Annual Report 2010

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 zehnte umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat auch im Jahr 2010 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 2010 trugen wir dazu bei, die Kommunikation zwischen WissenschaftlerInnen und Öffentlichkeit zu fördern. Dazu diente u.a. zwei Vernissagen, die viele Gäste in das PKI lockte.

Neben unserer regulären Lehrtätigkeit im 3. Studienjahr Medizin sowie neben 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. Simon und Prof. Kaufmann sind Mitglieder von Betreuungskommissionen 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 24 DoktorandInnen (18 PhD, 6 MD), und 3 DoktorandInnen haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Wir freuen uns, dass sich im Jahr 2010 eine neue Forschungsgruppe unter Leitung von Herrn Dr. Stephan von Gunten im Institut etablieren konnte und eine erfolgreiche Forschung durchführt.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2010 insgesamt 28 Originalarbeiten sowie 7 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >200). MitarbeiterInnen des Instituts wurden zu insgesamt 36 Vorträgen bzw. Seminaren eingeladen. Mehrere MitarbeiterInnen des PKI wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 7 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. Das von Prof. Simon und Prof. Brunner (Universität Konstanz, Deutschland) organisierte „6th Swiss Apoptosis Meeting (SAM)“ zog über 200 TeilnehmerInnen aus dem In- und Ausland an. Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Das PKI nimmt auch ausserhalb der Universität wissenschaftspolitische Verantwortung für die Medizin und die Biowissenschaften wahr. Prof. Simon amtete bis Februar 2010 als Präsident der Union der Schweizerischen Gesellschaften für Experimentelle Biologie (USGEB). Gleichzeitig ist er als Past-Präsident der European Cell Death Organization (ECDO) tätig, wobei gegenwärtig die Umgestaltung dieser Organisation in eine wissenschaftliche Akademie im Zentrum der Aktivitäten steht.

Ich danke allen Mitarbeiterinnen und Mitarbeitern für ihren Einsatz, welcher auch im Jahr 2010 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 2011

1.2. Foreword

This is the tenth 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 2010 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 2010. 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. Simon and Prof. Kaufmann are members of the tutoring committees “Medical Biology” and “Cell Biology”, respectively, 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, 18 PhD students and 6 MD students work at the PKI, and three students (3 MD) successfully finished their doctoral and Master studies, respectively, in 2010.

A new research group was established under the leadership of Dr. Stephan von Gunten and its start at the PKI was promising.

In 2010, members of the PKI published 28 original and 7 review articles in international peer-reviewed journals (the sum of the “impact factors” is more than 200). Co-workers of

the institute were invited to 36 lectures or seminars. Several PKI members received research prizes. Seven co-workers are currently supported by grants of the Swiss National Science Foundation. Several prominent researchers visited the institute and presented seminars. The Bern Immunology Club (BIC) is also thanks to our contribution highly active and successful. An international congress (6th Swiss Apoptosis Meeting, SAM) was organized by Prof. Simon and Prof. Brunner (Univ. of Konstanz, Germany) and attracted 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 served as President of the Union of the Swiss Societies for Experimental Biology (USSEB) until February 2010. Currently, as Past-President of the European Cell Death Organization (ECDO), he is largely involved in the transition of this society into a scientific academy.

I thank all co-workers for their hard work that contributed to the success of the PKI in 2010. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, January 2011

2. Staff 2010

Director

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

Deputy Director

Prof. Dr. Andrea Huwiler, PhD

Prinicipal 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

Daniel Bachmann, research assistant*
Eva Ursina Bettler, MD student*
Dr. Sébastien Conus, PhD
Nohemy Echeverry, PhD student
Elena Federzoni, PhD student (until August 2010)
Daniel Fallegger, PhD student (since November 2010)
Ankathrin Foerster, PhD student (June – August 2010)
Dr. Barbara Geering, PhD
Adelheid Graf, M.Sc. student* (January – June 2010)
Barbara Grieder, PhD student (until March 2010)
Ursina Gurzeler, PhD student*
Zhaoyue He, PhD student
Dr. Susanne Hoesli, MD-PhD student* (since October 2010)
Faik Imeri, PhD student (since February 2010)
Dr. Camilla Jandus, MD, PhD*
Dr. Nataliya Kotelevets, PhD
Evelyne Kozlowski, technician
Meret Lehmann, MD student*
He Liu, PhD student*
Marianne Maillard-Van Laer, technician
Dr. Patricia Martin-Killias, PhD
Dipak Maskey, PhD student
Dr. Christina Merz - Stöckle, PhD*
Cristina Mihalache, PhD student
Morshed Mahbubul, PhD student*
Olexsandr Pastukhov, PhD student (since June 2010)
Susanne Probst, technician (until June 2010)

Nina Roth, MD student*
Saša Rožman, PhD student (since October 2010)
Inès Schmid, head technician
Dr. Schwalm Stephanie, PhD* (June – August 2010)
Manuel Simon, PhD student*
Simon Städler, MD student*
Matthias Stuck, MD student*
Petra Trütsch, M.Sc. student*
Thomas von Rütte, MD student*
Diana Waldmeier, M.Sc. student*
Dr. Wehrli Marc, MD-PhD student* (since February 2010)

External University Teachers

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

Guest scientists

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. Rabi Thangaiyan, PhD*, Rajiv Gandhi Center for Biotechnology, Kerela, India (Jun.-Sept. 10)

External Computer Support

Dominik Wyss*
Anne Simon*

Office

Sandra Suter, head secretary
Anita Dähler, secretary

Tamara Haeberlin*, Zurich, USGEB secretary to Prof. Simon (until February 2010)
Cornelia Pfister*, Pfizer AG, Zürich (support of the "Progress in Pharmacology" - Meeting)

Workshop

Hans Andres

House Keeping

Isa Conforti
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, Febr. 4, 2010

6th Swiss Apoptosis Meeting (SAM), Bern, Sept. 30 – Oct. 1, 2010

3. Teaching Activities
3.1. Lectures

Lectures for medical students

Date	Lecturer	Titel of the lecture
March 15, 2010	Dr. Stephan von Gunten	Antidiabetika
March 17, 2010	Dr. Stephan von Gunten	Fett-Lipidsenker, Gicht
April 12, 2010	Prof. Andrea Huwiler	Antiepileptika
April 12, 2010	Prof. Andrea Huwiler	Anti-Parkinson und Anti-Demenz
April 14, 2010	Prof. Andrea Huwiler	Lokalanästhetika
April 26, 2010	Dr. Stephan von Gunten	Hormone aus pharmakologischer Sicht 1
April 26, 2010	Dr. Stephan von Gunten	Hormone aus pharmakologischer Sicht 2
April 28, 2010	Prof. Andrea Huwiler	Narkosemittel I
April 28, 2010	Prof. Andrea Huwiler	Narkosemittel II und Muskelrelaxantien
April 28, 2010	Prof. Andrea Huwiler	Pharmakologie der Narkotika / Anästhesie 1
May 3, 2010	Prof. Andrea Huwiler	Psychopharmakologie
May 5, 2010	Prof. Andrea Huwiler	Antidepressiva, Anxiolythika und Stimmungsstabilisatoren
May 10, 2010	Prof. Andrea Huwiler	Antipsychotika
May 19, 2010	Prof. Andrea Huwiler	Schmerz und Analgesiologie 1
May 19, 2010	Prof. Andrea Huwiler	Schmerz und Analgesiologie 2
June 6, 2010	Prof. Hans-Uwe Simon	Immunmodulation
Sept. 13, 2010	Prof. Thomas Kaufmann	Adaptation und Zellschäden
Sept. 20, 2010	Prof. Hans-Uwe Simon	Pharmakodynamik 1
Sept. 20, 2010	Prof. Hans-Uwe Simon	Pharmakodynamik 2
Sept. 22, 2010	Prof. Hans-Uwe Simon	Entzündungshemmung
Sept. 22, 2010	Prof. Hans-Uwe Simon	Einführung in die Toxikologie

