütter, U. Zangemeister-Wittke
Sphingosine-1-phosphate (S1P) regulates a broad spectrum of fundamental cellular processes like proliferation, death, migration and cytokine production. Therefore, elevated levels of S1P may be causal to various pathologic conditions including cancer, fibrosis, inflammation, autoimmune diseases and aberrant angiogenesis. Here we report that S1P lyase from the prokaryote Symbiobacterium thermophilum (StSPL) degrades extracellular S1P in vitro and in blood. Moreover, we investigated its effect on cellular responses typical of fibrosis, cancer and aberrant angiogenesis using renal mesangial cells, endothelial cells, breast (MCF-7) and colon (HCT 116) carcinoma cells as disease models. In all cell types, wild-type StSPL, but not an inactive mutant, disrupted MAPK phosphorylation stimulated by exogenous S1P. Functionally, disruption of S1P receptor signaling by S1P depletion inhibited proliferation and expression of connective tissue growth factor in mesangial cells, proliferation, migration and VEGF expression in carcinoma cells, and proliferation and migration of endothelial cells. Upon intravenous injection of StSPL in mice, plasma S1P levels rapidly declined by 70% within 1 h and then recovered to normal 6 h after injection. Using the chicken chorioallantoic membrane model we further demonstrate that also under in vivo conditions StSPL, but not the inactive mutant, inhibited tumor cell-induced angiogenesis as an S1P-dependent process. Our data demonstrate that recombinant StSPL is active under extracellular conditions and holds promise as a new enzyme therapeutic for diseases associated with increased levels of S1P and S1P receptor signaling.
See original publication No. 2

Original publications

1. **A. Huwiler**, N. Kotelevets, C. Xin, O. Pastukhov, J. Pfeilschifter, U. Zangemeister-Wittke: Loss of sphingosine kinase-1 in carcinoma cells increases reactive oxygen species formation and sensitizes to drug-induced DNA damage.
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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, JB Kerr, LA 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 amino acid 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 Eμ-*Myc* transgenic mice. Collectively, these results indicate that *Bok* may play 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

Original publications

1. F. Ke, A. Voss, JB Kerr, LA 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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Review articles

1. S. von Gunten, **T. Kaufmann**: Glucocorticoids "On Air".
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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 2011.

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

Inflammation-associated autophagy-related programmed necrotic death of human neutrophils characterized by organelle fusion events
C.C. Mihalache, S. Yousefi, S. Conus, P.M. Villiger, E.M. Schneider, H.-U. Simon
The most common form of neutrophil death, under both physiological and inflammatory conditions, is apoptosis. Here, we report a novel form of programmed necrotic cell death, associated with cytoplasmic organelle fusion events, that occurs in neutrophils exposed to granulocyte/macrophage colony-stimulating factor (GM-CSF) and other inflammatory cytokines upon ligation of CD44. Strikingly, this type of neutrophil death requires phosphatidylinositol 3'-kinase (PI3K) activation, a signalling event usually involved in cellular survival pathways. In the death pathway reported here, PI3K is required for the generation of reactive oxygen species (ROS), which somehow trigger the generation of large cytoplasmic vacuoles, generated by the fusion of CD44-containing endosomes with autophagosomes and secondary, but not primary, granules. Neutrophils demonstrating vacuolization undergo rapid cell death that depends on receptor-interacting protein 1 (RIP1) kinase activity and papain family protease(s), but not caspases, that are most likely activated and released, respectively, during or as a consequence of organelle fusion. Vacuolized neutrophils are present in infectious and autoimmune diseases under *in vivo* conditions. Moreover, isolated neutrophils from such patients are highly sensitive toward CD44-mediated PI3K activation, ROS production, and cell death, suggesting that the newly described autophagy-related form of programmed neutrophil necrosis plays an important role in inflammatory responses.
See original publication No. 2

A novel TNFR1-triggered apoptosis pathway mediated by class 1A PI3Ks in neutrophils
B. Geering, U. Gurzeler, E. Federzoni, T. Kaufmann, H.-U. Simon
The most common form of neutrophil death is apoptosis. Here, we report surprising differences in the molecular mechanisms used for caspase activation between FAS/CD95- and TNF receptor 1 (TNFR1)-stimulated neutrophils. Whereas FAS-induced apoptosis was followed by caspase-8 activation and required Bid to initiate the mitochondrial amplification loop, TNF-α-induced apoptosis strikingly involved class IA phosphoinositide 3-kinases (PI3Ks), which were activated by mitogen-activated protein kinase p38. TNF-α-induced PI3K activation resulted in the generation of reactive oxygen species, which activated caspase-3, a

mechanism that did not operate in neutrophils without active NADPH oxidase. Taken together, in neutrophils, pro-apoptotic pathways following TNFR1 stimulation are initiated by p38 and PI3K, but not caspase-8, a finding that should be considered in anti-inflammatory drug development strategies.
See original publication No. 3

Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis
A. Straumann, S. Conus, L. Degen, C. Frei, C. Bussmann, C. Beglinger, A. Schoepfer, H.-U. Simon
BACKGROUND & AIMS: Topical corticosteroids have proven highly effective in inducing clinical and histologic remission in eosinophilic esophagitis (EoE). However, the long-term management of this chronic-inflammatory disease is not yet defined. **METHODS:** In a randomized, double-blind, placebo-controlled, 50-week trial, we evaluated in 28 patients the efficacy of twice daily 0.25 mg swallowed budesonide to maintain quiescent EoE in remission. Pre- and post-treatment activity was assessed clinically, endoscopically, histologically, immuno-histologically and by endosonography. The primary endpoint was the therapy's ability to maintain EoE in histologic remission. Secondary endpoints were the efficacy in symptom control, in preventing tissue remodeling and safety. **RESULTS:** Despite low-dose budesonide, the esophageal eosinophil load increased from 0.4 to 31.8 eosinophils/hpf (*P*=.017), but with placebo the increase was significantly larger (*P*=.024), from 0.7 to 65.0 eosinophils/hpf; (*P*=.0001). The symptom scores in the two groups developed in a similar manner. Moreover, budesonide, but not placebo, reduced non-eosinophilic markers of inflammation, epithelial cell apoptosis and remodeling events. Compared to controls, patients had a significantly thickened esophageal wall in endosonography (3.05 mm vs. 2.18 mm; *P*<.0001). Budesonide therapy was associated with a significant reduction of the mucosal thickness (0.75 mm to 0.45 mm; *P*=.025), but epithelial thickness remained stable (261.22 µm vs. 277.23 µm; *P*=.733). No serious adverse events occurred. **CONCLUSIONS:** Low-dose budesonide was beneficial compared with placebo in maintaining EoE in histologic and clinical remission. Signs of esophageal remodeling showed a trend toward normalization. Long-term administration of topical corticosteroids was well-tolerated without inducing epithelial atrophy.
See original publication No. 4

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Comment in: Clin. Gastroenterol. Hepatol. 9 (2011), 370-372 (Alexander JA and Katzka DA)

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2. T. Bieber, **H.-U. Simon**: Allergen-specific immunotherapy: current concepts and future directions.
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3. B. Geering, **H.-U. Simon**: A novel signaling pathway in TNFα-induced neutrophil apoptosis.
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6. J. Bousquet, J.M. Anto, P.J. Sterk, ..., **H.-U. Simon**, ..., C. Auffray: Systems medicine and integrated care to combat chronic noncommunicable diseases.
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8. L. Galluzzi, I. Vitale, J.M. Abrams, ..., **H.-U. Simon**, ..., G. Kroemer: Molecular definitions of cell death subroutines: recommendations of the nomenclature committee on cell death 2012.
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9. C. Mihalache, **H.-U. Simon**: Autophagy regulation in macrophages and neutrophils.
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11. A. Klion, **H.-U. Simon**: Therapeutic approaches to patients with hypereosinophilic syndrome.
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12. **H.-U. Simon**, B. Levin: Autophagy in myocardial differentiation and cardiac development.
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J. Allergy Clin. Immunol., in press.

Book chapter

1. D. Simon, **H.-U. Simon**: Eosinophils in autoimmune bullous diseases. In: Autoimmune diseases of the skin, 3rd edition (Ed. M. Hertl); Springer, Wien - New York, 2011, p. 505-515.

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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. The group leader 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.

Dimeric IVIG contains natural anti-Siglec-9 autoantibodies and their anti-idiotypes
A. Schaub, S. von Gunten, M. Vogel, S. Wymann, M. Rüegsegger, B.M. Stadler, M. Spycher, H.-U. Simon, S. Miescher
(Collaboration with CSL Behring AG, Bern, and Institute of Immunology, Univ. of Bern)
Background: Intravenous immunoglobulin (IVIG) preparations are increasingly used for the treatment of allergic and autoimmune diseases. Naturally occurring autoantibodies against Siglec-9 and Fas are thought to contribute to the anti-inflammatory effects of IVIG via cell death regulation of leukocytes and tissue cells. Dimeric IVIG fractions are suspected to contain idiotypic (Id)-anti-idiotypic complexes of antibodies, which might also include anti-Siglec-9 and anti-Fas autoantibodies. **Methods:** Dimeric IVIG fractions were separated from monomeric IVIG by size exclusion chromatography and remonomerized by low pH treatment. Binding studies of total, monomeric and dimeric IVIG were performed using surface plasmon resonance and flow cytometry on primary human neutrophils. **Results:** Anti-Siglec-9 and anti-Fas autoantibodies were contained in both monomeric and dimeric IVIG fractions, but anti-Siglec-9 antibodies were highly enriched in dimeric IVIG. The propensity to engage in dimer formation was paratope-dependent. IVIG binding to Siglec-9 was specific and sialylation-independent. Interestingly, we detected anti-idiotypic antibodies (anti-Ids) against anti-Siglec-9 autoantibodies in dimeric, but not in monomeric fractions of IVIG. **Conclusions:** Our study supports the concept that idiotype-anti-idiotype (Id-anti-Id) interactions contribute to the dimer formation in IVIG preparations. To our knowledge this is the first description of Id-anti-Id dimers of death receptor-specific antibodies in IVIG. Such Id-anti-Id interactions might determine the activity of immunomodulatory antibodies present both in IVIG and the patient.
See original publication No. 1

Original publications

1. A. Schaub,* **S. von Gunten,*** M. Vogel, S. Wymann, M. Rüegsegger, B.M. Stadler, M. Spycher, H.-U. Simon, S. Miescher: Dimeric IVIG contains natural anti-Siglec-9 autoantibodies and their anti-idiotypes.
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4. S.J. North, **S. von Gunten**, A. Antonopoulos, A. Trollope, D.W. Jr. Macglashan, J. Jang-Lee, A. Dell, D.D. Metcalfe, A.S. Kirshenbaum, B.S. Bochner, S.M. Haslam: Glycomic analysis of human mast cells, eosinophils and basophils.
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Review articles

1. C. Jandus, H.-U. Simon, **S. von Gunten**: Targeting siglecs--a novel pharmacological strategy for immuno- and glycotherapy.
   Biochem. Pharmacol. 15 (2011), 323 - 332.

