# Annual Report 2009

# Institut für Pharmakologie (PKI)

# der Universität Bern

# Institute of Pharmacology,

# University of Bern

**Address:** **Friedbühlstrasse 49**
**CH-3010 Bern**
**Switzerland**

**Tel.: +41-31-632-3281**
**Fax: +41-31-632-4992**
**E-mail: sandra.suter@pki.unibe.ch**

**An online copy of this report can be obtained at http://www.pki.unibe.ch/**

## Table of Contents:

# 1. Introduction

## 1.1. Vorwort

Dies ist der neunte umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat auch im Jahr 2009 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 2009 trugen wir dazu bei, die Kommunikation zwischen WissenschaftlerInnen und Öffentlichkeit zu fördern. Dazu diente u.a. eine Doppel-Vernissage, 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 neu 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 21 DoktorandInnen (10 PhD, 11 MD), und 4 DoktorandInnen haben im Berichtsjahr ihre Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des Instituts für Pharmakologie publizierten im Jahr 2009 insgesamt 30 Originalarbeiten sowie 12 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >300). MitarbeiterInnen des Instituts wurden

zu insgesamt 36 Vorträgen bzw. Seminaren eingeladen. Mehrere MitarbeiterInnen des PKI wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 5 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. Gegenwärtig bereiten wir das 6. Swiss Apoptosis Meeting vor (Bern, 30.9. – 1.10.2010) (gemeinsam mit Prof. Brunner (Institut für Pathologie, Univ. Bern). Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Das PKI nimmt auch ausserhalb der Universität wissenschaftspolitische Verantwortung für die Medizin und die Biowissenschaften wahr. Prof. Simon amtet gegenwärtig als Präsident der Union der Schweizerischen Gesellschaften für Experimentelle Biologie (USGEB). Bis Sept. 2009 war er auch Präsident der European Cell Death Organization (ECDO).

Ich danke allen Mitarbeitern und Mitarbeiterinnen für ihren Einsatz, welcher auch im Jahr 2009 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 2010

## 1.2. Foreword

This is the ninth 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 2009 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 2009. 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 newly 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, 10 PhD students and 11 MD students work at the PKI, and four students (4 MD) successfully finished their doctoral studies in 2009.

In 2009, members of the Institute of Pharmacology published 30 original and 12 review articles in international peer-reviewed journals (the sum of the “impact factors” is more than 300). Co-workers of the institute were invited to 36 lectures or seminars. Several PKI members received research prizes. Five co-workers are currently supported by grants of the Swiss National Science Foundation. Several prominent researchers visited the institute and presented seminars. The Bern Immunology Club (BIC) is also thanks to our contribution

highly active and successful. Currently, we organize the 6th Swiss Apoptosis Meeting (Bern, Sept. 30 – Oct. 1, 2010) (together with Prof. Brunner, Institute of Pathology, Univ. of Bern). In summary, research plays an important role at the PKI and is performed at a high level.

The PKI also takes over responsibilities outside of the university. For instance, Prof. Simon served as President of the Swiss Society of Pharmacology and Toxicology (SSPT) and Experimental Pharmacology (SSEP). He is currently President of the Union of the Swiss Societies for Experimental Biology (USSEB) and served as President of the European Cell Death Organization (ECDO) until Sept. 2009.

I thank all co-workers for their hard work that contributed to the success of the PKI in 2009. I also thank all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD
Director

Bern, January 2010

# 2. Staff 2009

### Director

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

### Deputy Director

Prof. Dr. Andrea Huwiler, PhD

### Permanent Members

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

### Scientific Staff

Dr. Nicola Andina, MD, PhD student (until January 2009)
Daniel Bachmann, research assistant*
Dr. Sébastien Conus, PhD
Lukas Dürst, MD student* (until Sept. 2009)
Nohemy Echeverry, PhD student
Elena Federzoni, PhD student
Cornelia Frei, M.Sc. student* (January – June 2009)
Dr. Barbara Geering, PhD
Barbara Grieder, PhD student (since Oct. 2009)
Ursina Gurzeler, PhD student* (since April 2009)
Zhaouye He, PhD student
Dr. Nataliya Kotelevets, PhD*
Evelyne Kozlowski, technician
Meret Lehmann, MD student* (since May 2009)
He Liu, PhD student*
Marianne Maillard-Van Laer, technician
Patricia Martin-Killias, PhD student*
Dipak Maskey, PhD student
Cristina Mihalache, PhD student
Olexsandr Pastukhov, M.Sc.*
Susanne Probst, technician
Dr. Shuyu Ren, PhD (until October 2009)
Nina Roth, MD student* (since July 2009)
Dr. Souzan Salemi, PhD (until September 2009)
Inès Schmid, head technician
Dr. Jan Schmidt-Mende, MD, PhD (until January 2009)
Manuel Simon, PhD student
Simon Städler, MD student*

Dr. Christina Stöckle, PhD (since April 2009)
Matthias Stuck, MD student* (since June 2009)
David Troi, MD student* (until Oct. 2009)
Petra Trütsch, MD student* (since September 2009)
Dr. Stephan von Gunten, MD, PhD, MME
Thomas von Rütte, MD student*
Dr. Cuiyan Xin, PhD* (until October 2009)
Rahel Wüthrich, M.Sc. student* (January – June 2009)

**External University Teachers**

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

**Guest scientists**

PD Dr. Dagmar Simon, MD*, Dept. of Dermatology, Inselspital, University of Bern
PD Dr. Alex Straumann, MD*, Dept. of Gastroenterology, University of Basel
PD Dr. Mario Tschan, PhD*, Dept. of Clinical Research, University of Bern
Dr. Susanne Hösli, MD*, Medical Faculty, University of Bern

**External Computer Support**

Dominik Wyss*

**Office**

Sandra Suter, head secretary
Anita Dähler, secretary

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

**Workshop**

Hans Andres

**House Keeping**

Isa Conforti
Elisa Piccirilli

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

**Members of the Institute of Pharmacology of the University of Bern together with participants of an international summer school in Bönigen (Aug. 2009).**


**Members of the Institute of Pharmacology of the University of Bern during a trip to Romont (July 2009).**

# 3. Teaching Activities
## 3.1. Lectures

***Lectures for medical students***

| Date | Lecturer | Titel of the lecture |
|---|---|---|
| March 16, 2009 | Dr. Stephan von Gunten | Antidiabetika |
| March 18, 2009 | Dr. Stephan von Gunten | Fett-Lipidsenker, Gicht |
| April 6, 2009 | Prof. Andrea Huwiler | Antiepileptika |
| April 6, 2009 | Prof. Andrea Huwiler | Therapie von Morbus Parkinson und Demenz |
| April 8, 2009 | Prof. Andrea Huwiler | Lokalanästhetika |
| April 27, 2009 | Dr. Stephan von Gunten | Hormone aus pharmakologischer Sicht 1 |
| April 27, 2009 | Dr. Stephan von Gunten | Hormone aus pharmakologischer Sicht 2 |
| May 4, 2009 | Prof. Andrea Huwiler | Pharmakologie der Narkotika / Anästhesie 1 |
| May 6, 2009 | Prof. Andrea Huwiler | Psychopharmakologie |
| May 11, 2009 | Prof. Andrea Huwiler | Antidepressiva, Anxiolythika und Stimmungsstabilisatoren |
| May 18, 2009 | Prof. Andrea Huwiler | Antipsychotika |
| May 27, 2009 | Prof. Andrea Huwiler | Schmerz und Analgesiologie 1 |
| May 27, 2009 | Prof. Andrea Huwiler | Schmerz und Analgesiologie 2 |
| May 27, 2009 | Prof. Andrea Huwiler | Altern: Auswirkungen auf die Pharmako-Dynamik und Pharmakokinetik |
| June 9, 2009 | Prof. Hans-Uwe Simon | Immunmodulation |
| Sept. 14, 2009 | Prof. Thomas Kaufmann | Adaptation und Zellschäden |
| Sept. 16, 2009 | Prof. Hans-Uwe Simon | Pharmakodynamik 1 |
| Sept. 21, 2009 | Prof. Hans-Uwe Simon | Pharmakodynamik 2 |
| Sept. 23, 2009 | Prof. Hans-Uwe Simon | Einführung in die Toxikologie |
| Sept. 30, 2009 | Prof. Hans-Uwe Simon | Entzündungshemmung |

| | | |
|---|---|---|
| Oct. 26, 2009 | Prof. Hans-Uwe Simon | Pharmakotherapie bei Lungenkrankheiten |
| Nov. 2, 2009 | PD Dr. Peter Späth<br>Prof. Uwe Zangemeister-Wittke | Antithrombotische Therapie II & Antikoagulantien |
| Nov. 2, 2009 | Prof. Uwe Zangemeister-Wittke | Wirkprinzipien der Antihypertensiva |
| Nov. 3, 2009 | Prof. Uwe Zangemeister-Wittke | Behandlung der Herzinsuffizienz und Angina Pectoris |
| Nov. 10, 2009 | Prof. Uwe Zangemeister-Wittke | Antiarrhythmika |
| Nov. 18, 2009 | Prof. Uwe Zangemeister-Wittke | Pharmakologie des vegetativen Nervensystems |
| Dec. 7, 2009 | Prof. Uwe Zangemeister-Wittke | Diuretika |