Oct. 5, 2010	Prof. Thomas Kaufmann	Zellschäden (allg. Pathologie-Vorlesung)
Oct. 25, 2010	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Nov. 2, 2010	PD Dr. Peter Späth Prof. Uwe Zangemeister-Wittke	Antithrombotische Therapie & Antikoagulantien
Nov. 2, 2010	Prof. Uwe Zangemeister-Wittke	Antihypertensiva
Nov. 2, 2010	Prof. Uwe Zangemeister-Wittke	Behandlung der Herzinsuffizienz und Angina Pectoris
Nov. 10, 2010	Prof. Uwe Zangemeister-Wittke	Antiarrhythmika
Nov. 17, 2010	Prof. Uwe Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Dec. 6, 2010	Prof. Uwe Zangemeister-Wittke	Diuretika

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

Date	**Lecturer**	**Title of the lecture**
Febr. 15, 2010	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Einführung, Rezeptoren
Febr. 15, 2010	Prof. Hans-Uwe Simon	Allgemeine Pharmakologie: Dosis-Wirkungskurven
Febr. 17, 2010	Prof. Hans-Uwe Simon	Antagonisten / Applikation
Febr. 24, 2010	Prof. Uwe Zangemeister-Wittke	Aufnahme / Verteilung
March 1, 2010	Prof. Uwe Zangemeister-Wittke	Arzneimittelmetabolismus / Elimination
March 1, 2010	Prof. Uwe Zangemeister-Wittke	Gesamtkinetik / Dosierung
March 3, 2010	Prof. Andrea Huwiler	Interaktionen / Pharmakogenetik, allg.
March 15, 2010	PD Dr. Armand Cachelin	Schwache Analgetika
March 15, 2010	PD Dr. Armand Cachelin	Starke Analgetika

March 17, 2010	PD Dr. Armand Cachelin	Immunsuppression
March 24, 2010	PD Dr. Peter Späth	Orale Antikoag./Plättchenhemmer
March 31, 2010	Dr. Sibylle Bürgi	Lokalanästhetika
April 14, 2010	Dr. Sibylle Bürgi	Insulin, orale Antidiabetika
April 21, 2010	Dr. Stephan von Gunten	Magensäurehemmung
April 26, 2010	Prof. Uwe Zangemeister-Wittke	Vegetatives Nervensystem
April 26, 2010	Prof. Uwe Zangemeister-Wittke	Herz-Kreislaufpräparate
April 28, 2010	Prof. Andrea Huwiler	Narkose-/Beruhigungsmittel
Mai 10, 2010	Dr. Stephan von Gunten	Psychopharmaka
May 10, 2010	Prof. Uwe Zangemeister-Wittke	Examensvorbereitung

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. 25, 2010	Prof. Hans-Uwe Simon	Introduction
Febr. 25, 2010	Prof. Hans-Uwe Simon	Immunopharmacology
May 27, 2010	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. 11, 2010	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 2, 2010	Prof. Andrea Huwiler	Lipid mediators involved in inflammation
May 12, 2010	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. 12, 2010	Prof. Thomas Kaufmann	Isolation of leukocytes

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

Date	Lecturer	Title of the lecture
March 15, 2010	Prof. Hans-Uwe Simon	Pharmacodynamics I
March 15, 2010	Prof. Hans-Uwe Simon	Pharmacodynamics II
March 22, 2010	Prof. Hans-Uwe Simon	Toxicology
March 22, 2010	Prof. Hans-Uwe Simon	Pharmacology of inflammation
May 3, 2010	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. 24, 2010	Prof. Thomas Kaufmann	Immune system
Oct. 1, 2010	Prof. Uwe Zangemeister-Wittke	Heart and vascular system
Oct. 8, 2010	Prof. Shida Yousefi	Antiinfectious therapy
Oct. 22, 2010	Prof. Andrea Huwiler	Nervous system
Oct. 29, 2010	Dr. Stephan von Gunten	Endocrine and reproductive system
Nov. 5, 2010	Prof. Shida Yousefi	Lungs and kidneys
Nov. 19 2010	PD Dr. Peter Späth	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
Nov. 1, 2010	Prof. Thomas Kaufmann	Cell damage

External teaching activities: University of Zurich (Molecular Medicine)

Date	Lecturer	Title of the lecture
March 15-16, 2010	Prof. Uwe Zangemeister-Wittke	Introduction into tumor biology
May 2010 (total 5h)	Prof. Uwe Zangemeister-Wittke	Human and dental students: Molecular Cell Biology

3.2. Coordination PBL Medical Students, 3rd year (2010/2011)

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 2010/2011)

Medical students 3rd year:
Dr. Sébastien Conus
Prof. Thomas Kaufmann
Dr. Nataliya Kotelevets
Dr. Christina Merz-Stöckle
Dr. Barbara Geering

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

3.4. Seminars of Invited Speakers

Date	Teacher	Title of the seminar
Jan. 13, 2010	Prof. Aurel Perren Institute of Pathology University of Bern	Wo entstehen endokrine Pankreas-tumoren: Von der Histogenese zu Tumor-Stammzellen
Jan. 20, 2010	Prof. Robert Rieben Dept. of Clin. Research University of Bern	Attenuation of acute inflammatory reations by IVIG and endothelial cell protectants
Febr 3, 2010	Prof. Winfried S. Wels Georg-Speyer-Haus Universität Frankfurt (D)	Retargeted killer cells for cancer immunotherapy
Febr 10, 2010	Prof. Urs Albrecht Biochemistry, Univ. of Fribourg	Circadian clock in mood related behavior
March 17, 2010	Prof. Urs Frey Dept. of Paediatrics Inselspital, Bern	The Bern infant lung development cohort BILD: Environmental impacts on lung growth and development in infants
April 7, 2010	Prof. Pedro Romero Ludwig Institute for Cancer Research, Lausanne	Specific immunotherapy of cancer with molecularly defined vaccines

April 9, 2010	Prof. Gerd Döring Institut für Medizinische Mikrobiologie & Hygiene Universität Tübingen (D)	How *Pseudomonas aeruginosa* copes with hypoxia
April 14, 2010	Dr. Steffen Frese Dept. of Clin. Research University of Bern	Inhibition of topoisomerase I: A new strategy for the treatment of systemic lupus erythematosus
April 21, 2010	Dr. Yitzhak Zimmer Dept. of Clin. Research University of Bern	Breaching the DNA damage response (DDR) by targeting the Met receptor tyrosine kinase
May 19, 2010	Dr. Thomas Kiefer Institut für Molekulare Medizin und Zellforschung Universität Freiburg i. Br. (D)	Bcl-2 and physiological binding partners
June 15, 2010	Prof. Roland Riek Laboratorium für Physikalische Chemie ETH Zürich	Structure activity relationship of protein aggregates in health and disease
June 16, 2010	Prof. Michael Arand Institute of Pharmacology and Toxicology University of Zurich	Epoxides - from chemical hazard to physiological regulation
June 23, 2010	Dr. Ueli Nachbur La Trobe University Bundoora, Melbourne (Australia)	TNF-alpha signaling: The view from downunder
June 30, 2010	Dr. Kenneth McCullough Institute of Virology and Immunoprophylaxis (IVI) Mittelhäusern (CH)	Viruses, vaccines and dendritic cells: a question of life, the universe and everything?
July 7, 2010	Prof. Marcus Thelen Institute for Research in Biomedicine Bellinzona (CH)	The yin yang of chemokine receptor functions
July 28, 2010	Dr. Philipp Jost III. Medizinische Klinik Technische Universität München (D)	Regulation of death receptor-mediated immuno-pathology of the liver
Aug. 16, 2010	Prof. David Huang The Walter and Eliza Hall Institute of Medical Research, Melbourne (Australia)	Targeting Bcl-2 for treating cancers