2. **S. von Gunten**, T. Kaufmann: Glucocorticoids "On Air".
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European Patent Office Application: 10194942.8 - 2406

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Jennifer Mildenberger, 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 and neutrophils.

Eosinophil and neutrophil extracellular DNA traps in human allergic asthmatic airways
R. Dworski, H.-U. Simon, A. Hoskins, S. Yousefi
BACKGROUND: Asthma is a heterogeneous inflammatory airway disorder that involves eosinophilic and noneosinophilic phenotypes. Unlike in healthy lungs, eosinophils are often present in atopic asthmatic airways, although a subpopulation of asthmatic subjects predominantly experience neutrophilic inflammation. Recently, it has been demonstrated that eosinophils and neutrophils generate bactericidal extracellular traps consisting of DNA and cytotoxic granule proteins.
OBJECTIVE: We sought to explore whether living eosinophils and neutrophils infiltrating human atopic asthmatic airways actively form extracellular DNA traps in vivo.
METHODS: Quantitative analysis of eosinophils releasing DNA was performed in endobronchial biopsy specimens from 20 human subjects with mild atopic asthma at baseline and after local allergen challenge and 10 healthy subjects. DNA was stained with propidium iodine and major basic protein with specific antibody. Differential cell counts and cytokines/chemokines were assessed in bronchoalveolar lavage fluid.
RESULTS: Asthmatic airways were infiltrated with a significantly higher number of eosinophils than healthy airways (39.3 ± 4.6 vs 0.4 ± 0.9, $P < .0001$). All asthmatic subjects but only 1 control subject expressed eosinophils releasing DNA that colocalized with major basic protein (33.65 ± 20.33 vs 0.3 ± 0.9 per high-power field, $P < .0001$). Four asthmatic subjects mostly expressed neutrophilic inflammation and neutrophil DNA traps. Allergen challenge had no significant quantitative effect on eosinophil or neutrophil DNA traps. Airway

eosinophils or DNA traps did not correlate with either bronchoalveolar lavage levels of IL-5, IFN-γ, or eotaxin or the provoking doses of methacholine or allergen in asthmatic subjects.
CONCLUSIONS: Extracellular DNA traps are generated by eosinophils and neutrophils in human atopic asthmatic airways in vivo. The mechanism and role of this new finding will necessitate further investigation.
See original publication No. 1

Eosinophil extracellular DNA traps in skin diseases
D. Simon, S. Hoesli, N. Roth, S. Staedler, S. Yousefi, H.-U. Simon
BACKGROUND: In the skin, eosinophils are found in a broad spectrum of diseases, including infectious diseases. **OBJECTIVE:** In this study, we investigated whether eosinophil extracellular traps, structures containing DNA in association with eosinophil granule proteins able to bind and kill bacteria, are present in the skin under various pathologic conditions. **METHODS:** Immunofluorescence staining was performed on sections of paraformaldehyde-fixed and paraffin-embedded skin biopsy tissues of 25 different eosinophilic skin diseases by using propidium iodide and an antibody to eosinophil cationic protein. Slides were evaluated by laser scanning microscopy. **RESULTS:** Eosinophils releasing DNA together with eosinophil cationic protein were detected in infectious skin diseases such as ectoparasitosis and larva migrans. Further, we observed the extracellular DNA structures in allergic/reactive diseases (Wells syndrome, hypereosinophilic syndrome, positive reaction of atopy patch test, allergic contact dermatitis, drug hypersensitivity) and in autoimmune diseases (bullous pemphigoid, pemphigus foliaceus, dermatitis herpetiformis). The average number of eosinophils releasing DNA in the skin was usually below 10%, although in Wells syndrome the proportion was up to 30%. In areas with clusters of eosinophils, up to 50% of the eosinophils were seen to generate eosinophil extracellular traps. **CONCLUSION:** Eosinophil extracellular traps are seen in both infectious and noninfectious inflammatory skin diseases and are particularly common in Wells syndrome.
See original publication No. 2

Original publications

1. R. Dworski, H.-U. Simon, A. Hoskins, **S. Yousefi**: Eosinophil and neutrophil extracellular DNA traps in human allergic asthmatic airways
   J. Allergy Clin. Immunol. 127 (2011), 1260 - 1266.

2. D. Simon, S. Hoesli, N. Roth, S. Staedler, **S. Yousefi,** H.-U. Simon: Eosinophil extracellular DNA traps in skin diseases
   J. Allergy Clin. Immunol. 127 (2011), 194 - 199.