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

| **Date** | **Lecturer** | **Title of the lecture** |
|---|---|---|
| Febr. 9, 2009 | Prof. Hans-Uwe Simon | Allgemeine Pharmakologie: Einführung, Rezeptoren |
| Febr. 9, 2009 | Prof. Hans-Uwe Simon | Allgemeine Pharmakologie: Dosis-Wirkungskurven |
| Febr. 11, 2009 | Prof. Hans-Uwe Simon | Antagonisten / Applikation |
| Febr. 18, 2009 | Prof. Uwe Zangemeister-Wittke | Aufnahme / Verteilung |
| Febr. 23, 2009 | Prof. Uwe Zangemeister-Wittke | Arzneimittelmetabolismus / Elimination |
| Febr. 23, 2009 | Prof. Uwe Zangemeister-Wittke | Gesamtkinetik / Dosierung |
| Febr. 23, 2009 | PD Dr. Peter Späth | Orale Antikoag./Plättchenhemmer |
| Febr. 25, 2009 | Prof. Andrea Huwiler | Interaktionen / Pharmakogenetik, allg. |
| March 9, 2009 | Prof. Uwe Zangemeister-Wittke | Vegetatives Nervensystem |

| | | |
|---|---|---|
| March 9 , 2009 | Prof. Uwe Zangemeister-Wittke | Herz-Kreislaufpräparate |
| March 18, 2009 | PD Dr. Armand Cachelin | Immunsuppression |
| March 23, 2009 | PD Dr. Armand Cachelin | Schwache Analgetika |
| March 23, 2009 | PD Dr. Armand Cachelin | Starke Analgetika |
| March 35, 2009 | Dr. Sibylle Bürgi | Lokalanästhetika I |
| April 1, 2009 | Dr. Sibylle Bürgi | Lokalanästhetika II |
| April 8, 2009 | Dr. Sibylle Bürgi | Insulin, orale Antidiabetika |
| April 20, 2009 | Dr. Sibylle Bürgi | Antibiotika I |
| April 20, 2009 | Dr. Sibylle Bürgi | Antibiotika II |
| April 22, 2009 | Prof. Andrea Huwiler | Narkose-/Beruhigungsmittel |
| April 29, 2009 | Dr. Stephan von Gunten | Psychopharmaka |
| May 4, 2009 | Dr. Stephan von Gunten | Magensäurehemmung |
| May 4, 2009 | Prof. Uwe Zangemeister-Wittke | Examensvorbereitung |
| Sept. 29, 2009 | Prof. Thomas Kaufmann | Zellschäden (allg. Pathologie-Vorlesung) |

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

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

| **Date** | **Lecturer** | **Title of the lecture** |
|---|---|---|
| Febr. 19, 2009 | Prof. Hans-Uwe Simon | Introduction |
| Febr. 19, 2009 | Prof. Hans-Uwe Simon | Immunopharmacology |
| April 23, 2009 | 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. 12, 2009 | 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 26, 2009 | Prof. Andrea Huwiler | Lipid mediators involved in inflammation |
| May 14, 2009 | Prof. Shida Yousefi | Resolution of inflammation - apoptosis |

***Practical work for Natural Science Faculty: Immunology II (Coordinator: Prof. Christoph Müller)***

| Date | Lecturer | Title of the lecture |
|---|---|---|
| Oct./Nov. 2009 (total 8h) | Prof. Thomas Kaufmann | Isolation of leukocytes |

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

| Date | Lecturer | Title of the lecture |
|---|---|---|
| Febr. 23, 2009 | Prof. Hans-Uwe Simon | Pharmacodynamics I |
| Febr. 23, 2009 | Prof. Hans-Uwe Simon | Pharmacodynamics II |
| April 6, 2009 | Prof. Hans-Uwe Simon | Toxicology |
| April 6, 2009 | Prof. Hans-Uwe Simon | Pharmacology of inflammation |
| April 27, 2009 | 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. Hans-Uwe Simon)***

| Date | Lecturer | Title of the lecture |
|---|---|---|
| Sept. 18, 2009 | Prof. Hans-Uwe Simon | Immune system |
| Sept. 25, 2009 | Prof. Uwe Zangemeister-Wittke | Heart and vascular system |
| Oct. 9, 2009 | Prof. Andrea Huwiler | Nervous system |
| Oct. 16, 2009 | Dr. Stephan von Gunten | Endocrine and reproductive system |
| Oct. 26, 2009 | Prof. Thomas Kaufmann | Cell damage (within Pathology lecture series) |
| Oct. 30, 2009 | Prof. Shida Yousefi | Lungs and kidneys |
| Nov. 6, 2009 | PD Dr. Peter Späth | Haemopoietic system and haemostasis |
| Nov. 13, 2009 | Prof. Shida Yousefi | Antiinfectious therapy |

***External teaching activities: University of Basel (Drug Discovery and Development)***

| Date | Lecturer | Title of the lecture |
|---|---|---|
| Nov. 18, 2009 | Prof. Hans-Uwe Simon | New approaches in the treatment of atopic eczema and eosinophilic esophagitis |

***External teaching activities: University of Zurich (Molecular Medicine)***

| Date | Lecturer | Title of the lecture |
|---|---|---|
| March 2-3, 2009 | Prof. Uwe Zangemeister-Wittke | Introduction into tumor biology |
| May 2009 (total 6h) | Prof. Uwe Zangemeister-Wittke | Human and dental students: Molecular Cell Biology |

***External teaching activities: University of Fribourg (Institute of Biochemistry)***

| Date | Lecturer | Title of the lecture |
|---|---|---|
| Nov.-Dec., 2009 (total 8h) | Prof. Thomas Kaufmann | Apoptosis: Mechanisms, techniques, and therapeutic targets. |

## 3.2. Coordination PBL Medical Students, 3rd year (2009/2010)

***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 2009/2010)

***Medical students 3rd year:***

| | |
|---|---|
| Dr. Sébastien Conus | Dr. Christina Stöckle |
| Prof. Thomas Kaufmann | Dr. Barbara Geering |

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

## 3.4. Inaugural Lectures

| Date | Lecturer | Title |
|---|---|---|
| Febr. 25, 2009 | Prof. Shida Yousefi,<br>Institute of Pharmacology<br>University of Bern | DNA release by granulocytes: Anti-bacterial catapults |

## 3.5. Seminars of Invited Speakers

| Date | Teacher | Title of the seminar |
|---|---|---|
| April 1, 2009 | Prof. Luca Scorrano<br>Dept. of Cell Physiology and Metabolism<br>University of Geneva | Keeping mitochondria and ER in shape: a matter of life and death |
| April 7, 2009 | Dr. Carole Bourquin<br>Medizinische Klinik<br>Klinikum der Universität München (D) | Immunotherapy of cancer with RNA oligonucleotides |
| April 14, 2009 | Prof. Harald Reuter<br>Institute of Pharmacology<br>University of Bern | Pharmacology in Bern: a personal view |
| April 15, 2009 | Dr. Camilla Jandus<br>Ludwig Institute for Cancer Research<br>Lausanne | Dissecting tumor specific CD4 T cell responses in melanoma patients |
| April 22, 2009 | Dr. Stefan Müller<br>Dept. Clinical Research<br>University of Bern | Can neutrophil malfunction lead to Crohn's disease? Testing a to disease hypothesis |
| May 6, 2009 | Prof. Valentin Djonov<br>Gross Anatomy & Vascular Biology<br>University of Fribourg | Multiple actions of angiogenic inhibitors and ionizing radiation tumors |
| May 26, 2009 | Prof. Peter Ruth<br>Institut für Pharmazie<br>Universität Tübingen (D) | New roles of $Ca^{2+}$ -activated $K^{+}$ channels in vital functions |
| June 3, 2009 | PD Dr. Silke Fischer<br>Institut für Med. Mikro-biologie und Hygiene<br>Universität of Ulm (D) | Modulation of apoptosis by the intracellular pathogen Leishmania |
| June 16, 2009 | Prof. Hugues Abriel<br>Dept. Clinical Research<br>University of Bern | Regulation of the voltage-gated cardiac sodium channels by associated proteins |
| June 24, 2009 | Prof. Marion Schneider<br>Experim. Anästhesiologie<br>Universität of Ulm (D) | Immune alterations, biomarker profiling and staging in patients with trauma and sepsis |

| | | |
|---|---|---|
| Aug. 14, 2009 | Dr. Lynn Wong<br>LaTrobe, University<br>of Melbourne (Aus) | RIPK1 is not essential for TNFR1 induced activation of NFκB |
| Oct. 14, 2009 | Dr. Hans U. Lutz,<br>Institute of Biochemistry<br>ETH Zurich | Anti-C3 and anti-idiotypic naturally occurring antibodies together modulate C3 convertase activity in vitro and possibly in vivo |
| Nov. 18, 2009 | Dr. Antoine Attinger<br>Glenmark<br>Pharmaceuticals S.A.,<br>La Chaux-de-Fonds | Development of an anti-alpha2 integrin antibody for the treatment of inflammatory disorders |
| Nov. 25, 2009 | Dr. José M. Carballido<br>Novartis Institutes<br>for Biomedical Research,<br>Basel | Enhancing immunity by sensing metabolism associated molecular patterns |

## 3.6. Bern Immunology Club (BIC)

| Date | Teacher | Title of the seminar |
|---|---|---|
| Jan. 28, 2009 | Prof. Erich Gulbins<br>Dept. Molecular Biology<br>University of<br>Duisburg-Essen (D) | Ceramide in tumor metastasis and treatment |
| March 25, 2009 | Stephan Kuchen,<br>University of Bern | Human B cell response to IL-21 and BAFF in the context of autoimmune diseases |
| April 12, 2009 | Dr. Reina Mebius,<br>Dept. Molecular<br>Cell Biol. and Immunol.<br>Amsterdam (NL) | Common mechanisms in the formation of secondary and tertiary lymphoid organs |
| June 24, 2009 | Prof. Andrew Macpherson<br>Universitätstklinik<br>Viszerale Chirurgie und<br>Medizin, Inselspital, Bern | Mutualism between the adaptive and innate arms of the immune system with commensal intestinal bacteria |
| Sept. 30, 2009 | Prof. Manfred Kopf<br>ETH Zürich | Regulation of immune responses by oxidative stress and the lipid microenvironment |
| Oct. 28, 2009 | Prof. Matthias Mack<br>Pneumologie<br>Universitätsklinikum<br>Regensburg (D) | Basophils as important regulators of memory immune responses |

| | | |
|---|---|---|
| Nov. 25, 2009 | Dr. Charaf Benarafa<br>Theodor Kocher Institute, Bern | Role of the serine protease inhibitor serpinB1 in neutrophil homeostasis and 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_10/index_eng.html