Aug. 25, 2010	Prof. Bengt Fadeel Div. of Mol. Toxicology Karolinska Institutet Stockholm, Sweden	The importance of being eaten: from macrophage clearance of apoptotic cells to recognition and biodegradation of nanomaterials
Sept. 8, 2010	PD Dr. Frank Essmann Interfakultäres Institut für Biochemie, Univ. Tübingen (D)	New aspects of apoptosis and senescence regulation
Oct. 13, 2010	Prof. Lutz Hein Institute of Exp. & Clin. Pharmacology and Toxicology, University of Freiburg i.Br. (D)	Pre- and postsynaptic targets of adrenergic receptor signaling
Oct. 27, 2010	Dr. Daniel F. Legler Biotechnology, Institute Thurgau (BITg) University of Konstanz (D)	Modulation of human dendritic cell functions and migration by prostaglandin E2
Nov. 24, 2010	Dr. Oliver Gautschi Medizinische Onkologie Inselspital, Bern	The role of inhibitor of differentiation (ID) genes in cancer

3.5. Bern Immunology Club (BIC)

Date	**Teacher**	**Title of the seminar**
Jan. 27, 2010	Prof. Alexander Flügel Institute für Multiple Sklerose Forschung University of Göttingen (D)	How encephalitogenic T cells invade the CNS in the course of Experimental Autoimmune Encephalomyelitis
Febr. 24, 2010	Dr. Philipp Lepper Universitätsklinik für Pneumologie Inselspital, Bern	Toll-like receptors as drugable targets in Univericardiovascular and respiratory medicine
March 24, 2010	Prof. Thomas Bieber (Univ. Bonn, D) Prof. Stephan Weidinger (Univ. Munich, D) Prof. Freddy Radke (EPFL, Lausanne)	*Clinical Immunology Conference* Atopic Dermatitis: Defect(s) in barrier and/or immune function(s)
	(Organization: Prof. H.-U. Simon and Prof. D. Simon (Bern))	

April 28, 2010	Prof. Taco Kuijpers Div. Ped. Hematology Amsterdam (NL)	Neutrophil defects: causative or contributing factors in failing host defense
May 26, 2010	Dr. Andri Rauch Universitätsklinik für Infektiologie, Inselspital, Bern	The interleukin 28B gene and HCV-infection recovery
June 30, 2010	Dr. Christophe v. Garnier Universitätsklinik für Pneumologie Inselspital, Bern	Nanoparticles and lung DCs: Friends or foes?"
Sept. 29, 2010	Prof. Andreas Villunger Division of Dev. Immunol. Med. Univ. Innsbruck (A)	Lymphocyte homeostasis by BH3-only proteins
Oct. 27, 2010	Prof. Michael Hertl Klinik für Dermatologie und Allergologie Univ. Gießen und Marburg (D)	Targeted therapies in autoimmune diseases of the skin
Nov. 24, 2010	Dr. Daniel Lottaz Universitätsklinik für Rheumatologie, Inselspital, Bern	Proteolysis in chronic inflammation

For the current program of the Bern Immunology Club (BIC), please consult the following website:
http://www.bic.unibe.ch/content/teaching/bic_lectures_11/index_eng.html

3.6. Academic Degrees

Eva Ursina Bettler, Dr. med. (MD), University of Bern
Thesis: Mepolizumab does not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa in eosinophilic esophagitis
Institute of Pharmacology, Bern, October 2010
Supervisors: Prof. Hans-Uwe Simon, Dr. Sébastien Conus, PhD

Matthias Stuck, MMed, University of Bern
Thesis: A systematic literature review of Foxp3 expression in Th2-mediated inflammatory disorders
Institute of Pharmacology, Bern, October 2010
Supervisor: Prof. Hans-Uwe Simon

Nina Roth, MMed, University of Bern
Thesis: Characterisation of eosinophilic inflammation in the skin: Tissue damage and fibrosis
Institute of Pharmacology, Bern, October 2010
Supervisors: Prof. Hans-Uwe Simon, Prof. Dr. Dagmar Simon

Adelheid Graf, M.Sc. pharm, University of Basel
Thesis: Atg5 expression in benign melanocytic nevi and malignant melanoma
Institute of Pharmacology, Bern, June 2010
Supervisor: Prof. Hans-Uwe Simon

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

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

A novel mode of action of the putative sphingosine kinase inhibitor 2-(p-hydroxyanilino)-4 (p-chlorophenyl) thiazole (SKI II): induction of lysosomal sphingosine kinase 1 degradation.
S. Ren, C. Xin, J. Pfeilschifter, A. Huwiler
BACKGROUND: Sphingosine kinase 1 (SK1) is a key enzyme in the generation of sphingosine 1-phosphate (S1P) which critically regulates a variety of important cell responses such as proliferation and migration. Therefore, inhibition of SK-1 has been suggested to be an attractive approach to treat tumor growth and metastasis formation.
RESULTS: We show here that the previously developed putative SK-1 inhibitor 2-(p-hydroxyanilino)-4-(p-chlorophenyl) thiazole (SKI II) displays an additional facet of action complementary to the known inhibition of enzymatic SK-1 activity. In various human cell lines including glomerular podocytes and mesangial cells, the human endothelial cell line EA.hy 926, and the lung cancer cell line NCI H358, SKI II reduced TGFbeta- and TPA-stimulated cellular SK-1 activity by downregulating SK-1 protein expression without affecting

SK-1 mRNA expression. By using cycloheximide to block the de novo protein synthesis, the protein expression of SK-1 under untreated conditions was stable over 24h. Under SKI II treatment, the half-live drastically decreased to approximately 0.8h. Mechanistically, this degradation occurred through a lysosomal pathway and involved cathepsin B since the general lysosomal inhibitor chloroquine and the specific cathepsin B inhibitor CA-074ME were able to reverse the effect of SKI II. Surprisingly, in vitro SK-1 activity assays revealed only a very weak direct inhibitory effect of SKI II on SK-1 overexpressed HEK293 cell lysates.
CONCLUSION: These data show for the first time that the previously developed SK inhibitor SKI II hardly inhibits SK-1 directly but rather acts by triggering the lysosomal degradation of SK-1 in various cell types. This finding discloses a new mode of action of SKI II and strongly suggests that additional direct targets of SKI II may exist other than SK-1.
See original publication No. 1

Sphingosine kinase 1 is critically involved in nitric oxide-mediated human endothelial cell migration and tube formation.
S. Schwalm, J. Pfeilschifter, A. Huwiler
BACKGROUND AND PURPOSE: Sphingosine kinases (SKs) convert sphingosine to sphingosine 1-phosphate (S1P), which is a bioactive lipid that regulates a variety of cellular processes including proliferation, differentiation and migration.
EXPERIMENTAL APPROACH: We used the human endothelial cell line EA.hy926 to investigate the effect of nitric oxide (NO) donors on SK-1 expression, and on cell migration and tube formation.
KEY RESULTS: We showed that exposure of EA.hy926 cells to Deta-NO (125-1000 microM) resulted in a time- and concentration-dependent up-regulation of SK-1 mRNA and protein expression, and activity with a first significant effect at 250 microM of Deta-NO. The increased SK-1 mRNA expression resulted from an enhanced SK-1 promoter activity. A similar effect was also seen with various other NO donors. In mechanistic terms, the NO-triggered effect occurred independently of cGMP, but involved the classical mitogen-activated protein kinase cascade because the MEK inhibitor U0126 abolished the NO-induced SK-1 expression. The effect of NO was also markedly reduced by the thiol-reducing agent N-acetylcysteine, suggesting a redox-dependent mechanism. Functionally, Deta-NO triggered an increase in the migration of endothelial cells in an adapted Boyden chamber assay, and also increased endothelial tube formation in a Matrigel assay. These responses were both abolished in cells depleted of SK-1.
CONCLUSIONS AND IMPLICATIONS: These data show that NO donors up-regulate specifically SK-1 expression and activity in human endothelial cells, and SK-1 in turn critically contributes to the migratory capability and tube formation of endothelial cells. Thus, SK-1 may be considered an attractive novel target to interfere with pathological processes involving angiogenesis.
See original publication No. 2