3. M.D. Sury, L. Vorlet-Fawer, C. Agrinis, **S. Yousefi**, D. Grandgirard, S.L. Lieb, S. Christen: Restoration of Akt activity by the bisperoxovanadium compound bpv (pic) attenuates bippocampal apoptosis in experimental neonatal pneumococcal meningitis.
   Neurobiol. Dis. 41 (2011), 201 - 208.

4. C.C. Mihalache, **S. Yousefi**, S. Conus, P.M. Villiger, E.M. Schneider, H.-U. Simon: Inflammation-associated autophagy-related programmed necrotic death of human neutrophils characterized by organelle fusion events
   J. Immunol. 186 (2011), 6532 - 6542.

5. 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. (2011), 1-4; doi:10.1038/cr.2011.200

6. 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., in press.

Group Prof. Uwe Zangemeister-Wittke

Group members: Nataliya Kotelevets, PhD
Vitalij Muzenko, M.Sc. ESKAS fellowship student
Manuel Simon, PhD student
Nikolas Stefan, PhD student[1]
Kevin Oberson, technician (30%)
Linda Vorak, Master student[1]

[1]Institute of Biochemistry, University of Zürich

Our research is focused on translational aspects in molecular oncology. We investigate mechanisms of drug resistance in solid tumors and try to identify sphingolipid signaling pathways and their regulators for molecular intervention to facilitate tumor cell death and design new therapeutic strategies. Major targets of interest are sphingosine kinase 1 and its prosurvival product sphingosine-1-phosphate (S1P). As a new approach to counteract the oncogenic potential of these signaling cascade we developed a recombinant enzyme, S1P lyase, which irreversibly degrades and depletes the pool of circulating S1P. This protein therapeutic has implication for the treatment of various hyperproliferative diseases associated with aberrant S1P signaling (PCT/EP2011/071446).

In a second project performed at the Institute of Biochemistry at Zurich University we focus on tumor-targeting using rationally engineered proteins as drug delivery systems. To this end, affinity-maturated Designed Ankyrin Repeat Proteins (DARPins) were developed as novel binding proteins with specificity for the tumor-associated antigen EpCAM. Using the DARPin compatible click chemistry in particular, we have developed various state-of-the-art nanomedicines comprising tumor-targeted biotoxins and synthetic nanoparticles equipped with cytotoxic or gene targeted payloads for intracellular drug delivery.

Three representative abstracts are shown which reflect our current research philosophy:

Loss of sphingosine kinase-1 in carcinoma cells increases reactive oxygen species formation and sensitizes to drug-induced DNA damage

A. Huwiler, N. Kotelevets, C. Xin, O. Pastukhov, J. Pfeilschifter, U. Zangemeister-Wittke

BACKGROUND AND PURPOSE: Sphingosine kinases (SK) catalyse the formation of sphingosine 1-phosphate, which is a key lipid mediator regulating cell responses such as proliferation, survival and migration. Here we have investigated the effect of targeted inhibition of SK-1 on cell damage and elucidated the mechanisms involved. **EXPERIMENTAL APPROACH:** Three human carcinoma cell lines (colon HCT-116, breast MDA-MB-231, lung NCI-H358) were used, which were either transduced with shRNA constructs to deplete SK-1, or treated with a SK-1 inhibitor. Cell growth and viability were assayed by [(3) H] thymidine incorporation and colony formation. Reactive oxygen species (ROS) were measured by fluorescence and apoptosis by annexin V with flow cytometry. Proteins were analysed by Western blotting. DNA damage was induced by doxorubicin. **KEY RESULTS**: Knock-down of

SK-1 by shRNA strongly inhibited DNA synthesis and colony formation of carcinoma cells. SK-1 knock-down (SK-1kd) cells revealed dysfunctional extracellular signal-regulated protein kinase and PKB/Akt cascades, and contained increased levels of ROS. After SK-1kd, treatment with doxorubicin increased DNA damage, measured by histone-2AX phosphorylation. Similar effects were found in cells with a SK-1 inhibitor and doxorubicin. The increased damage response in SK-1kd cells was accompanied by greater reduction of DNA synthesis and colony formation, and by more pronounced apoptosis. Addition of a NADPH oxidase inhibitor reduced the increased apoptosis in doxorubicin-treated SK-1kd cells. **CONCLUSIONS AND IMPLICATIONS:** SK-1kd in carcinoma cells triggered oxidative stress by increasing intracellular Ros production. Targeted inhibition of SK-1 represents a promising approach to sensitize cells to DNA damage and facilitate apoptosis upon doxorubicin treatment.

See original publication No. 1

A novel fusion toxin derived from an EpCAM-specific designed ankyrin repeat protein has potent antitumor activity

P. Martin-Killias, N. Stefan, S. Rothschild, A. Plückthun, U. Zangemeister-Wittke

Erratum in: Clin Cancer Res. 2011 Jun 1; 17(11): 3850. Patricia, Martin-Killias [corrected to Martin-Killias, Patricia].