## 3.7. Academic Degrees

***Jennifer Wittwer, Dr. med. (MD), University of Bern***
Thesis: Alefasept (lymphocyte function-associated molecule 3/ IgG fusion protein) treatment for atopic eczema.
Institute of Pharmacology, Bern, April 2009
Supervisors: Prof. Hans-Uwe Simon, PD Dr. Dagmar Simon

***Lukas Dürst, Dr. med. (MD), University of Bern***
Thesis: MediOnline (ein neues Computer-Lernprogramm zum Erlernen der wichtigsten pharmakologischen Substanzen)
Institute of Pharmacology, Bern, September 2009
Supervisors: Prof. Andrea Huwiler, Prof. Peter Frey (IML Bern)

***David Antonio Troi, Dr. med. (MD), University of Bern***
Thesis: Expression of RhoH/TTF in neutrophilic granulocytes Assessed by indirect immunofluorescence staining and Subsequent confocal laser scanning analysis
Institute of Pharmacology, Bern, October 2009
Supervisors: Prof. Hans-Uwe Simon, Prof. Shida Yousefi, PhD

***Pascale Susanne Gronzka, Dr. med. (MD), University of Bern***
Thesis: Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic esophagitis: a randomized, placebo-controlled, double-blind trial
Institute of Pharmacology, Bern, November 2009
Supervisors: Prof. Hans-Uwe Simon, Dr. Sébastien Conus, PhD

***Cornelia Frei, M.Sc. pharm., University of Basel***
Thesis: Budesonide treatment in eosinophilic esophagitis (maintenance study)
Institute of Pharmacology, Bern, June 2009
Supervisors: Prof. Hans-Uwe Simon, Dr. Sébastien Conus, PhD

***Rahel Wüthrich, M.Sc. pharm., University of Basel***
Thesis: Characterization of eosinophilic skin inflammation
Institute of Pharmacology, Bern, June 2009
Supervisors: Prof. Hans-Uwe Simon, PD Dr. Dagmar Simon

# 4. Research Activities

## 4.1. Research Projects and Publications

### *Group Prof. Andrea Huwiler*

Group members: Marianne Maillard – Van Laer, technician[1]
Dr. Shuyu Ren, PhD[1]
Dr. Cuiyan Xin, PhD[1]
Barbara Grieder, PhD student[1]
Lukas Dürst, MD student[1]
Dr. Alexander Koch, PhD[2]
Stephanie Schwalm, PhD student[2]
Lotte P. Hofmann, Vet.med., PhD student[2]
Ankathrin Förster, PhD student[2]
Mahsa Ebadi, 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.

**Involvement of the ABC-transporter ABCC1 and the sphingosine-1-phosphate receptor subtype S1P3 in the cytoprotection of human fibroblasts by the glucocorticoid dexamethasone**

B. Nieuwenhuis, A. Lüth, A. Huwiler, J. Chun, J. Pfeilschifter, M. Schäfer-Korting, B. Kleuser

Glucocorticoids (GC) represent the most commonly used drugs for the treatment of acute and chronic inflammatory skin diseases. However, the topical long-term therapy of GC is limited by the occurrence of skin atrophy. Most interestingly, although GC inhibit proliferation of human fibroblasts, they exert a pronounced anti-apoptopic action. In the present study, we further elucidated the molecular mechanism of the GC dexamethasone (Dex) to protect human fibroblasts from programmed cell death. Dex not only significantly alters the expression of the cytosolic isoenzyme sphingosine kinase 1 but also initiated an enhanced intracellular formation of the sphingolipid sphingosine 1-phosphate (S1P).

Investigations using S1P (3) ((-/-)) -fibroblasts revealed that this S1P-receptor subtype is essential for the Dex-induced cytoprotection. Moreover, we demonstrate that the ATP-binding cassette (ABC)-transporter ABCC1 is upregulated by Dex and may represent a crucial carrier to transport S1P from the cytosol to the S1P(3)-receptor subtype. **See original publication No. 1**

**SphK1 is pivotal for FceRI-mediated mast cell signalling and functional responses in vitro and in vivo**

P.N. Pushparaj, J. Manikandan, H.K. Tay, S. Chen H'ng, S.D. Kumar, J. Pfeilschifter, A. Huwiler, A.J. Melendez

Mast cell degranulation is pivotal to allergic diseases; investigating novel pathways triggering mast cell degranulation would undoubtedly have important therapeutic potential. FcepsilonRI-mediated degranulation has contradictorily been shown to require SphK1 or SphK2, depending on the reports. We investigated the in vitro and in vivo specific role(s) of SphK1 and SphK2 in FcepsilonRI-mediated responses, using specific small interfering RNA-gene silencing. The small interfering RNA-knockdown of SphK1 in mast cells inhibited several signaling mechanisms and effector functions, triggered by FcepsilonRI stimulation including: Ca(2+) signals, NFkappaB activation, degranulation, cytokine/chemokine, and eicosanoid production, whereas silencing SphK2 had no effect at all. Moreover, silencing SPHK1 in vivo, in different strains of mice, strongly inhibited mast cell-mediated anaphylaxis, including inhibition of vascular permeability, tissue mast cell degranulation, changes in temperature, and serum histamine and cytokine levels, whereas silencing SPHK2 had no effect and the mice developed anaphylaxis. Our data differ from a recent report using SPHK1(-/-) and SPHK2(-/-) mice, which showed that SphK2 was required for FcepsilonRI-mediated mast cell responses. We performed experiments in mast cells derived from SPHK1(-/-) and SPHK2(-/-) mice and show that the calcium response and degranulation, triggered by FcepsilonRI-cross-linking, is not different from that triggered in wild-type cells. Moreover, IgE-mediated anaphylaxis in the knockout mice showed similar levels in temperature changes and serum histamine to that from wild-type mice, indicating that there was no protection from anaphylaxis for either knockout mice. Thus, our data strongly suggest a previously unrecognized compensatory mechanism in the knockout mice, and establishes a role for SphK1 in IgE-mediated mast cell responses. **See original publication No. 2**

**Transforming growth factor-β2 upregulates sphingosine kinase-1 activity, which in turn attenuates the fibrotic response to TGF-β2 by impeding CTGF expression**

S. Ren, A. Babelova, K. Moreth, C. Xin, W. Eberhardt, A. Doller, H. Pavenstädt, L. Schaefer, J. Pfeilschifter, A. Huwiler

Transforming growth factor-beta2 (TGF-beta2) stimulates the expression of pro-fibrotic connective tissue growth factor (CTGF) during the course of renal disease. Because sphingosine kinase-1 (SK-1) activity is also upregulated by TGF-beta, we studied its effect on CTGF expression and on the development of renal fibrosis. When TGF-beta2 was added to an immortalized human podocyte cell line we found that it activated the promoter of SK-1, resulting in upregulation of its mRNA and protein expression. Further, depletion of SK-1 by small interfering RNA or its pharmacological inhibition led to accelerated CTGF expression in the podocytes. Over-expression of SK-1 reduced CTGF induction, an effect mediated by intracellular sphingosine-1-phosphate. In vivo, SK-1 expression was also increased in the podocytes of kidney sections of patients with diabetic nephropathy when compared to normal sections of kidney obtained from patients with renal cancer. Similarly, in a mouse model of streptozotocin-induced diabetic nephropathy, SK-1 and CTGF were upregulated in

podocytes. In SK-1 deficient mice, exacerbation of disease was detected by increased albuminuria and CTGF expression when compared to wild-type mice. Thus, SK-1 activity has a protective role in the fibrotic process and its deletion or inhibition aggravates fibrotic disease.
**See original publication No. 3**

### *Original publications*


1. B. Nieuwenhuis, A. Lüth, **A. Huwiler,** J. Chun, J. Pfeilschifter, M. Schäfer-Korting, B. Kleuser: Involvement of the ABC-transporter ABCC1 and the sphingosine-1-phosphate receptor subtype S1P3 in the cytoprotection of human fibroblasts by the glucocorticoid dexamethasone.
   J. Mol. Med. 87 (2009), 645-657.

2. P.N. Pushparaj, J. Manikandan, H.K. Tay, H'ng Chen, S.D. Kumar, J. Pfeilschifter, **A. Huwiler**, A.J. Melendez: SphK1 is pivotal for FceRI-mediated mast cell signalling and functional responses in vitro and in vivo.
   *J. Immunol*. 183 (2009), 221-227.

3. S. Ren, A. Babelova, K. Moreth, C. Xin, W. Eberhardt, A. Doller, H. Pavenstädt, L. Schaefer, J. Pfeilschifter, **A. Huwiler**: Transforming growth factor-β2 upregulates sphingosine kinase-1 activity, which in turn attenuates the fibrotic response to TGF-β2 by impeding CTGF expression.
   Kidney Int. 76 (2009), 857-867.
   Comment in: Kidney Int. 7 (2009), 815-817 (Long and Price)

4. B. Czech, W. Pfeilschifter, N.M. Omrani, M.A. Strobel, T. Kahles, T. Neumann-Haefelin, A. Rami, **A. Huwiler**, J. Pfeilschifter: The immunomodulatory sphingosine 1-phosphate analog FTY720 reduces lesion size and improves neurological outcome in a mouse model of cerebral ischemia.
   *Biochem. Biophys. Res. Commun.* 389 (2009), 251-256.


### *Review articles*


1. **A. Huwiler,** J. Pfeilschifter: Lipids as targets for novel anti-inflammatory therapies. Pharmacol. Ther. 124 (2009), 96-112.