Glucocorticoids protect renal mesangial cells from apoptosis by increasing cellular sphingosine-1-phosphate.
A.Förster, T. Emmler, S. Schwalm, M. Ebadi, DM Heringdorf, B. Nieuwenhuis, B. Kleuser, A. Huwiler, J. Pfeilschifter.
Neutral ceramidase (NCDase) and sphingosine kinases (SphKs) are key enzymes regulating cellular sphingosine-1-phosphate (S1P) levels. In this study we found that stress factor-induced apoptosis of rat renal mesangial cells was significantly reduced by dexamethasone treatment. Concomitantly, dexamethasone increased cellular S1P levels, suggesting an activation of sphingolipid-metabolizing enzymes. The cell-protective effect of

glucocorticoids was reversed by a SphK inhibitor, was completely absent in SphK1-deficient cells, and was associated with upregulated mRNA and protein expression of NCDase and SphK1. Additionally, in vivo experiments in mice showed that dexamethasone also upregulated SphK1 mRNA and activity, and NCDase protein expression in the kidney. Fragments (2285, 1724, and 1126 bp) of the rat NCDase promoter linked to a luciferase reporter were transfected into rat kidney fibroblasts and mesangial cells. There was enhanced NCDase promoter activity upon glucocorticoids treatment that was abolished by the glucocorticoid receptor antagonist RU-486. Single and double mutations of the two putative glucocorticoid response element sites within the promoter reduced the dexamethasone effect, suggesting that both glucocorticoid response elements are functionally active and required for induction. Our study shows that glucocorticoids exert a protective effect on stress-induced mesangial cell apoptosis in vitro and in vivo by upregulating NCDase and SphK1 expression and activity, resulting in enhanced levels of the protective lipid second messenger S1P.
See original publication No. 3

Original publications

1. S. Ren, C. Xin, J. Pfeilschifter, **A. Huwiler:** A novel mode of action of the putative sphingosine kinase inhibitor 2-(p-hydroxyanilino)-4-(p-chlorophenyl) thiazole (SKI II): induction of lysosomal sphingosine kinase 1 degradation. Cell. Physiol. Biochem. 26 (2010), 97-104.

2. S. Schwalm, J. Pfeilschifter, **A. Huwiler**: Sphingosine kinase 1 is critically involved in nitric oxide-mediated human endothelial cell migration and tube formation. Br. J. Pharmacol. 160 (2010), 1641-1651.

3. A. Förster, T. Emmler, S. Schwalm, M. Ebadi, D. Meyer zu Heringdorf, B. Nieuwenhuis, B. Kleuser, **A. Huwiler**,* J**.** Pfeilschifter: Glucocorticoids protect renal mesangial cells from apoptosis by increasing cellular sphingosine-1-phosphate levels. Kidney Int. 77 (2010), 870-879. *Corresponding author

4. P. Puneet, CT Yap, L. Wong, Y. Lam, D.R. Koh, S. Moochhalla, J. Pfeilschifter, **A. Huwiler,** A.J. Melendez: SphK1 a signalling mediator of endotoxin and polymicrobial sepsis lethality. Science 328 (2010), 1290-1294. Comment in: Nat. Rev. Drug Discov. 9 (2010), 516-517. (Bird L) Comment in: Nat. Rev. Immunol. 10 (2010), 464. (Bird L) Comment in: Sci. Transl. Med. 2 (2010), 36ps29 (O'Neill LA)

5. **A. Huwiler**, N. Kotelevets, C. Xin, O. Pastukhov, J. Pfeilschifter, U. Zange-meister-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.

6. M. ter Braak, R.F. Claas, B. Hegen, S. Labocha, N. Ferreiros, J. Pfeilschifter, **A. Huwiler**, G. van Echten-Deckert, D. Meyer zu Heringdorf: Cis-4-methylsphingosine is a sphingosine-1-phosphate receptor modulator. Biochem. Pharmacol., in press.

Patent applications

B.Johansen, **A. Huwiler**: Compositions and methods for the treatment of glomerulonephritis. US patent application US 20100311843A1, June 4, 2010.

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. Patent application 10 193 347.1, December 1, 2010.

Group Prof. Thomas Kaufmann

Group members: Nohemy Echeverry, PhD student
Ursina Gurzeler, PhD student
Daniel Bachmann, research assistant

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 additionally 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.

Review article

1. P.J. Jost, **T. Kaufmann**: Cancer caused by too much apoptosis - An intriguing contradiction?
Hepatology 51 (2010), 1110-1112.

Group Prof. Hans-Uwe Simon

Group members:
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Thomas von Rütte, MD student

*Joint supervision together with Prof. S. Yousefi.
**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. As a consequence, in 2010, we were involved in re-defining and re-classification of the hypereosinophilic syndrome. 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 2010.

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

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

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

See original publication No. 1

Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis

A. Straumann, S. Conus, L. Degen, S. Felder, M. Kummer, H. Engel, C. Bussmann, C. Beglinger, A. Schoepfer, H.-U. Simon
(Collaboration with the Department of Gastroenterology, University of Basel, and Institute of Clinical Pathology Viollier, Basel)

Background & Aims: Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus characterized by dense tissue eosinophilia; it is refractory to proton pump inhibitor therapy. EoE affects all age groups, but most frequently individuals between 20–50 years. Topical corticosteroids are effective in pediatric patients with EoE, but no controlled studies of corticosteroids have been reported in adult patients. Methods: We performed a randomized, double-blind, placebo-controlled trial to evaluate the effect of oral budesonide (1 mg, twice daily for 15 days) in adolescent and adult patients with active EoE. Pre- and post-treatment disease activity was assessed clinically, endoscopically, and histologically. The primary endpoint was reduced mean numbers of eosinophils in the esophageal epithelium (number/hpf =esophageal eosinophil load). Esophageal biopsy and blood samples were analyzed using immunofluorescence and immunoassays,

respectively, for biomarkers of inflammation and treatment response. Results: A 15-day course of therapy significantly decreased the number of eosinophils in the esophageal epithelium of patients given budesonide (from 68.2 to 5.5 eosinophils/hpf; *P*<0.0001), but not in the placebo group (from 62.3 to 56.5 eosinophils/hpf, *P*=0.48). Dysphagia scores significantly improved among patients given budesonide compared with those given placebo (5.61 vs. 2.22; *P*<0.0001). White exudates and red furrows were reversed in patients given budesonide, based on endoscopy examination. Budesonide, but not placebo, also reduced apoptosis of epithelial cells and molecular remodeling events in the esophagus; no serious adverse events were observed. Conclusions: A 15-day course of treatment with budesonide is well tolerated and highly effective in inducing a histological and clinical remission in adolescent and adult patients with active EoE.

See original publication No. 2

Eosinophil extracellular DNA traps in skin diseases

D. Simon, S. Hoesli, N. Roth, S. Staedler, S. Yousefi, H.-U. Simon

(Collaboration with the Department of Dermatology, University Hospital Bern, Inselspital)

Background: In the skin, eosinophils are found in a broad spectrum of diseases, including infectious diseases. In this study, we investigated whether eosinophil extracellular traps (EETs), structures containing DNA in association with eosinophil granule proteins able to bind and kill bacteria, are present in the skin under various pathologic conditions. Material and methods: Immunofluorescence staining was performed on sections of paraformaldehyde-fixed and paraffine-embedded skin biopsy tissues of 25 different eosinophilic skin diseases using propidium iodide (PI) and an antibody to eosinophil cationic protein (ECP). Slides were evaluated by laser scanning microscopy. Results: Eosinophils releasing DNA together with ECP 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%, only 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 EETs. Conclusion: EETs are seen in both infectious and non-infectious inflammatory skin diseases, and particularly common in Wells' syndrome.