PURPOSE: Designed ankyrin repeat proteins (DARPins) hold great promise as a new class of binding molecules to overcome the limitations of antibodies for biomedical applications. Here, we assessed the potential of an epithelial cell adhesion molecule (EpCAM)-specific DARPin (Ec4) for tumor targeting as a fusion toxin with Pseudomonas aeruginosa exotoxin A. **EXPERIMENTAL DESIGN**: DARPin Ec4 was genetically fused to a truncated form of Pseudomonas aeruginosa exotoxin A (ETA″) and expressed in Escherichia coli. The cytotoxicity of Ec4-ETA″ was measured against tumor cell lines of various histotypes in vitro. Tumor localization and antitumor activity were determined in mice bearing 2 different EpCAM-positive tumor xenografts. **RESULTS:** Ec4-ETA″ expressed very well in soluble form in the cytoplasm of E. coli and yielded up to 40 mg after purification per liter of culture. The protein was monomeric and the disulfides of ETA″ formed spontaneously. Ec4-ETA″ bound to EpCAM with low nanomolar affinity, similar to free Ec4. Furthermore, it was highly cytotoxic against various EpCAM-positive tumor cell lines in vitro with IC (50) values less than 0.005 pmol/L. This effect was competed by free Ec4, but not by unspecific DARPins. Upon systemic administration in athymic mice, Ec4-ETA″ efficiently localized to EpCAM-positive tumors to achieve maximum accumulation 48 to 72 hours after injection, whereas an irrelevant control fusion toxin did not accumulate. Tumor targeting with Ec4-ETA″ resulted in a strong antitumor response including complete regressions in some animals. **CONCLUSIONS:** Our data show for the first time the potential of DARPins for the generation of protein therapeutics for tumor targeting, and that Ec4-ETA″ deserves attention for clinical development.

See original publication No. 2

A prokaryotic S1P lyase degrades extracellular S1P in vitro and in vivo: implication for treating hyperproliferative disorders

A. Huwiler, F. Bourquin, N. Kotelevets, O. Pastukhov, G. Capitani, M.G. Grütter, U. Zangemeister-Wittke

Sphingosine-1-phosphate (S1P) regulates a broad spectrum of fundamental cellular processes like proliferation, death, migration and cytokine production. Therefore, elevated levels of S1P may be causal to various pathologic conditions including cancer, fibrosis, inflammation, autoimmune diseases and aberrant angiogenesis. Here we report that S1P lyase from the prokaryote Symbiobacterium thermophilum (StSPL) degrades extracellular

S1P in vitro and in blood. Moreover, we investigated its effect on cellular responses typical of fibrosis, cancer and aberrant angiogenesis using renal mesangial cells, endothelial cells, breast (MCF-7) and colon (HCT 116) carcinoma cells as disease models. In all cell types, wild-type StSPL, but not an inactive mutant, disrupted MAPK phosphorylation stimulated by exogenous S1P. Functionally, disruption of S1P receptor signaling by S1P depletion inhibited proliferation and expression of connective tissue growth factor in mesangial cells, proliferation, migration and VEGF expression in carcinoma cells, and proliferation and migration of endothelial cells. Upon intravenous injection of StSPL in mice, plasma S1P levels rapidly declined by 70% within 1 h and then recovered to normal 6 h after injection. Using the chicken chorioallantoic membrane model we further demonstrate that also under in vivo conditions StSPL, but not the inactive mutant, inhibited tumor cell-induced angiogenesis as an S1P-dependent process. Our data demonstrate that recombinant StSPL is active under extracellular conditions and holds promise as a new enzyme therapeutic for diseases associated with increased levels of S1P and S1P receptor signaling.
See original publication No. 3

Original publications

1. A. Huwiler, N. Kotelevets, C. Xin, O. Pastukhov, J. Pfeilschifter, **U. Zangemeister-Wittke**: Loss of sphingosine kinase-1 in carcinoma cells increases reactive oxygen species formation and sensitizes to drug-induced DNA damage.
   Br. J. Pharmacol. 162 (2011), 532 - 543.

2. P. Martin-Killias, N. Stefan, S. Rothschild, A. Plueckthun, **U. Zangemeister-Wittke**:
   A novel fusion toxin derived from an EpCAM-specific designed ankyrin repeat protein has potent antitumor activity.
   Clin. Cancer Res. 17 (2011), 100 - 110.

3. A. Huwiler, F. Bourquin, N. Kotelevets, O. Pastukhov, G. Capitani, M.G. Grütter, **U. Zangemeister-Wittke**: A prokaryotic S1P lyase degrades extracellular S1P in vitro and in vivo: implication for treating hyperproliferative disorders.
   PLoS One 6(8) (2011), e22436. doi:10.1371/journal.pone.0022436

4. A. Lange, H. Gustke, G. Glassmeier, M. Heine, **U. Zangemeister-Wittke**, J.R. Schwarz, U. Schumacher, T. Lange: Neuronal differentiation by indomethacin and IBMX inhibits proliferation of small cell lung cancer cells in vitro.
   Lung Cancer 4 (2011), 178 - 187.

5. N. Stefan, P. Martin-Killias, S. Wyss-Stoeckle, A. Honegger, **U. Zangemeister-Wittke**, A. Plueckthun: DARPins recognizing the tumor-associated antigen EpCAM selected by phage and ribosome display and engineered for multivalency.
   J. Mol. Biol. 413 (2011), 826 - 843.

6. M. Simon, **U. Zangemeister-Wittke**, A. Plueckthun: Facile double-functionalization of Designed Ankyrin Repeat Proteins using click and thiol chemistries.
   Bioconjug. Chem., in press.