2. **A. Huwiler,** J. Pfeilschifter: Lipid signalling –Ample opportunities for novel drug targets. BIOforum Europe 10/2009, 22-23.

## *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.

A particular interest of our research lies in the members of the Bcl-2 protein family, which are crucial regulators of apoptosis. Besides cell death regulation in haematopoietic cells, we are interested in apoptosis pathways in hepatocytes. Abnormal hepatocyte apoptosis is a cause or contributing factor in many chronic as well as acute liver diseases in humans, including viral and autoimmune hepatitis, alcoholic liver disease, fat liver and endotoxin-induced liver failure. Apoptosis of hepatocytes is induced when so called 'death receptors', located on the cell surface, are bound by their complementary 'death ligands', present on specific immune cells or in a soluble form. The exact signalling pathways contributing to development and progression of these diseases are presently unclear. Among the most important death ligands with respect to liver damage are TNFa, Fas ligand (CD95 ligand) and TRAIL.

The generation and use of genetically modified mice allows analysis of the regulation of apoptosis in organs/tissues of the developing and mature organism as well as the development of tumours and autoimmunity in case of a de-regulated apoptotic program. We are using mouse strains lacking important apoptosis regulators, such as pro- and anti-apoptotic members of the Bcl-2 family. Members of the BH3-only subgroup, which acts as sensors of apoptotic stress signals, are of particular interest and there are now mice available lacking one or several BH3-only proteins. On the other hand, we have shown that anti-apoptotic proteins of the 'inhibitor of apoptosis' family (IAP) are crucial in preventing death receptor-induced hepatocyte apoptosis. Using both *in vitro* as well as *in vivo* approaches, we aim to further characterise the role of those regulators.

**XIAP discriminates between type I and type II Fas-induced apoptosis**

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

FAS (also called APO-1 and CD95) and its physiological ligand, FASL, regulate apoptosis of unwanted or dangerous cells, functioning as a guardian against autoimmunity and cancer development. Distinct cell types differ in the mechanisms by which the 'death receptor' FAS triggers their apoptosis. In type I cells, such as lymphocytes, activation of 'effector caspases' by FAS-induced activation of caspase-8 suffices for cell killing, whereas in type II cells, including hepatocytes and pancreatic b-cells, caspase cascade amplification through caspase-8-mediated activation of the proapoptotic BCL-2 family member BID (BH3 interacting domain death agonist) is essential. Here we show that loss of XIAP (X-chromosome linked inhibitor of apoptosis protein) function by gene targeting or treatment with a second mitochondria derived activator of caspases (SMAC11, also called DIABLO12; direct IAP-binding protein with low pI) mimetic drug in mice rendered hepatocytes and b-cells independent of BID for FAS-induced apoptosis. These results show that XIAP is the critical discriminator between type I and type II apoptosis signaling and suggest that IAP inhibitors should be used with caution in cancer patients with underlying liver conditions.

**See original publication No. 1**

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

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

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

**See original publication No. 2**

**MEK/ERK-mediated phosphorylation of Bim is required to ensure survival of T and B lymphocytes during mitogenic stimulation**

L.A. O'Reilly, E.A. Kruse, H. Puthalakath, P.N. Kelly, T. Kaufmann, D.C.S. Huang, A. Strasser

Survival and death of lymphocytes are regulated by the balance between pro- and antiapoptotic members of the Bcl-2 family; this is coordinated with the control of cell cycling and differentiation. Bim, a proapoptotic BH3-only member of the Bcl-2 family, can be regulated by MEK/ERK-mediated phosphorylation, which affects its binding to pro-survival Bcl-2 family members and its turnover. We investigated Bim modifications in mouse B and T lymphoid cells after exposure to apoptotic stimuli and during mitogenic activation. Treatment with ionomycin or cytokine withdrawal caused an elevation in Bim(EL), the most abundant Bim isoform. In contrast, in mitogenically stimulated T and B cells, Bim(EL) was rapidly phosphorylated, and its levels declined. Pharmacological inhibitors of MEK/ERK signaling prevented both of these changes in Bim, reduced proliferation, and triggered apoptosis of

mitogen-stimulated T and B cells. Loss of Bim prevented this cell killing but did not restore cell cycling. These results show that during mitogenic stimulation of T and B lymphocytes MEK/ERK signaling is critical for two distinct processes, cell survival, mediated (at least in part) through phosphorylation and consequent inhibition of Bim, and cell cycling, which proceeds independently of Bim inactivation.
**See original publication No. 3**

### *Original publications*

1. P.J. Jost, S. Grabow, D. Gray, M.D. McKenzie, U. Nachbur, D.C.S. Huang, P. Bouillet C.B. Borner CB, J. Silke, A. Strasser, **T. Kaufmann**: XIAP discriminates between type I and type II Fas-induced apoptosis.
Nature 460 (2009), 1035-1039.

2. **T. Kaufmann**, P.J. Jost, M. Pellegrini, H. Puthalakath, G. Gugasyan, S. Gerondakis, E. Cretney, M.J. Smyth, J. Silke, R. Hakem, P. Bouillet, T.W. Mak, V.M. Dixit, A. Strasser: Fatal Hepatitis Mediated by Tumor Necrosis Factor TNFa Requires Caspase-8 and Involves the BH3-only Proteins Bid and Bim.
Immunity 30 (2009), 56-66.

3. L.A. O'Reilly, E.A. Kruse, H. Puthalakath, P.N. Kelly, **T. Kaufmann**, D.C.S. Huang, A. Strasser: MEK/ERK-mediated phosphorylation of Bim is required to ensure survival of T and B lymphocytes during mitogenic stimulation.
J Immunol. 183 (2009), 261-269.

4. A. Jabbour, J.E. Heraud, C.P. Daunt, **T. Kaufmann**, J. Sandow, L.A. O'Reilly, B.A. Callus, A. Lopez, A. Strasser, D.L. Vaux, P.G. Ekert: Puma indirectly activates Bax to cause apoptosis in the absence of Bid or Bim.
Cell Death Differ. 16 (2009), 555-563.

### *Review article*

1. K. Bianchi, P.J. Jost, **T. Kaufmann**, R. Rutkowski: International EMBO Workshop on "Model Organisms in Cell Death Research", Obergurgl (Austria); meeting report.
Cell Death Differ. 16 (2009), 1180-1183.

## *Group Prof. Hans-Uwe Simon*

Group members:
Dr. Nicola Andina, MD, PhD student
Dr. Sébastien Conus, PhD
Elena Federzoni, PhD student*
Cornelia Frei, M.Sc. student
Stephanie Felder, MD student
Dr. Barbara Geering, PhD
Zhaouye He, PhD student
Susanne Hösli, MD student**
Evelyne Kozlowski, technician*
Meret Lehmann, MD student**
He Liu, PhD student
Dipak Maskey, PhD student*
Cristina Mihalache, PhD student
Nina Roth, MD student**
Dr. Souzan Salemi, PhD
Inès Schmid, head technician*
Dr. Jan Schmidt-Mende, MD, PhD
Simon Städler, MD student**
Dr. Christina Stöckle, PhD
David Troi, MD student*
Dr. Stephan von Gunten, MD, PhD, MME
Matthias Stuck, MD student
Thomas von Rütte, MD student*
Rahel Wüthrich, M.Sc. student**

*Joint supervision together with Prof. S. Yousefi.
**Joint supervision together with PD Dr. D. Simon.

We are interested in the role of apoptosis and autophagy in inflammatory diseases and cancer. Several diseases serve as models to study such processes. In particular, we investigate pathogenic mechanisms of the following diseases: Atopic dermatitis, hypereosinophilic syndromes, eosinophilic esophagitis, cystic fibrosis, sepsis, and malignant melanoma. Our research goal is the identification of new drug targets for future therapeutic approaches in these diseases. Besides the pathogenic aspects of our research, we have developed several in vitro and in vivo test systems to determine potential effects of a given drug on the immune system. Moreover, we are involved in several clinical drug studies. Our research requires a network of physician-scientists from many different clinics. Most of the participating groups are located at the Medical Faculty of the University of Bern. Results of these collaborative interactions are seen in the following abstracts, which briefly describe our research activities in 2009.

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

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

Background: Eosinophil differentiation, activation, and survival are largely regulated by interleukin-5 (IL-5). IL-5 – mediated transmembrane signal transduction involves both Lyn - mitogen-activated protein kinases (MAPK) and Janus kinase 2 (Jak2) – signal transduction and activator of transcription (STAT) pathways. Objective: We asked whether additional signalling molecules/pathways are critically involved in IL-5 – mediated eosinophil survival. Methods: Eosinophil survival and apoptosis was measured in the presence and absence of IL-5 and defined pharmacological inhibitors in vitro. The specific role of the serine/threonine kinase Pim-1 was tested using HIV-TAT fusion proteins containing wild-type Pim-1 or a dominant-negative form of Pim-1. The expression of Pim-1 in eosinophils was analyzed by immunoblotting and immunofluorescence. Results: Although pharmacological inhibition of phosphatidylinositol-3 kinase (PI3K) by LY294002, wortmannin, or the selective PI3K p110$\delta$ isoform inhibitor IC87114 was successful in each case, only LY294002, but not the other two PI3K inhibitors, blocked increased IL-5 – mediated eosinophil survival. This suggested that LY294002 inhibited, besides PI3K, another kinase, which is critically involved in this process. Indeed, Pim-1 was rapidly and strongly expressed in eosinophils following IL-5 stimulation in vitro and readily detected in eosinophils under inflammatory conditions in vivo. Moreover, by using specific protein transfer, we identified Pim-1 as a critical element in IL-5 – mediated anti-apoptotic signalling in eosinophils. Conclusions: Pim-1 but not PI3K plays a major role in IL-5 – mediated anti-apoptotic signalling in eosinophils. Clinical implication: Pim-1 represents a potential new anti-eosinophil drug target.