See original publication No. 3

A new definition of the hypereosinophilic syndrome

H.-U. Simon, M.E. Rothenberg, B.S. Bochner, P.F. Weller, A.J. Wardlaw, M.E. Wechsler, L.J. Rosenwasser, F. Roufosse, G.J. Gleich, A.D. Klion

(Collaboration with Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, USA; Johns Hopkins University School of Medicine, Baltimore, MD, USA; Harvard Medical School, Boston, MA, USA; Institute for Lung Health, Infection, Immunity and Inflammation, University of Leicester, Leicester, UK; Children's Mercy Hospital, UMKC School of Medicine, Kansas City, MO, USA; Hôpital Erasme, Service de Médecine Interne, Université Libre de Bruxelles, Brussels, Belgium; Department of Dermatology, University of Utah, Salt Lake City, UT, USA; National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA)

Due to advances in our understanding of the hypereosinophilic syndrome (HES) and the availability of novel therapeutic agents, the original criteria defining these disorders are becoming increasingly problematic. Here, we discuss shortcomings with the current definition of HES and recent developments in the classification of these disorders. Despite

significant progress in our understanding of the pathogenesis of some forms of HES, the current state of knowledge is still insufficient to formulate a new comprehensive etiologic definition of hypereosinophilic syndromes. Nevertheless, we suggest a new working definition that overcomes some of the most obvious limitations with the original definition.
See position paper No. 1

Original publications

1. A. Straumann, S. Conus, P. Grzonka, H. Kita, G. Kephart, C. Bussmann, C. Beglinger, D.A. Smith, J. Patel, M. Byrne, **H.-U. Simon**: Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomized, placebo-controlled, double-blind trial.
Gut 59 (2010), 21-30.

2. A. Straumann, S. Conus, L. Degen, S. Felder, M. Kummer, H. Engel, C. Bussmann, C. Beglinger, A. Schoepfer, **H.-U. Simon**: Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis.
Gastroenterology 139 (2010), 1526-1537.
Comment in: Gastroenterology 139 (2010), 1429-1430 (Tack J and Carethers JM)

3. D. Simon, S. Hoesli, N. Roth, S. Staedler, S. Yousefi, **H.-U. Simon**: Eosinophil extracellular DNA traps in skin diseases.
J. Allergy Clin. Immunol., in press.

4. A. El-Hashim, S. Yousefi, I. Edafiogho, R. Raghupathy, M.H. Yousif, **H.-U. Simon**: Anti-inflammatory and immunosuppressive effects of the enaminone E121.
Eur. J. Pharmacol. 632 (2010), 73-78.

5. J. Schmidt-Mende, B. Geering, S. Yousefi, **H.-U. Simon**: Lysosomal degradation of RhoH protein upon antigen receptor activation in T but not B cells.
Eur. J. Immunol. 40 (2010), 525-529.

6. S. Conus, A. Straumann, E. Bettler, **H.-U. Simon**: Mepolizumab does not alter levels of eosinophils, T cells, and mast cells in the duodenal mucosa in eosinophilic esophagitis.
J. Allergy Clin. Immunol. 126 (2010), 175-177.

7. M.C. Stuck, A. Straumann, **H.-U. Simon**: Relative lack of T regulatory cells in adult eosinophilic esophagitis - no normalization after corticosteroid therapy.
Allergy, in press.

8. A. Straumann, S. Conus, L. Degen, C. Frei, C. Bussmann, C. Beglinger, A. Schoepfer, **H.-U. Simon**: Long-term budesonide maintenance treatment is partailly effective for patients with eosinophilic esophagitis.
Clin. Gastroenterol. Hepatol., in press.

9. A.M. Schoepfer, N. Gonsalves, C. Bussmann, S. Conus, **H.-U. Simon**, A. Straumann, I. Hirano: Esophageal dilation in eosinophilic esophagitis: Effectiveness, safety, and impact on the underlying inflammation. Am. J. Gastroenterol. 105 (2010), 1062-1070. Comment in: Am. J. Gastroenterol. 105 (2010), 713-714 (Hirano I)

10. B. Berent-Maoz, S. Salemi, D. Mankuta, **H.-U. Simon**, F. Levi-Schaffer: Human mast cells express intracellular TRAIL. Cell. Immunol. 262 (2010), 80-83.

11. A. Britschgi, **H.-U. Simon**, A. Tobler, M.F. Fey, M.P. Tschan: Epigallocatechin-3-gallate induces cell death in acute myeloid leukaemia cells and supports all-trans retinoic acid-induced neutrophil differentiation via death-associated protein kinase 2. Br. J. Haematol. 149 (2010), 55-64.

12. R. Dworski, **H.-U. Simon**, A. Hoskins, S. Yousefi: Eosinophil and neutrophil extracellular DNA traps in human allergic asthmatic airways. J. Allergy Clin. Immunol., in press.

13. 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. Allergy, in press.

Position paper

1. **H.-U. Simon**, M.E. Rothenberg, B.S. Bochner, P.F. Weller, A.J. Wardlaw, M.E. Wechsler, L.J. Rosenwasser, F. Roufosse, G.J. Gleich, A.D. Klion: Refining the definition of hypereosinophilic syndrome. J. Allergy Clin. Immunol. 126 (2010), 45-49.

Review articles

1. S. von Gunten, **H.-U. Simon**: Cell death modulation by intravenous immunoglobulin. J. Clin. Immunol. 30 (Suppl. 1) (2010), S24-S30.

2. T. Bieber, **H.-U. Simon**: Shaping the future of Allergy. Allergy 65 (2010), 1.

3. H. Bantel, **H.-U. Simon**: ΔNp73β is oncogenic in hepatocellular carcinoma by blocking apoptosis signaling via death receptors and mitochondria. Cell Cycle 9 (2010), 2710-2711.

4. M.P. Tschan, **H.-U. Simon**: The role of autophagy in anticancer therapy: promises and uncertainties. J. Intern. Med. 268 (2010), 410-418.

Book chapters

1. M.I. Colombo, **H.-U. Simon**: Autophagy. In: Cell Death (Eds. G. Melino and D. Vaux); Encyclopedia of Life Sciences (ELS), John Wiley & Sons Ltd., Chichester UK, 2010, p, 175-188. DOI:10.1002/9780470015902.a0021581

2. 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.

Group Dr. Stephan von Gunten

Group members: Dr. Camilla Jandus, MD, PhD
Dr. Marc Wehrli, MD-PhD student

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. 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 publication

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.
   Allergy, in press.
   *Shared First-Authorship

Review article

1. **S. von Gunten**, H.-U. Simon: Cell death modulation by intravenous immunoglobulin.
   J. Clin. Immunol. 30 (Suppl. 1) (2010), S24-S30.