Patent application

U. Zangemeister-Wittke, A. Huwiler, F. Bourquin, M. Grütter: Use of prokaryotic sphingosine-1-phosphate lyases and of sphingosine-1-phosphate lyases lacking a transmembrane domain for treating hyperproliferative and other diseases. PCT/EP2011/071446

Additional Publications by PKI Members

PD Dr. Peter Späth

Original articles

P.J. Späth, T. Hunziker: Will immunoglobulin therapy of autoimmune blistering skin diseases survive the new financial management of inpatients?
Dermatol. 22 (2011), 138 -139.

N. Yuki, H. Watanabe, T. Nakajima, **P.J. Späth**: IVIG blocks complement deposition mediated by anti-GM1 antibodies in multifocal motor neuropathy
J. Neurol. Neurosurg. Psych. 82 (2011), 87 – 91.

Reviews

M. Delforge, C.M. Farber, **P. Späth**, S. Kavers, T. Witte, S.A. Misbah, R. Hübner, F. Haerynck, D. Latinne, L. Muyelle, M. Toungouz, V. Deneys: Recommended indications for the administration of polyclonal immunoglobulin preparations.
Acta Clin. Belg. 66 (2011), 346 - 360.

P. J. Späth: Highlights from the 7th C1 Inhibitor Deficiency Workshop, Budapest, Hungary.
J. Angioedema 1 (2011), 7 - 12.

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., in press. doi:10.1002/eji.201142064

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, in press. doi: 10.1002/ijc.26297

4.2. Congress Invitations

Prof. Hans-Uwe Simon

Deutsche Gesellschaft für Dermatologie und Venerologie, Arbeitsgemeinschaft Dermatologische Forschung (ADF); Tübingen (D), February 17-19, 2011;
Eos WANTED - dead or alive?

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI); San Francisco, CA (USA), March 18-22, 2011;
Programmed granulocyte necrosis.

Swiss Society of Dermatology and Venerology; Bern (CH), May 5-6, 2011;
EADV lecture: Eosinophilic syndromes, new definition of hypereosinophilic syndromes.

Working conference on eosinophil disorders and syndromes; Vienna (A), May 27-28, 2011;
Mechanisms underlying eosinophilia in atopic disorders and HES.

30th Congress of the European Academy of Allergy and Clinical Immunology (EAACI), Istanbul (Turkey), June 11-15, 2011;
Effector functions of eosinophils.

7th Biennial Symposium of the International Eosinophil Society (IES), Québec (Canada), June 22-25, 2011;
Eosinophils and extracellular traps.

10th World Congress on Inflammation, Paris (F), June 25-29, 2011;
Apoptosis, autophagy and inflammation.

Workshop on Cell Death, Villa Vigoni, Loveno di Menaggio, Como (I), June 29 - July 2, 2011;
From apoptosis and autophagy to inflammation (and cancer).

19th Euroconference on Apoptosis (ECDO), Stockholm (Sweden), Sept. 14-17, 2011;
Autophagy and its assessment in mammalian cells.

Leopoldina Minisymposium der Sektion Pharmakologie/Physiologie, Halle (D), Sept. 22, 2011;
Autophagy and cancer.

4th BBBB International Conference on Pharmaceutical Sciences, Bled (Slovenia), Sept. 29 - Oct. 1, 2011;
Old and new allergic diseases: From diagnosis to drug therapy.

13. Jahreskongress für Klinische Pharmakologie, Zurich (CH), Oct. 20-22, 2011;
Personalisierte Medizin: Neue Aufgaben für die Pharmakologie.

European Academy of Dermatology and Venereology (EADV)-Workshop: Chronic inflammation and autoimmunity, Bellinzona (CH), Nov. 11, 2011;
Autophagy and cancer.

A. Menarini Diagnostics Int. Symposium on Autoimmunity, Lisbon (Portugal), Dec. 2-3, 2011;
Therapeutic targeting of eosinophils.

PD Dr. Peter Späth

2nd Congress of the Romanian Society of Allergology and Clinical Immunology, Cluj, Romania, May 6 - 7, 2011;
Bradykinin-mediated, non-allergic recurrent angioedema associated or not with C1-esterase inhibitor deficiency.

7th C1 Inhibitor Deficiency Workshop, Budapest, Hungary, May 20 - 22, 2011;
Closing remarks and summary of the workshop achievements.

4.3. Seminar Invitations

Prof. Hans-Uwe Simon

National Jewish Health, Department of Medicine, Division of Allergy and Immunology, Denver (CO, USA), March 23, 2011; guest of Prof. Rafeul Alam:
Eosinophils WANTED: Dead or Alive?

University of Konstanz, Graduiertenkolleg RTG 1331, Konstanz (D), April 7, 2011; guest of PD Dr. Daniel Legler:
From apoptosis and autophagy to inflammation.

University of Tübingen, Department of Dermatology, Tübingen (D), May 11, 2011; guest of Prof. Mark-Jürgen Berneburg:
Autophagy, stem cells and cancer.

University of Magdeburg, Department of Internal Medicine, Magdeburg (D), Oct. 13, 2011; guest of Prof. Peter Mertens:
Programmed necrosis - a novel type of death in inflammatory neutrophils.