**See original publication No. 1**

**Induction of Bim limits cytokine-mediated prolonged survival of neutrophils**

N. Andina, S. Conus, E.M. Schneider, M.F. Fey, H.-U. Simon
(Collaboration with the Institute of Medical Onclology, Inselspital, University of Bern, and
Sektion Experimentelle Anästhesiologie, Universitätsklinikum Ulm, Germany)

Under inflammatory conditions, neutrophil apoptosis is delayed due to survival factor exposure, a mechanism that prevents the resolution of inflammation. One important pro-inflammatory cytokine involved in the regulation of neutrophil survival/activation is granulocyte-macrophage colony stimulating factor (GM-CSF). Although GM-CSF mediates anti-apoptotic effects in neutrophils, it does not prevent apoptosis, and the survival effect is both time-dependent and limited. Here, we identified the pro-apoptotic Bcl-2 family member Bim as an important life-span limiting molecule in neutrophils, particularly under conditions of survival factor exposure. Strikingly, GM-CSF induced Bim expression in both human and mouse neutrophils that was blocked by pharmacological inhibition of phosphatidylinositol-3 kinase (PI3K). Increased Bim expression was also seen in human immature bone marrow neutrophils as well as in blood neutrophils from septic shock patients, both cell populations are known to be exposed to GM-CSF under *in vivo* conditions. The functional role of Bim was investigated using Bim-deficient mouse neutrophils in the presence and absence of the survival cytokine interleukin (IL)-3. Lack of Bim expression resulted in a much higher efficacy of IL-3 to block neutrophil apoptosis. These data demonstrate a functional role for Bim in the regulation of neutrophil apoptosis and suggest that GM-CSF and other neutrophil hematopoietins initiate a pro-apoptotic counterregulation that involves up-regulation of Bim.

**See original publication No. 2**

**RhoH/TTF negatively regulates leukotriene production in neutrophils**

A. Daryadel, S. Yousefi, D. Troi, I. Schmid, J. Schmidt-Mende, C. Mordasini, C.A. Dahinden, A. Ziemiecki, H.-U. Simon
(Collaboration with the Departments of Clinical Research and Immunology, University of Bern, and Tiefenau Hospital Bern)

Leukotriene $B_4$ ($LTB_4$) is an important pro-inflammatory lipid mediator generated by neutrophils upon activation. Granulocyte/macrophage colony-stimulating factor (GM-CSF) stimulation is known to enhance agonist-mediated $LTB_4$ production of neutrophils within minutes, a process called “priming”. Here, we demonstrate that GM-CSF also limits the production of $LTB_4$ by neutrophils *via* a transcriptional mechanism at later time points. We identified hematopoietic specific Ras homologous (RhoH)/translocation three four (TTF), which was induced following GM-CSF stimulation in neutrophils, as a key regulator in this process. Neutrophils derived from RhoH/TTF-deficient (*Rhoh*$^{-/-}$) mice demonstrated increased $LTB_4$ production upon activation compared with normal mouse neutrophils. Moreover, neutrophils from cystic fibrosis patients expressed enhanced levels of RhoH/TTF and generated less $LTB_4$ upon activation compared with normal human neutrophils. Taken together, these data suggest that RhoH/TTF represents an inducible feedback inhibitor in neutrophils that is involved in the limitation of innate immune responses.

**See original publication No. 3**

**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. 4**

### *Original publications*


1. N. Andina, S. Didichenko, J. Schmidt-Mende, C.A. Dahinden, **H.-U. Simon**: Pim-1 but not PI3K is essential in the anti-apoptotic signalling cascade initiated by IL-5 in eosinophils.
   J. Allergy Clin. Immunol. 123 (2009), 603-611.

2. N. Andina, S. Conus, E.M. Schneider, M.F. Fey, **H.-U. Simon**: Induction of Bim limits cytokine-mediated prolonged survival of neutrophils.
   Cell Death Differ. 16 (2009), 1248-1255.

3. A. Daryadel, S. Yousefi, D. Troi, I. Schmid, J. Schmidt-Mende, C. Mordasini, C.A. Dahinden, A. Ziemiecki, **H.-U. Simon**: RhoH/TTF negatively regulates leukotriene production in neutrophils.
   J. Immunol. 182 (2009), 6527-6532.

4. 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.

5. S. Yousefi, C. Mihalache, E. Kozlowski, I. Schmid, **H.-U. Simon**: Viable neutrophils release mitochondrial DNA to form neutrophil extracellular traps.
   Cell Death Differ. 16 (2009), 1438-1444.

6. S. Salemi, S. Yousefi, D. Simon, I. Schmid, L. Moretti, L. Scapozza, **H.-U. Simon**: A novel FIP1L1-PDGFRA mutant destabilizing the inactive conformation of the kinase domain in chronic eosinophilic leukemia/hypereosinophilic syndrome.
   Allergy 64 (2009), 913-918.

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

8. D. Simon, E. Kozlowski, **H.-U. Simon**: NK-T cells in atopic dermatitis.
   Allergy 64 (2009), 1681-1684.

9. S. von Gunten, S.M. Jakob, B. Geering, J. Takala, **H.-U. Simon**: Different patterns of Siglec-9-mediated neutrophil death responses in septic shock.
   Shock 32 (2009), 386-392.

10. **H.-U. Simon**, B. Malhotra: The pharmacokinetic profile of fesoterodine: Similarities and differences to tolterodine.
    Swiss Med. Wkly. 139 (2009), 146-151.

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

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

13. P.J. Bousquet, J. Brozek, C. Bachert, ....., **H.-U. Simon**, ……., J. Bousquet: The CONSORT statement checklist in allergen-specific immunotherapy – a GA$^2$LEN paper.
Allergy 64 (2009), 1737-1745.

14. P.U. Ogbogu, B.S. Bochner, J.H. Butterfield, G.J. Gleich, J. Huss-Marp, J.E. Kahn, K.M. Leiferman, T.B. Nutman, F. Pfab, J. Ring, M.E. Rothenberg, F. Roufosse, M.-H. Sajous, J. Sheikh, D. Simon, **H.-U. Simon**, M.L. Stein, A. Wardlaw, P.F. Weller, A.D. Klein: Hypereosinophilic syndromes: a multicenter, retrospective analysis of clinical characteristics and response to therapy.
J. Allergy Clin. Immunol. 124 (2009), 1319-1325.

15. 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., in press; doi:10.1038/ajg.2009.657

16. 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., in press.

17. 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); in press, doi:10.1002/eji.200939556

***Review articles***

1. S. Yousefi, **H.-U. Simon**: Autophagy in cancer and chemotherapy.
Results Probl. Cell Differ., 2009, 183-190.

2. **H.-U. Simon**: Cell death in allergic diseases.
Apoptosis 14 (2009), 439-446.

3. S. Yousefi, **H.-U. Simon**: Autophagy in cells of the blood.
Biochim. Biophys. Acta (BBA) 1793 (2009), 1461-1464.

4. S. Bialik, A. Eisenberg, **H.-U. Simon**, A. Kimchi: Life and death partners: Apoptosis, autophagy and the cross-talk between them.
Cell Death Differ. 16 (2009), 966-975.

5. L. Galluzzi, S.A. Aaronson, J. Abrams, ….., **H.-U. Simon**, ……., G. Kroemer: Guidelines for the use and interpretation of assays for monitoring cell death in higher eukaryotes.
Cell Death Differ. 16 (2009), 1093-1107.

6. S. von Gunten, **H.-U. Simon**: Cell death modulation by IVIG.
J. Clin. Immunol., in press.

***Book chapters***

1. **H.-U. Simon**: Regulation of cell survival. In: Middleton's Allergy: Principles and Practice, 7th edition (Eds. N.F. Adkinson, W.W. Busse, B.S. Bochner, S.T. Holgate, E.F.R. Simons, R.F. Lemanske Jr.); MOSBY Elsevier, Edinburgh – London – New York – Oxford – Philadelphia – St. Louis – Sydney – Toronto, 2009, p. 413-421.

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

3. S. Yousefi, **H.-U. Simon**: Autophagy in cancer and chemotherapy. In: Death receptors and cognate ligands in cancer (Ed. H. Kalthoff); Springer, Berlin – Heidelberg, 2009, p. 183-190, doi:10.1007/400_2008_25

4. M.I. Colombo, **H.-U. Simon**: Autophagy. In: Encyclopedia of Life Sciences (ELS), John Wiley & Sons, Ltd: Chichester, 2009. DOI:10.1002/9780470015902.a0021581

## *Group Prof. Shida Yousefi*

Group members: Elena Federzoni, PhD student*
Evelyne Kozlowski, technician*
Dipak Maskey, PhD student*
Inès Schmid, head technician*
David Troi, MD student*
Thomas von Rütte, MD 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.