Group Prof. Shida Yousefi

Group members: Elena Federzoni, PhD student*
Evelyne Kozlowski, technician*
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Saša Rožman, PhD student*
Inès Schmid, head technician*
Thomas von Rütte, MD student*
Diana Waldmeier, 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
(Collaboration with Vanderbilt University School of Medicine, Nashville, TN, USA)
Background: Asthma is a heterogeneous inflammatory airway disorder which involves eosinophilic and non-eosinophilic phenotypes. Unlike in normal lungs, eosinophils are often present in atopic asthmatic airways although a subpopulation of asthmatic subjects predominantly develops neutrophilic inflammation. Recently, it has been demonstrated that eosinophils and neutrophils generate bactericidal extracellular traps consisting of DNA and cytotoxic granule proteins. Objective: To explore if 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 biopsies from 20 mild human atopic asthmatics at baseline and after local allergen challenge, and 10 normal subjects. DNA was stained with propidium iodine and major basic protein (MBP) with specific antibody. Differential cell counts and cytokines/chemokines were assessed in bronchoalveolar fluids. Results: Asthmatic airways were infiltrated with a significantly higher number of eosinophils than normal airways (39.3±4.6 vs. 0.4±0.9, $p<0.0001$). All asthmatics but only one control subject expressed eosinophils releasing DNA that colocalized with MBP (33.65±20.33 vs. 0.3±0.9 per hpf, $p<0.0001$). Four asthmatics 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 BAL levels of IL-5, IFN-γ, or eotaxin, or the provoking doses of methacholine or allergen in asthmatics. 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

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., in press.

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., in press.

3. A. El-Hashim, **S. Yousefi**, I. Edafiogho, R. Raghupathy, M.H. Yousif, H.-U. Simon: Anti-inflammatory and immunosuppressive effects of the enaminone E121.
Eur. J. Pharmacol. 632 (2010), 73-78.

4. J. Schmidt-Mende, B. Geering, **S. Yousefi**, H.-U. Simon: Lysosomal degradation of RhoH protein upon antigen receptor activation in T but not B cells.
Eur. J. Immunol. 40 (2010), 525-529.

5. M.D. Sury, L. Vorlet-Fawer, C. Agarinis, **S. Yousefi**, D. Grandgirard, S.L. Leib, S. Christen. Restoration of Akt activity by the bisperoxovanadium compound bpV(pic) attenuates hippocampal apoptosis in experimental neonatal pneumococcal meningitis.
Neurobiol. Dis. 41 (2011), 201-208.

Group Prof. Uwe Zangemeister-Wittke

Group members: Dr. Nataliya Kotelevets, PhD
Manuel Simon, PhD student[1]
Dr. Rabi Thangaiyan, PhD, visiting scientist
Petra Trütsch, M.Sc. student
Oleksandr Pasthukov, M.Sc. ESKAS fellowship student
Susanne Probst, technician
Dr. Patricia Martin-Killias, PhD[1]
Nikolas Stefan, PhD student[1]

[1]Institute of Biochemistry, University of Zürich

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

In addition, we are interested in improving tumor-targeted drug delivery using rationally engineered protein-based delivery systems. For this purpose, we have developed affinity-maturated Designed Ankyrin Repeat Proteins (DARPins) as novel binding proteins with specificity for the epithelial cell adhesion molecule (EpCAM). Various nanomedicines including tumor-targeted biotoxins, DARPinosomes and PLGA particles encapsulating cytotoxic payloads for intracellular delivery are under investigation.

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
(Collaboration with the Institute of Biochemistry, University of Zurich)

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 EpCAM-specific DARPin (Ec4) for tumor targeting as a fusion toxin with Pseudomonas exotoxin A. EXPERIMENTAL DESIGN: DARPin Ec4 was genetically fused to a truncated form of exotoxin A (ETA") and expressed in E. coli. The cytotoxicity of Ec4-ETA" was measured against tumor cell lines of various histotypes in vitro. Tumor localization and anti-tumor activity were determined in mice bearing two 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 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 IC50 values less than 0.005 pM. 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 48-72 h after

injection, whereas an irrelevant control fusion toxin did not accumulate. Tumor targeting with Ec4-ETA" resulted in a strong anti-tumor response including complete regressions in some animals. CONCLUSIONS: Our data demonstrate 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. 1

Original publications

1. P. Martin-Killias, N. Stefan, S. Rothschild, A. Plückthun, **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.

2. 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.

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. Patent application 10 193 347.1, December 1, 2010.

Additional Publications of PKI Members

PD Dr. Peter Späth

Original articles

M. Lucas, K. Hugh-Jones, A. Welby, S. Misbah, **P. Spaeth,** H. Chapel: Immunomodulatory therapy to achieve maximum efficacy: doses, monitoring, compliance, and self-infusion at home.
J. Clin. Immunol. 30 (2010), 84-89.

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

B. Wais-Nöcker, U. Stiner, **P. Späth,** W. A. Wuillemin
Klinische Facetten des hereditären Angioödems bei einem Schweizer Patientenkollektiv.
Praxis 99 (2010), 1135-1141.

Position paper

T. Bowen, M. Cicardi, H. Farkas, ..., **P. Späth,** L. Varga, Z.Y. Xiang: 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema.
Allergy Asthma Clin. Immunol. 28 (2010), 24.

Dr. Christina Merz-Stöckle

Original articles

L. Sevenich, S. Hagemann, **C. Stoeckle**, E. Tolosa, C. Peters, T. Reinheckel: Expression of human cathepsin L or human cathepsin V in mouse thymus mediates positive selection of T helper cells in cathepsin L knock-out mice.
Biochimie 92 (2010), 1674-1680.

P. Seizer, S. Schiemann, T. Merz, K. Daub, B. Bigalke, K. Stellos, I. Müller, **C. Stöckle**, K. Müller, M. Gawaz, A.E. May: CD36 and macrophage scavenger receptor a modulate foam cell formation via inhibition of lipid-laden platelet phagocytosis.
Semin. Thromb. Hemost. 36 (2010), 157-162.

Dr. Camilla Jandus

Original article

L. Derré, J.P. Rivals, **C. Jandus**, S. Pastor, D. Rimoldi, P. Romero, O. Michielin, D. Olive, D.E. Speiser: BTLA mediates inhibition of human tumor-specific CD8+ T cells that can be partially reversed by vaccination.
J. Clin. Invest. 120 (2010), 157-167.

Book chapter

L. Derré,* **C. Jandus**,* P. Baumgaertner, V. Posevitz, E. Devevre, P. Romero, D.E. Speiser: Quantitative multiparameter assays to measure the effect of adjuvants on human antigen-specific CD8 T cell responses. In: Vaccine Adjuvants, Methods in Molecular Biology 626 (2010), p. 231-249.
*Shared First-Authorship

4.2. Congress Invitations

Prof. Thomas Kaufmann

Swiss Apoptosis Meeting, Bern (CH), Sept. 30 - Oct. 1, 2010;
Investigating the function of the Bcl-2 family member Bok.

Prof. Hans-Uwe Simon

Sonderforschungsbereiches (SFB) 773, Univ. Tübingen, Blaubeuren (D), Jan. 27-28, 2010;
Death(s) of neutrophils.

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI); New Orleans, LA (USA), Febr. 26 - March 02, 2010;
The release of mitochondrial DNA and basic proteins by eosinophils upon TLR stimulation.

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI); New Orleans, LA (USA), Febr. 26 - March 02, 2010;
Do we need a new definition of the hypereosinophilic syndrome?

51. Jahrestagung der Deutschen Gesellschaft für Pharmakologie und Toxikologie (DGPT); Mainz (D), March 23-25, 2010;
EPHAR lecture: Autophagy, stem cells, and cancer.

1st Conference of the European Research Institute for Integrated Cellular Pathology (ERI-ICP); Paris (F), April 22-23, 2010;
Caspase-dependent and -independent mechanisms of neutrophil death.

Collegium Internationale Allergologicum (CIA); Ischia (I), April 25-30, 2010;
New extracellular structures generated by eosinophils: Role of mitochondrial DNA.

Workshop on Cell Death: “From basic principles to clinical application”, Villa Vigoni, Loveno di Menaggio, Como (I), May 12-15, 2010;
Different forms of programmed neutrophil death in inflammation.

Nobel Symposium No 144: "The Cell Cycle and Apoptosis in Disease", Nobel Forum, Karolinska Institutet, Stockholm (Sweden), May 23-26, 2010;
Apoptosis and other forms of neutrophil death in inflammatory diseases.