University of Freiburg, Department of Experimental and Clinical Pharmacology and Toxicology, Freiburg (D), Nov. 8, 2011; guest of Prof. Klaus Aktories:
Roles of autophagy-related protein ATG5 in tumorigenesis and anticancer drug therapy.

University of Zurich, Institute of Experimental Immunology, Cutting Edge Topics: Immunology and Infection Biology, Zurich (CH), Nov. 22, 2011; guest of Prof. Dr. Christian Münz:
Autophagy and cancer.

Actelion Pharmaceuticals Ltd, Allschwil (CH), Dec. 22, 2011; guest of Dr. Hans Hoogkamer:
From HES to CSS.

PD Dr. Peter Späth

University Hospital Freiburg i.Br., Freiburg, Germany; Center for Chronic Immunodeficiencies Fellow Seminars, Oct. 27, 2011:
Complement Deficiencies - How to Diagnose & Treat.

Dr. Stephan von Gunten

Ludwig Center for Cancer Research of the University of Lausanne, Lausanne (CH), Nov. 29, 2011; guest of Prof. Pedro Romero:
Immunoregulation by Siglec receptors: novel insights and therapeutic perspectives.

CSL Behring AG, Bern (CH), Dec. 14, 2011:
Neutrophil death regulation by IgA and its receptor CD89 (I).

Dr. Marc Wehrli

CSL Behring AG, Bern (CH), Dec. 14, 2011:
Neutrophil death regulation by IgA and its receptor CD89 (II).

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 - Pharmacology of Pain, Bern (CH),
Jan. 27, 2011

10th III-International Summer School, Sigriwil (CH), Aug. 21 – 23, 2011

Bern Immunology Club (together with the other founder members); Institute of Pharmacology, University of Bern, one meeting in each month of 2011

Prof. Shida Yousefi

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis, Bern (CH), April 20 - 21, 2011.

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis, Bern (CH), Nov. 1 - 2, 2011.

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 - Pharmacology of Pain, Morning session;
Bern (CH), Jan. 27, 2011.

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI);
Session: "Novel aspects of cell death regulation in inflammation";
San Francisco (CA, USA), March 18-22, 2011.

Working Conference on Eosinophilic Disorders and Syndromes; Session: "Clinical Immunology and Disease Heterogeneity";
Vienna (A), May 27-28, 2011.

30th Congress of the European Academy of Allergy and Clinical Immunology (EAACI);
Workshop 6: "New approaches for hypereosinophilic syndromes";
Istanbul (Turkey), June 11-15, 2011.

Workshop on Cell Death in Innate and Adaptive Immunity and Cancer; Session 1: "Cell death and inflammation";
Villa Vigoni, Loveno di Menaggio, Como (I), June 29 - July 02, 2011.

19th Euroconference on Apoptosis; Session 8: " Biochemistry and physiology of cell death III";
Stockholm (SE), Sept. 14-17, 2011.

19th Euroconference on Apoptosis; EDCO key note lecture (M.G. Rosenfeld);
Stockholm (SE), Sept. 14-17, 2011.

PD Dr. Peter Späth

International Plasma Protein Congress; Session 7: Therapy development;
Lisbon, Portugal, March 15–16, 2011.

Summer School for Pediatricians, Charité; Session: "Case presentations 4";
Berlin, Germany, June 24-25, 2011.

4.6. Referee Work for Peer-Reviewed Journals

Dr. Sébasien Conus

Cell Death Differ.
Allergy

Dr. Barbara Geering

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

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.
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
FEBS Lett.

Prof. Thomas Kaufmann

Apoptosis
Allergy
Cell Commun. Signal.
Cell Death Differ.
Cell Death Dis.
Front. Mol. Cell. Oncol.
Hepatol.
Immunol. Cell Biol.
J. Hepatol.
Oncogene
PLoS One

Dr. Christina Merz-Stöckle

Allergy
Int. Arch. Allergy Immunol.

Prof. Hans-Uwe Simon

Allergy
Am. J. Physiol. - Lung Cell Mol. Physiol.
Apoptosis
Autophagy
Biochem. Pharmcol.
Blood
Cell Biol. Toxicol.
Clin. Exp. Allergy
EMBO Journal
EMBO Reports
Eur. J. Haematol.
Eur. J. Immunol.
FASEB J.
Cell Death Differ.
Cytokine
Nature Chem Biol.
Infect. Immun.
J. Clin. Invest.
J. Allergy Clin. Immunol.
J. Cell Biol.
J. Exp. Med.
J. Immunol.
J. Leukoc. Biol.
Lancet
N. Engl. J. Med.
Plant Sciences
Proc. Natl. Acad. Sci. USA
Trends Immunol.
Trends Pharmacol. Sci.
Cell Death Dis.
Mitochondrion

PD Dr. Peter Späth

Allergy

Dr. Stephan von Gunten

Allergy
Cell Death Differ.
Cell Death Dis.
J. Immunotoxicol.

Prof. Shida Yousefi

Allergy
Autophagy
Arch. Biochem. Biophys.
Cell Death Differ.