**Viable neutrophils release mitochondrial DNA to form neutrophil extracellular traps**
S. Yousefi, C. Mihalache, E. Kozlowski, I. Schmid, H.-U. Simon
Neutrophil extracellular traps (NETs) represent extracellular structures able to bind and kill microorganisms. It is believed that they are generated by neutrophils undergoing cell death, allowing these dying or dead cells to kill microbes. We show that, following priming with granulocyte/macrophage colony-stimulating factor (GM-CSF) and subsequent short-term toll-like receptor 4 (TLR4) or complement factor 5a (C5a) receptor stimulation, viable neutrophils are able to generate NETs. Strikingly, NETs formed by living cells contain mitochondrial, but no nuclear, DNA. Pharmacological or genetic approaches to block reactive oxygen species (ROS) production suggested that NET formation is ROS-dependent. Moreover, neutrophil populations stimulated with GM-CSF and C5a exhibited increased survival compared with resting neutrophils, which did not generate NETs. In conclusion, mitochondrial DNA release by neutrophils and NET formation do not require neutrophil death and do also not limit the lifespan of these cells.
**See original publication No. 1**

**A novel FIP1L1-PDGFRA mutant destabilizing the inactive conformation of the kinase domain in chronic eosinophilic leukaemia/hypereosinophilic syndrome**
S. Salemi, S. Yousefi, D. Simon, I. Schmid, L. Moretti, L. Scapozza, H.-U. Simon
(Collaboration with the Department of Dermatology, Inselspital, University Hospital Bern, and School of Pharmaceutical Sciences, University of Geneva)
Background: The Fip1 like 1 – platelet-derived growth factor receptor alpha (FIP1L1-PDGFRA) gene fusion is a common cause of chronic eosinophilic leukemia (CEL)/hypereosinophilic syndrome (HES), and patients suffering from this particular subgroup of CEL/HES respond to low-dose imatinib therapy. Methods: In an imatinib resistant FIP1L1-PDGFRA positive patient, we analyzed the molecular structure of the fusion gene and analyzed the effect of several kinase inhibitors on FIP1L1-PDGFRA – mediated

proliferative responses in vitro. Results: Sequencing of the FIP1L1-PDGFRA fusion gene revealed the occurrence of a S601P mutation, which is located within the nucleotide binding loop. In agreement with the clinical observations, imatinib did not inhibit the proliferation of S601P mutant FIP1L1-PDGFRA – transduced Ba/F3 cells. Moreover, sorafenib, which has been described to inhibit T674I mutant FIP1L1-PDGFRA, failed to block S601P mutant FIP1L1-PDGFRA. Structural modeling revealed that the newly identified S601P mutated form of PDGFRA destabilizes the inactive conformation of the kinase domain that is necessary to bind imatinib as well as sorafenib. Conclusions: We identified a novel mutation in FIP1L1-PDGFRA resulting in both imatinib and sorafenib resistance. The identification of novel drug-resistant FIP1L1-PDGFRA variants may help to develop the next generation of target-directed compounds for CEL/HES and other leukemias.
**See original publication No. 2**

### *Original publications*

1. **S. Yousefi**, C. Mihalache, E. Kozlowski, I. Schmid, H.-U. Simon: Viable neutrophils release mitochondrial DNA to form neutrophil extracellular traps.
   Cell Death Differ. 16 (2009), 1438-1444.

2. S. Salemi, **S. Yousefi**, D. Simon, I. Schmid, L. Moretti, L. Scapozza, H.-U. Simon: A novel FIP1L1-PDGFRA mutant destabilizing the inactive conformation of the kinase domain in chronic eosinophilic leukemia/hypereosinophilic syndrome.
   Allergy 64 (2009), 913-918.

3. A. Daryadel, **S. Yousefi**, D. Troi, I. Schmid, J. Schmidt-Mende, C. Mordasini, C.A. Dahinden, A. Ziemiecki, H.-U. Simon: RhoH/TTF negatively regulates leukotriene production in neutrophils.
   J. Immunol. 182 (2009), 6527-6532.

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., in press.

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); in press, doi:10.1002/eji.200939556

### *Review articles*

1. **S. Yousefi**, H.-U. Simon: Autophagy in cancer and chemotherapy.
   Results Probl. Cell Differ., 2009, 183-190.

2. **S. Yousefi**, H.-U. Simon: Autophagy in cells of the blood.
   Biochim. Biophys. Acta (BBA) 1793 (2009), 1461-1464.

### *Book chapter*

1. **S. Yousefi**, H.-U. Simon: Autophagy in cancer and chemotherapy. In: Death receptors and cognate ligands in cancer (Ed. H. Kalthoff); Springer, Berlin – Heidelberg, 2009, p. 183-190, doi:10.1007/400_2008_25

## *Group Prof. Uwe Zangemeister-Wittke*

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

[1] Institute of Biochemistry, University of Zürich

Our research is focused on translational aspects in molecular oncology. A major goal is to investigate mechanisms of drug resistance in solid tumors and to identify survival pathways and their regulators for molecular intervention to facilitate tumor cell apoptosis. One major target in this program is sphingosine kinase 1 and we are evaluating 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 nanovesicles including DARPinosomes and PLGA particles encapsulating protein toxins as well as DARPin-protamin fusion proteins for intracellular delivery of therapeutic nucleic acids are under investigation.

**EpCAM-targeted delivery of nanocomplexed siRNA to tumor cells with Designed Ankyrin Repeat Proteins**

J. Johannes Winkler, P. Martin-Killias, A. Plückthun, U. Zangemeister-Wittke

Specific delivery to tumors and efficient cellular uptake of nucleic acids remain major challenges for gene-targeted cancer therapies. Here we report the use of a Designed Ankyrin Repeat Protein (DARPin) specific for the Epithelial Cell Adhesion Molecule (EpCAM) as carrier for siRNA complementary to the bcl-2 mRNA. For charge complexation of the siRNA, the DARPin was fused to a truncated human protamine-1 sequence. To increase the cell binding affinity and the amount of siRNA delivered into cells, DARPin dimers were generated and used as fusion proteins with protamine. All proteins expressed well in *E. coli* and, to remove tightly bound bacterial nucleic acids, they were purified under denaturing conditions by immobilized metal ion affinity chromatography, followed by refolding. The fusion proteins were capable of complexing 4-5 siRNA molecules per protamine, and fully retained the binding specificity for EpCAM as demonstrated on MCF-7 breast carcinoma cells. In contrast to unspecific lipofectamine transfection, down-regulation of anti-apoptotic bcl-2 using fusion protein complexed siRNA was strictly dependent on EpCAM binding and internalization. Inhibition of bcl-2 expression facilitated tumor cell apoptosis as demonstrated by increased sensitivity to the anti-cancer agent doxorubicin.

**See original publication No. 1**

**AKT/mTOR pathway activation and bcl-2 family proteins modulate the sensitivity of human small cell cancer cancer cells to RAD001**

M. Marinov, A. Ziogas, O.E. Pardo, LT. Tan, T. Dhillon, F.A. Mauri, H.A. Lane, L.R. Lemoine, U. Zangemeister-Wittke, M.J. Seckl, A. Arcaro

PURPOSE: The Akt/mammalian target of rapamycin (mTOR) pathway is frequently activated in human cancers and plays an important role in small cell lung cancer (SCLC) biology. We investigated the potential of targeting mTOR signaling as a novel antitumor approach in SCLC. EXPERIMENTAL DESIGN: The expression of mTOR in patient specimens and in a panel of SCLC cell lines was analyzed. The effects on SCLC cell survival and downstream signaling were determined following mTOR inhibition by the rapamycin derivative RAD001 (Everolimus) or down-regulation by small interfering RNA. RESULTS: We found elevated expression of mTOR in patient specimens and SCLC cell lines, compared with normal lung tissue and normal lung epithelial cells. RAD001 treatment impaired basal and growth factor-stimulated cell growth in a panel of SCLC cell lines. Cells with increased Akt pathway activation were more sensitive to RAD001. Accordingly, a constitutive activation of the Akt/mTOR pathway was sufficient to sensitize resistant SCLC cells to the cytotoxic effect of RAD001. In the sensitive cells, RAD001 showed a strong additive effect to the proapoptotic action of the chemotherapeutic agent etoposide. Intriguingly, we observed low Bcl-2 family proteins levels in the SCLC cells with a constitutive Akt pathway activation, whereas an increased expression was detected in the RAD001-resistant SCLC cells. An antisense construct targeting Bcl-2 or a Bcl-2-specific inhibitor was able to sensitize resistant SCLC cells to RAD001. Moreover, SCLC tumor growth in vivo was significantly inhibited by RAD001. CONCLUSION: Together, our data show that inhibiting mTOR signaling with RAD001 potently disrupts growth and survival signaling in human SCLC cells.

**See original publication No. 2**

**Increased cytotoxicity of cisplatin in SK-MEL 28 melanoma cells upon down-regulation of melanoma inhibitor of apoptosis protein**

P. Mousavi-Shafaei, AA. Ziaee, U. Zangemeister-Wittke

BACKGROUND: Malignant melanoma is a highly metastatic cutaneous cancer and typically refractory to chemotherapy. Deregulated apoptosis has been identified as a major cause of cancer drug resistance, and upregulated expression of the inhibitor of apoptosis protein melanom, an inhibitor of apoptosis (ML-IAP) is frequent in melanoma. METHODS: Based on the conclusion that ML-IAP expression contributes to a malignant phenotype, we down-regulated the ML-IAP mRNA using sequence optimized antisense oligonucleotides. RESULTS: As measured by real-time PCR, oligonucleotides M706 and M711 inhibited ML-IAP mRNA expression by 47% and 52%, respectively in the highly metastatic and drug resistant SK-MEL28 cell line. Oligonucleotide M706, which was previously evaluated in G361 cells as the most efficient inhibitor of ML-IAP expression, was chosen to compare cell viability and drug sensitivity of these two melanoma cell lines with different p53 functionality. Protein expression was reduced by oligonucleotide M706 to 49% of the normal level and resulted in a dose-dependent specific reduction of cell viability with a maximum of 39% at 600 nM. Typical morphological changes showed that loss of viability was mainly due to cell death. In combination experiments, the use of oligonucleotide M706 resulted in a two-fold increase of cisplatin cytotoxicity at different concentrations of oligonucleotide and cisplatin ($P<0.05$). This is in line with our previous findings in G361 melanoma cell line, in which oligonucleotide M706 caused a 3-fold increase in cisplatin cytotoxicity. CONCLUSION: Our data suggest the use of ML-IAP antisense oligonucleotides to overcome drug resistance in metastatic melanoma, in spite of its p53 status.