29th Congress of the European Academy of Allergy and Clinical Immunology (EAACI), London (UK), June 05-09, 2010;
Mitochondrial DNA release from eosinophils.

40th Meeting of the German Society for Immunology (DGfI), Leipzig (D), Sept. 22-25, 2010;
Activation and death pathways in eosinophils and neutrophils.

6th Swiss Apoptosis Meeting (SAM), Bern (CH), Sept. 30 - Oct. 1, 2010;
Autophagy in adult stem cells.

European Academy of Dermatology and Venereology (EADV)-Workshop: From the Bench to the Clinic, Bellinzona (CH), Nov. 18, 2010; Autophagy.

PD Dr. Peter Späth

XIth Meeting of the International Patient Organization for Primary Immunodeficiencies (IPOPI), Istanbul (TR), October 6-9, 2010;
Preparation of a high light report (in print) from the IPOPI meeting, the XIVth Meeting of the European Society for Immunodeficiencies (ESID) and the IXth Meeting of the International Nursing Group for Immunodeficiencies (INGID).

Annual Meeting of the Romanian Hereditary Angioedema Network, Târgu Mures (ROM), October 14-15, 2010;
A short overview of bradykinin-mediated hereditary angioedema associated or not with C1-INH deficiency.

Dr. Stephan von Gunten

7th International Congress on Autoimmunity, Ljubljana (SL), May 5-9, 2010;
Novel insights into carbohydrate recognition by the humoral immune system.

Consortium for Functional Glycomics (CFG), Bethesda MD (USA), May 20-21, 2010;
Granulocyte death-inducing anti-Siglec autoantibodies in intravenous immunoglobulin (IVIG).

Prof. Uwe Zangemeister-Wittke

The 27th International conference on advances in the application of antibodies in clinical oncology, Mykonos (GR), June 21-23, 2010;
EpCAM-specific designed ankyrin repeat proteins for tumor targeting.

Prof. Shida Yousefi

Training Course "Concepts and Methods in Programmed Cell Death" in association with the 6th Swiss Apoptosis Meeting, Bern (CH), Sept. 29, 2010;
Autophagy: Physiology and role in disease.

4.3. Seminar Invitations

Prof. Thomas Kaufmann

Interfacultary Institute of Biochemistry, Univ. of Tübingen, Tübingen (D), April 15, 2010;
guest of Prof. K. Schulze-Osthoff:
Novel insights into the crosstalk between the death receptor and the mitochondrial apoptotic pathway.

Prof. Hans-Uwe Simon

University of Geneva, Dept. of Immunology and Allergy, Geneva (CH), June 22, 2010;
guest of Prof. Carlo Chizzolini:
Redefinition and work-up of hypereosinophilic syndromes.

Venetian Institute of Molecular Medicine, Padova (I), Nov. 5, 2010; guest of Prof. Luca Scorrano:
Extracellular DNA traps in infection, autoimmunity, and allergy.

Institut für Pharmazie, Universität Tübingen, Tübingen (D), Dec. 8, 2010; guest of Prof. Peter Ruth:
Extracellular DNA traps generated by eosinophils and neutrophils.

PD Dr. Peter Späth

Luzerner Kantonsspital, Zentrum für Labormedizin, Jan. 27, 2010:
Primary immune deficiencies: Case presentations – Clinic and laboratory.

Athens Medical Society Teaching Courses; Vytina (GR), Febr. 26, 2010:
Manufacturing, pathogen safety and clinical use of intravenous immunoglobulins.

Athens Medical Society Teaching Courses; Kastoria (GR), March 5, 2010:
Intravenous immunoglobulins - 'Recent' developments.

CME Teaching Courses in Neurology, St. Gilgen (A), Oct. 1-2, 2010:
Mechanism of action of immunoglobulin preparations.

CME Teaching Courses in Neurology, Villach (A), Nov. 12-13, 2010:
Mechanism of action of immunoglobulin preparations.

Launch meeting for Privigen, CSL Behring Milan (I), Sept. 9, 2010:
'State-of-the-art' IVIG: Production and clinical use – History, recent progresses, actual issues and outlook.

Central Diagnostic Laboratory of the Vasta Romagna Region, Pievestina (I), Dec. 4, 2010:
Pathophysiological role and diagnostic relevance of abnormalities of the complement system.

Dr. Stephan von Gunten

Weiterbildung, Quick-Soups Rheumatologie, Department of Rheumatology, Clinical Immunology & Allergology, University Hospital Bern, Bern (CH), Feb. 10, 2010;
Immunoregulatory effects of Siglecs and IVIG.

Cardiovascular Research Conference (CRC), Department of Clinical Research, University of Bern, Bern (CH), March 3, 2010; guest of Prof. Robert Rieben:
Immunoregulatory effects of Siglecs and intravenous immunoglobulin.

Medipol Symposium, Institute of Pharmacology, Univ. of Bern, Bern (CH), Dec. 8, 2010;
Targeting Siglecs by glycomimetics.

Prof. Uwe Zangemeister-Wittke

Department of Pharmacology, Medical University of South Carolina (MUSC, USA), July 14, 2010.
IgG and non-IgG scaffolds for disease targeting.

Centro Genética Humana, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo, Santiago de Chile (Cl), October 20, 2010.
EpCam as a therapeutic target on carcinoma cells with stem-like potential.

PhD examination committee of Mag. Martina Stessl, Department of Medicinal Chemistry, University of Vienna, Vienna (A), August 3, 2010.
Discussion session on a proteomic study on off-target effects of therapeutic oligonucleotides.

4.4. Organization of Meetings and Courses

Prof. Thomas Kaufmann

Co-organiser of 6th Training Course "Concepts and Methods in Programmed Cell Death", Bern (CH), Sep. 29, 2010

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), Febr. 4, 2010

Clinical Immunological Conference (together with D. Simon): Atopic Dermatitis, Bern (CH), March 24, 2010

9th III-Bern International Summer School, Kandersteg (CH), Aug. 8 - 10, 2010

6th Swiss Apoptosis Meeting (together with T. Brunner, Univ. of Konstanz (D))
Bern (CH), Sept. 30 - Oct. 1, 2010

Bern Immunology Club (together with the other founder members); Institute of Pharmacology, University of Bern, one meeting in each month of 2010

PD Dr. Peter Späth

CME Teaching Courses in Neurology: Use of IVIG for CNS diseases;
together with the Dept. of Neurology, Oö. Gesundheits- und Spitals-AG, Linz (A)**,** Oct. 1-2, 2010, and Dept. of Neurology, Landeskrankenhaus Villach (A), Nov. 12-13, 2010

Dr. Stephan von Gunten

Medipol Symposium, Institute of Pharmacology, University of Bern, Bern (CH),
Dec. 8, 2010.

Prof. Shida Yousefi

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis, Bern (CH), April 19-20, 2010.

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis, Bern (CH), Oct. 5-6, 2010.