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)
Norwegian Research Council

Prof. Thomas Kaufmann

Agence Nationale de la Recherche (ANR), France
Swiss Cancer League
Swiss National Science Foundation

Prof. Hans-Uwe Simon

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

Dr. Stephan von Gunten

Swiss Cancer League

Prof. Uwe Zangemeister-Wittke

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

4.8. Awards

Dr. Nicola Andina

Award of the Buergi Price 2011
Swiss Society of Pharmacology and Toxicology (SSPT)
Zürich, April 28, 2011

Dr. Christina Merz-Stöckle

Young Investigator Award
7th Biennial International Symposium of the International Eosinophil Society (IES)
Québec (Canada), June 21–25, 2011

Nohemy Echeverry

Best Poster Award
19th European Cell Death Organization Meeting (ECDO)
Stockholm (S), September 14–17, 2011

5. Administrative, Advisory, and Honorary Posts

Dr. Sébastien Conus

Webmaster of the PKI

Coordinator for Chemicals at the PKI

Zhaoyue He

Coordinator for PC work 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 at the PKI

Prof. Hans-Uwe Simon

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

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), 2009-2011

Member of the Cells and Cytokine Committee (Workshops) of the American Academy of Allergy, Asthma and Immunology (AAAAI), 1997-2013

Member of the Council of the Swiss Society of Experimental Pharmacology (SSEP), 2006-2012

President-elect, International Eosinophil Society (IES), 2011-2013

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

Member of the Advisory Board of the Max and Elsa Beer-Brawand-Fonds, since 2009

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)

Member of the Scientific Committee, Swiss Cancer League, 2009 – 2014

Member of Scientific Advisory Board, HELMHOLTZ Zentrum für Umweltforschung (UFZ), Leipzig (D), 2009-2014

Member of the Council of the Collegium Internationale Allergologicum (CIA), 2010-2014

Mentor, junior EAACI member program, 2011-2013

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

Advisor to the Department of Research & Development of CSL Behring AG, Bern Switzerland, ending June 2011

Dr. Stephan von Gunten

Member of the Editorial Board, Allergy

Webmaster at the PKI

Coordinator for FACS at the PKI

Coordinator for the library at the PKI

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

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 2011 for approximately 1000 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 2011, 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. Public Work

7.1. Art Exhibition

Tekeal Riley, Bern, Switzerland
Vernissage: Nov. 24, 2011

8. Sponsors

8.1. Research Grants

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

Dr. Stephan von Gunten

Swiss National Science Foundation (grant No.310030_135734/1)
CSL Behring AG, Bern
Novartis Stiftung für medizinisch-biologische Forschung
Department of Clinical Research (DCR) Prize 2010, University of Bern

Dr. Susanne 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. 3100AO-111806/1)
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)
Novartis Stiftung für medizinisch-biologische Forschung
Josephine Clark-Fonds der Medizinischen Fakultät
Uni Bern Forschungsstiftung

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 Hösli)

PD Dr. Peter Späth

Medical Research Council, Singapore (together with Prof. Nobuhiro Yuki, Singapore)

Darko Stojkovo

Fellowship, EUROPEAN (Erasmus) (Sept. 2011 – Jan. 2012)

Prof. Shida Yousefi

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

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. 310030_119859)
Swiss National Science Foundation (grant No. 310030E_132762/1)
Swiss National Science Foundation (grant No. 310030E_138201/1)
Krebsliga des Kantons Bern
Unitectra Technology Transfer Fonds

8.2. Meetings

Swiss Society of Pharmacology and Toxicology (SSPT): Progress in Pharmacology Bern (CH), Jan. 27, 2011

Pfizer AG, Zurich
Servier SA, Satigny

10th III-International Summer School, Sigriwil (CH), Aug. 21 – 23, 2011

Allergopharma AG, Therwil
Becton Dickinson Biosciences, Allschwil
Carl Zeiss AG, Feldbach
Pfizer AG, Zurich
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

8.3. Seminars „Progress in Pharmacology“

2011:
CSL Behring AG, Bern
Pfizer AG, Zurich

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

8.4. Seminars „Bern Immunology Club“

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

8.5. Travel Support

Dr. Christina Merz-Stöckle
Swiss Society of Experimental Pharmacology (Int. Eos. Society Symposium, Québec, Canada, June 21-25, 2011)

Dr. Camilla Jandus
Swiss Society of Experimental Pharmacology (ISREC Symposium, Lausanne, Sept. 7-10, 2011)

Zhaoyue He
Swiss Society of Experimental Pharmacology (Eur. Cell Death Org. Meeting, Stockholm, Sweden, Sept. 14-17, 2011)

He Liu
Swiss Society of Experimental Pharmacology (Eur. Cell Death Org. Meeting, Stockholm, Sweden, Sept. 14-17, 2011)

Ursina Gurzeler
Swiss Society of Experimental Pharmacology (Eur. Cell Death Org. Meeting, Stockholm, Sweden, Sept. 14-17, 2011)

Dipak Maskey
Graduate School for Cellular and Biomedial Sciences, Univ. Bern (Cold Spring Harbor Meeting on Cell Death, New York, USA, Oct. 11-15, 2011)

Nohemy Echeverry
Graduate School for Cellular and Biomedial Sciences, Univ. Bern, and Swiss Society of Experimental Pharmacology (Cold Spring Harbor Meeting on Cell Death, New York, USA, Oct. 11-15, 2011)

8.6. Other Support

Bürgi Fonds Seminar series of the institute