**See original publication No. 3**

**Increased numbers of spontaneous SCLC metastasis in absence of NK cells after subcutaneous inoculation of different SCLC cell lines into pfp/rag2 double knock out mice**

S. Sodeur, S. Ullrich, H. Gustke, U. Zangemeister-Wittke, U. Schumacher

Spontaneous metastases in small cell lung cancer (SCLC) occur regularly in patients but seldom if any in conventional xenograft mouse models. To overcome this problem, SCLC cells were grafted subcutaneously onto pore forming protein and recombination activating gene 2 double knock out (pfp/rag2) mice and in severe combined immunodeficient (scid) mice. Primary tumours grew well in both mouse strains, while metastases occurred frequently in the pfp/rag2 mice and infrequently in scid mice. Hence NK cells, which are inactive in pfp/rag2 mice, play an important role in SCLC metastasis formation in xenograft models. This observation is in agreement with clinical studies, where a high NK cell number in the blood is correlated with a better prognosis of the patient.

**See original publication No. 4**

## *Original publications*


1. J. Winkler, P. Martin-Killias, A. Plückthun, **U. Zangemeister-Wittke**: EpCAM-targeted delivery of nanocomplexed siRNA to tumor cells with designed ankyrin repeat proteins. Mol. Cancer Ther. 8 (2009), 2674-2683.

2. M. Marinov, A. Ziogas, O.E. Pardo, L.T. Tan, T. Dhillon, F.A. Mauri, H.A. Lane, L.R. Lemoine, **U. Zangemeister-Wittke**, M.J. Seckl, A. Arcaro: AKT/mTOR pathway activation and bcl-2 family proteins modulate the sensitivity of human small cell cancer cancer cells to RAD001.
   Clin. Cancer Res. 15 (2009), 1277-1287.

3. P. Mousavi-Shafaei, A.A. Ziaee, **U. Zangemeister-Wittke**: Increased cytotoxicity of cisplatin in SK-MEL 28 melanoma cells upon down-regulation of melanoma inhibitor of apoptosis protein.
   Iran Biomed J. 13 (2009), 27-34.

4. S. Sodeur, S. Ullrich, H. Gustke, **U. Zangemeister-Wittke**, U. Schumacher: Increased numbers of spontaneous SCLC metastasis in absence of NK cells after subcutaneous inoculation of different SCLC cell lines into pfp/rag2 double knock out mice.
   Cancer Letters 282 (2009), 146-151.

# ***Additional Publications of PKI Members***

## *Dr. Barbara Geering*

### *Review article*

K. Kok, **B. Geering**, B. Vanhaesebroeck: Regulation of phosphoinositide 3-kinase expression in health and disease.
Trends Biochem. Sci. 34 (2009),115-127.

## *Dr. Stephan von Gunten*

### *Original article*

**S. von Gunten**, D.F. Smith, R.D. Cummings, S. Riedel, S. Miescher, A. Schaub, R.G. Hamilton, B.S. Bochner: Intravenous immunoglobulin contains a broad repertoire of anticarbohydrate antibodies that is not restricted to the IgG2 subclass.
J Allergy Clin. Immunol. 123 (2009),1268-1276.

### *Book chapter*

**S. von Gunten**, B.S. Bochner: Expression and function of Siglec-8 in human eosinophils, basophils, and mast cells. In Allergy Frontiers: Classification and Pathomechanisms. (Pawankar R, Holgate ST and Rosenwasser LJ eds), pp 297-313, Springer, Tokyo, Japan.

## *PD Dr. Peter Späth*

### *Review article*

E. Fernandez-Cruz, S.V. Kaveri, H.H. Peter, A. Durandy, N. Cantoni, I. Quinti, R. Sorensen, J.B. Bussel, M.G. Danieli, A. Winkelmann, J. Bayry, G. Käsermann, **P. Späth**, M. Helbert, A. Salama, I.N. van Schaik, N. Yuki: 6th International Immunoglobulin Symposium: poster presentations.
Clin. Exp. Immunol. 158 (2009), 60-67.

## *Dr. Christina Stöckle*

### *Original articles*

**C. Stoeckle**, C. Gouttefangeas, M. Hammer, E. Weber, A. Melms, E. Tolosa: Cathepsin W expressed exclusively in CD8+ T cells and NK cells is secreted during target cell killing but is not essential for cytotoxicity in human CTLs.
Exp. Hematol. 37 (2009), 266-275.

**C. Stoeckle**, V. Sommandas, E. Adamopoulou, et al.: Cathepsin G is differentially expressed in primary human antigen-presenting cells.
Cell. Immunol. 255 (2009), 41-45.

C. Luther, **C. Stoeckle**, E. Adamopoulou, et al.: Prednisolone treatment induces tolerogenic dendritic cells and a regulatory milieu in myasthenia gravis patients.
J. Immunol. 183 (2009), 841-848.

***Review article***

**C. Stoeckle**, A.K. Gleske: Immunotherapy: from basic research to clinical applications.
Cancer Immunol. Immunother. 58 (2009), 1129-1136.

***Book chapter***

**C. Stoeckle**, E. Tolosa: Antigen processing and presentation in multiple sclerosis. In: Molecular basis of ME - research trends. Part I: The immune system (Martin R, Lutterotti A eds), 2009, Springer, Berlin/Heidelberg.

## 4.2. Congress Invitations

***Dr. Sébastien Conus***

Workshop on “Proteases and Inflammation”, Bern (CH), April 2, 2009;
The role of cathepsin D in neutrophil cell death and innate immune responses.

Pacific Coast Protease Spring School, Warner Springs (CA, USA), April 18-21, 2009;
Caspase-8 is activated by cathepsin D initiating neutrophil apoptosis during the resolution of inflammation.

***Dr. Stephan von Gunten***

The Sixth Plasma Product Biotechnology Meeting, Menorca (S), May 11-15, 2009;
Immunoregulatory effects of natural anti-Siglec autoantibodies in IVIg.

***Prof. Thomas Kaufmann***

12th TNF Meeting, El Escorial (E), April 26 – 29, 2009;
Lipopolysaccharide plus galactosamine-induced fatal hepatitis mediated by secreted TNF(alpha) requires caspase-8 and the two BH3-only proteins Bid and Bim.

EMBO Workshop ‘Model Organisms in Cell Death Research’, Obergurgl (A),
Jan. 31 – Feb. 4, 2009;
Fatal hepatitis mediated by TNF and BH3-only proteins.

***Prof. Hans-Uwe Simon***

41. Jahrestagung der Arbeitsgemeinschaft für Grundlagenforschung der DGZMK, Mainz (D),
Jan. 8 - 9, 2009;
Extrazelluläre antimikrobielle Aktivitäten von Granulozyten.

11th Allergy and Immunology Update / WBO and FBO course of the SSAI, Grindelwald (CH),
Jan. 23 - 25, 2009;
Current work-up of eosinophilia.

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI);
Washington, DC (USA), March 13 - 17, 2009;
Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense.

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI);
Washington, DC (USA), March 13 – 17, 2009;
Budesonide as induction treatment for active eosinophilic esophagitis in adolescents and adults: A randomized, double-blind, placebo-controlled study.

World Immune Regulation Meeting-III; Davos (CH), March 22 – 25, 2009;
Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense.

Symposium: Aktuelle Aspekte in der Endodontie; Jena (D), May 9, 2009;
Neue Aspekte der antimikrobiellen Abwehr.

Course on Cell Death and Autophagy; Lund (Sweden), May 9 – 11, 2009;
The physiologic role of autophagy and its relation to cell death regulation.

2nd Symposium on HAMLET and tumor-killing proteins; Lund (Sweden), May 12 – 14, 2009;
Cancer cell death regulation by autophagy.

Neue Therapien in der Dermatologie; Bern (CH), May 14, 2009;
Neue pharmakologische Ansätze.

XXVIII. Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Warsaw (Poland), June 6 -10, 2009;
Immunopathogenesis of eosinophilic esophagitis.

Workshop: “The role of autophagy in infectious diseases and cancer”, National Institute for Infectious Diseases “Lazzaro Spallanzani”, Rome (I), June 18 – 20, 2009;
Cancer cell death regulation by autophagy.

Translational research workshop: “Mechanisms of cell death in diseases”, Villa Vigoni, Loveno di Menaggio, Como (I), June 28 – July 1, 2009;
Autophagy and cell differentiation.

6th Biennial International Symposium “Eosinophils 2009” of the International Eosinophil Society, Bruges (Belgium), July 7 – 11, 2009;
Eosinophils and host defense against bacteria.

Minisymposium: “Membrane receptors: Function and organization”, Geneva (CH), Sept. 21, 2009; Autophagy and cancer.

17th Euroconference on Apoptosis, Paris (F), Sept. 23 – 26, 2009;
Role of autophagy in cancer.

1. Congress of the National Federation of the Italian Societies of Immunology, Allergy, and Clinical Immunology (IFIACI), Trieste (I), Sept. 30 - Oct. 3, 2009;
New mechanism of eosinophil activation.

59th Annual Meeting of the Japanese Society of Allergology, Akida (Japan), Oct. 29 – 31, 2009;
New insights into eosinophil survival and activation.

International Symposium: Eosinophils, other inflammatory cells and molecules in Allergy (in association with the 59th Annual Meeting of the Japanese Society of Allergology), Akida (Japan), Oct. 31, 2009;
Targeting eosinophils in eosinophil esophagitis.

International Forum on Immunoglobulin Research (IFIR), Fort Lauderdale (FL, USA), Nov. 19 – 22, 2009;
Anti-Fas and anti-Siglec natural autoantibodies in IVIG.

From the Bench to the Clinic: Immunological Update. Meeting organized under the patronate of the European Academy of Dermatology and Venerology, Bellinzona (CH), Dec. 3, 2009;

Molecular and functional characterization of extracellular traps generated by eosinophils and neutrophils.

***PD Dr. Peter Späth***

6th International Immunoglobulin Symposium, Interlaken (CH), March 26–28, 2009;
From the donor to the patient – Variations in anti-measles virus (MeV) antibody levels over decades, and
Therapeutic IgM – Compilation of clinical and preclinical data and an attempt of their interpretation.