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon

Symposium der Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie - Pharmacology of Pain; Bern (CH), Febr. 4, 2010

Honorary Chair of the Workshop on Cell Death: “From basic principles to clinical application”, Villa Vigoni, Loveno di Menaggio, Como (I), May 12-15, 2010

29th Congress of the European Academy of Allergy and Clinical Immunology (EAACI); Plenary Symposium 1: “Regulation of mucosal immunity”; London (UK), June 05-09, 2010

29th Congress of the European Academy of Allergy and Clinical Immunology (EAACI); Poster session: “Eosinophils and mast cell associated disorders II”; London (UK), June 05-09, 2010

29th Congress of the European Academy of Allergy and Clinical Immunology (EAACI); Symposium 29: “Hypereosinophilic syndromes”; London (UK), June 05-09, 2010

18th Euroconference on Apoptosis (ECDO); Session: “Non-apoptotic cell death”; Ghent (Belgium), Sept. 01-04, 2010

6th Swiss Apoptosis Meeting (SAM); Session: "Apoptosis/autophagy and cancer"; Bern (CH), Sept. 30-Oct. 1, 2010

PD Dr. Peter Späth

Summer School for Pediatricians, Charité; Session: "Case presentations II"; Berlin (D), June 25-26, 2010

4.6. Referee Work for Peer-Reviewed Journals

Dr. Sébasien Conus

Cell Death Differ.	Allergy

Dr. Barbara Geering

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

Allergy
Apoptosis
Cell Death and Differentiation
Cell Death and Disease
Frontiers Mol Cell Oncol
Hepatology
Immunology and Cell Biology
Journal of Hepatology
Oncogene
PLoS One

Dr. Christina Merz-Stöckle

Allergy

Prof. Hans-Uwe Simon

Advances in Medical Sciences
Allergy
Apoptosis
Autophagy
Biochem. Pharmacol.
Blood
Clin. Exp. Allergy
Clin. Exp. Immunol.
EMBO Journal
EMBO Reports
Eur. J. Haematol.
Eur. J. Immunol.
FASEB J.
Cell Death Differ.
Infect. Immun.
Int. J. Cancer
J. Allergy Clin. Immunol.
J. Cell Biol.
J. Exp. Med.
J. Immunol.
J. Leukoc. Biol.
Naunyn-Schmiedeberg Arch. Pharmacol.
N. Engl. J. Med.
Plant Sciences
Proc. Natl. Acad. Sci. USA
Trends Immunol.
Trends Pharmacol. Sci.
Cell Death & Disease

PD Dr. Peter Späth

Allergy

Dr. Stephan von Gunten

Allergy
Respiration
Mediators of Inflammation

Prof. Shida Yousefi

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

Prof. Uwe Zangemeister-Wittke

Bioconjug. Chem.
Lung Cancer
Cell Death Differ.
J. Biol. Chem.
PLoS One
J. Controled Release
J. Drug Targeting
Mol. Cell. Biol.
Nanotechnology

4.7. Referee Work for Grant Bodies

Dr. Sébastien Conus

Swiss Cancer League

Dr. Barbara Geering

Swiss Cancer League

Prof. Andrea Huwiler

Deutsche Forschungsgemeinschaft (DFG)
Norwegian Research Council

Prof. Thomas Kaufmann

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

Prof. Hans-Uwe Simon

Swiss National Science Foundation (SNF)
Italian Association for Cancer Res. (AIRC)
Deutsche Forschungsgemeinschaft (DFG)
Swiss Cancer League

Dr. Stephan von Gunten

Swiss Cancer League

Prof. Uwe Zangemeister-Wittke

Swiss Cancer League
Swiss National Science Foundation (SNF)

4.8. Awards

Anita Dähler, Secretary PKI

Support Prize of the Bern Immunology Club (BIC)
(Bern, Jan. 27, 2010)

Dr. Stephan von Gunten

DCR Research Prize 2010
Department of Clinical Research (DCR), University of Bern
(Bern, Nov. 3, 2010)

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 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

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), 1997-2011

Member of the Council of the Swiss Society of Pharmacology and Toxicology (SSPT), 2002-2011

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

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)

President, Union of the Swiss Societies for Experimental Biology (USSEB), 2007 - 2010

Member of the Scientific Committee, Swiss Cancer League, 2009 – 2011

Member of Scientific Advisory Board, HELMHOLTZ Zentrum für Umweltforschung (UFZ), Leipzig (D), 2009-2012

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

Member of the Editorial Board, Cell Death and Disease

PD Dr. Peter Späth

Advisor to the Department of Research & Development of CSL Behring AG, Bern Switzerland, since 2008

Dr. Stephan von Gunten

Member of the Editorial Board, Allergy

Participating Investigator at the Consortium of Functional Glycomics, National Institutes of Health (USA), 2009-2010

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

Member of the Editorial Board, Lung Cancer

Review Editor, Frontiers in Molecular and Cellular Oncology

Contact person of the Federal Committee for Work Safety (EKAS) at the PKI

Quality coach at the PKI

Biosafety coordinator at the PKI

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). Together with the Image analysis station, this facility was in operation in 2010 for approximately 1044 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 37 different research groups. In 2010, 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 Exhibitions

Aldona von Gunten – Liechti, Bern, Switzerland
Vernissage: April 8, 2010

Sabine und Christoph Hasler, Burgdorf, Switzerland
Vernissage: October 21, 2010

8. Sponsors

8.1. Research Grants

Dr. Sébastien Conus

Novartis Stiftung für medizinisch-biologische Forschung

Dr. Barbara Geering

L'Oréal fellowship "For Women in Science"
UniBern Forschungsstiftung

Dr. Stephan von Gunten

CSL Behring AG, Bern
UniBern Forschungsstiftung
Novartis Stiftung für medizinisch-biologische Forschung

Dr. Susanne Hösli

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

Prof. Andrea Huwiler

Swiss National Science Foundation (grant No. 3100AO-111806/1)
Deutsche Forschungsgemeinschaft
Norwegian Research Council and Avexxin AS
Wilhelm Sander-Stiftung
Novartis Stiftung
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

Dr. Christina Merz-Stöckle

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

Oleksandr Pastukhov

Fellowship, Eidgenössische Stipendienkommission für ausländische Studierende (ESKAS) (until June 2010)

Prof. Hans-Uwe Simon

Swiss National Science Foundation (grant No. 310000-107526)

Dr. Rabi Thangaiyan

Swiss National Science Foundation, International Short Visit (grant No. IZK0Z3_131439/1)

Prof. Shida Yousefi

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

Prof. Uwe Zangemeister-Wittke

Swiss National Science Foundation (grant No. 310030_119859)
Swiss National Science Foundation (grant No. 310030E-132762/1)
Bernische Krebsliga

8.2. Meetings

Swiss Society of Pharmacology and Toxicology (SSPT): Progress in Pharmacology Bern (CH), Febr. 4, 2010

Pfizer AG, Zurich
Eisai Pharma AG, Zürich
Mundipharma Medical Company, Basel

9th III-International Summer School, Kandersteg (CH), Aug. 8-10, 2010

Allergopharma AG, Therwil
Becton Dickinson Biosciences, Allschwil
Carl Zeiss AG, Feldbach
Eisai Pharma AG, Zürich
ENZO Life Science, Lausen
Essex Chemie AG, Luzern
GlaxoSmithKline AG, Münchenbuchsee
Lucerna Chem AG, Luzern
Pfizer AG, Zurich
Union of the Swiss Societies of Experimental Biology (USSEB)
Graduate School of Cellular and Biomedical Science, University of Bern

Swiss Apoptosis Meeting (SAM), Bern (CH), Sept. 30 – Oct. 1, 2010
BioConcept, Allschwil
BioRad, Reinach
Cell Death & Differentiation
Enzo Life Sciences, Lausen
LabForce AG, Nunningen
LuBio Science, Luzern
Lucerna Chem, Luzern
Max and Elsa Beer-Brawand-Fonds, Bern
Union of the Swiss Societies of Experimental Biology (USSEB)
Kontaktgruppe für Forschungsfragen (KGF), Basel

8.3. Seminars „Progress in Pharmacology“

2010:
CSL Behring AG, Bern
Pfizer AG, Zurich
GlaxoSmithKline AG, Münchenbuchsee
Novartis Pharma AG, Bern

2011:
CSL Behring AG, Bern
Pfizer AG, Zurich

8.4. Seminars „Bern Immunology Club“

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

8.5. Travel Support

Consortium for Functional Glycomics (CFG), National Institutes of Health (NIH)
Support of Dr. Stephan von Gunten

8.6. Other Support

Bürgi Fonds Seminar series of the institute