6th C1 Inhibitor Deficiency Workshop, Budapest (H), May 22-24, 2009;
Facets of hereditary angioedema in a cohort of Swiss patients, and
Non-allergic, non-infectious angioedema - Closing remarks.

Primary Immunodeficiencies and Paediatric Immunology, Larissa (GR), Dec. 4–6, 2009;
Treatment of angioedema due to deficiency of C1-inhibitor, and
Advances in the production and the administration of immunoglobulin preparations.

## 4.3. Seminar Invitations

***Prof. Thomas Kaufmann***

Institute of Infectious Diseases, University of Bern, Bern (CH), Dec. 11, 2009;
guest of Dr. Denis Grandgirard:
Analysing the crosstalk between the death receptor and mitochondrial apoptotic pathways.

***Prof. Hans-Uwe Simon***

Annual Meeting of the American Academy of Allergy Asthma and Immunology (AAAAI);
Washington, DC (USA), March 15, 2009:
Treatment of allergic diseases with biologics: Clinical applications and adverse effects.

Johns Hopkins Asthma and Allergy Center, Baltimore (MA, USA), March 18, 2009; guest of Prof. Dr. Bruce Bochner:
New insights into eosinophil survival and activation.

University of Basel, Dept. of Pharmaceutical Sciences, Basel (CH), Nov. 18, 2009; guest of Prof. Dr. Stephan Krähenbühl:
New approaches in the treatment of atopic eczema and eosinophilic esophagitis.

***PD Dr. Peter Späth***

Lucerne General Hospital – Interdisciplinary Teaching Courses, Center for Laboratory Medicine, Lucerne (CH), Febr. 12, 2009;
From the Donor to Blood and Plasma Products.

Universitätsklinik für Dermatologie – Fort- und Weiterbildung für Dermatologen, Rheumatologen und Immunologen: Intravenöse Immunglobuline: Wirkungsmechanismen, Indikationen und praktische Anwendungen, Bern (CH), Nov. 19, 2009;
Wechselwirkung von Komplement und IVIg im Rahmen der Hemmung einer überschiessenden Entzündung.

***Dr. Stephan von Gunten***

Universitätsklinik für Dermatologie – Fort- und Weiterbildung für Dermatologen, Rheumatologen und Immunologen: Intravenöse Immunglobuline: Wirkungsmechanismen, Indikationen und praktische Anwendungen, Bern (CH), Nov. 19, 2009;
Intravenöse Immunoglobuline: Wirkungsmechanismen, Indikationen und praktische Anwendungen.

***Prof. Uwe Zangemeister-Wittke***

EU project coordination seminar, Hammersmith Hospital, London (UK), June 17, 2009;
New approaches for the targeted therapy of lung cancer.

## 4.4. Organization of Meetings and Courses

***PD Dr. Peter Späth***

Teaching courses in neurology “Demyelinating, Inflammatory Peripheral Autoimmune Neuropathies” together with the Dept. of Neurology, Univ. Hospital, Innsbruck (A), Nov. 13, 2009.

6$^{th}$ C1 Inhibitor Deficiency Workshop, Budapest (H), May 22–24, 2009
(Member of the Scientific Program Committee)

Primary Immunodeficiencies and Paediatric Immunology, Larissa (GR), Dec. 4–6, 2009
(Member of the Scientific Committee)

***Prof. Hans-Uwe Simon***

Symposium of the Swiss Society of Pharmacology and Toxicology (together with task force SSPT): Fortschritte in der Pharmakologie - Tumorpharmakologie, Bern (CH), Jan. 29, 2009.

8$^{th}$ III-Bern International Summer School, Bönigen (CH), Aug. 9 - 11, 2009.

Bern Immunology Club (together with the other founder members); Institute of Pharmacology, University of Bern, one meeting in each month of 2009.

***Prof. Shida Yousefi***

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis. Bern (CH), April 7-8, 2009.

DKF, MIC, PIAF - Course in fluorescent staining, confocal microscopy, and image analysis. Bern (CH), Oct. 27-28, 2009.

## 4.5. Invited Chairperson at Congresses

***Prof. Hans-Uwe Simon***

Symposium der Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie - Tumorpharmakologie; Bern (CH), Jan. 29, 2009.

World Immune Regulation Meeting-III; Workshop 4: “Immune tolerance in allergy and asthma”; Davos (CH), March 22 – 25, 2009.

XXVIII. Congress of the European Academy of Allergology and Clinical Immunology (EAACI); Hot topic session: “Understanding cellular mechanisms in allergy”;
Warsaw (Poland), June 6 – 10, 2009.

6th Biennial International Symposium “Eosinophils 2009” of the International Eosinophil Society; Session 3: “The eosinophil: A central player in innate immunity?”; Bruges (Belgium),
July 7 – 11, 2009.

17$^{th}$ Euroconference on Apoptosis; 6$^{th}$ Training course on concepts and methods in programmed cell death; Paris (F), Sept. 23 – 26, 2009.

International Symposium: Eosinophils, other inflammatory cells and molecules in Allergy (in association with the 59$^{th}$ Annual Meeting of the Japanese Society of Allergology); Session 3: Activation and signalling in inflammatory cells; Akida (Japan), Oct. 31, 2009.

***PD Dr. Peter Späth***

6$^{th}$ C1 Inhibitor Deficiency Workshop, Session: „Basic Science and Dignosis of C1-INH Deficiency“; Budapest (H), May 22 – 24 May, 2009.

« Lebens-Lust » Festveranstaltung & Vernissage mit Roundtable; Festveranstaltung des Deutschen Grünen Kreuzes zum 30. Jahrestag der Einführung der Therapie des hereditären Angioödems mit plasmatischem C1-Esterase Inhibitor Konzentrat, Session: „Roundtable-Gespräch zum Thema «25 Jahre Frankfurter Therapiekonzept»“; Frankfurt a.M. (D),
Oct. 28, 2009.

Primary Immunodeficiencies and Paediatric Immunology, Session: “Angioedema due to deficiency of C1-inhibitor“; Larissa (GR), Dec. 4–6, 2009.

***Prof. Uwe Zangemeister-Wittke***

Symposium der Swiss Society of Pharmacology and Toxicology (SSPT): Fortschritte in der Pharmakologie - Tumorpharmakologie; Bern (CH), Jan. 29, 2009.

## 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.

***Dr. Stephan von Gunten***

Allergy

***Prof. Andrea Huwiler***

Biochim. Biophys. Acta
Blood
Br. J. Pharmacol.
Carcinogenesis
Circ. Res.
Clin. Chem. Lab. Med.
Diabetologica
Eur. J. Pharmacol.
Exp. Cell Res.
FEBS Lett.
Hormone and Metabol. Res.
J. Biol. Chem.
J. Cell. Biochem.
J. Cell. Physiol.
J. Exp. Pharmacol. Ther.
Kidney and Blood Pressure Research
Kidney Int.
Naunyn Schmiedeb. Arch. Pharmacol.
Planta Medica

***Prof. Thomas Kaufmann***

Cell Death Differ
Oncogene
Hepatology
Immunology and Cell Biology

***Prof. Hans-Uwe Simon***

Allergy
Apoptosis
Autophagy
Blood
Cell Death Differ.
Clin. Exp. Allergy
Clin. Exp. Immunol.
Eur. J. Immunol.
Expert Rev. Clin. Immunol.
Int. Arch. Allergy Immunol.
J. Allergy Clin. Immunol.
J. Exp. Med.
J. Mol. Med.
J. Immunol.
J. Leukoc. Biol.
N. Engl. J. Med.
Oncogene
Proc. Natl. Acad. Sci. USA

***Dr. Christina Stöckle***

Allergy

***Prof. Shida Yousefi***

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

***Prof. Uwe Zangemeister-Wittke***

Int. J. Cancer
J. Control Release
J. Biol. Chem.
Breast Cancer Res.
Nanotechnology
Mol. Pharmacol.
Cell Death Differ.
Lung Cancer
Mol. Cell. Biol.
Bioconjug. Chem.

## 4.7. Referee Work for Grant Bodies

***Dr. Sébastien Conus***

Swiss Cancer League

***Dr. Barbara Geering***

Swiss Cancer League

***Dr. Stephan von Gunten***

Swiss Cancer League

***Prof. Andrea Huwiler***

Deutsche Forschungsgemeinschaft (DFG)
Norwegian Research Council

***Prof. Thomas Kaufmann***

Swiss Cancer League
Swiss National Science Foundation

***Prof. Hans-Uwe Simon***

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

***Prof. Uwe Zangemeister-Wittke***

Swiss Cancer League
Medical Research Council (MRC), London
Swiss National Science Foundation
Austrian Fonds for the Promotion of Science and Research

## 4.8. Awards

***Dr. Sébastien Conus***

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

***Prof. Andrea Huwiler***

**Posterpreis**
Annual Meeting, Deutsche Gesellschaft für Nephrologie (DGfN)
(Hannover, Sept. 26 - 29, 2009)

***Dr. Barbara Geering***

**L'Oréal fellowship "For Women in Science"**
(Bern, Oct. 1, 2009)

***Prof. Shida Yousefi***

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

***PD Dr. Dagmar Simon (guest scientist at PKI)***

**Prize of the Allergie-Stiftung Ulrich Müller-Gierok**
(Geneva, March 19, 2009)

# 5. Administrative, Advisory, and Honorary Posts

***Dr. Sébastien Conus***

Webmaster of the PKI

Coordinator for Chemicals at the PKI

***Prof. Andrea Huwiler***

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

Member of the Collegium generale of the University of Bern

***Prof. 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***

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

Vice Workshop Representative of the Mechanisms of Allergy/Asthma/Immunology (MAAI) section of AAAAI, 2009-2011

Member of the Immunomodulation Committee (Workshops) of AAAAI, 2004-2009

Member of the Cells and Cytokine Committee (Workshops) of AAAAI, 1997-2011

Member of the Council of the Swiss Society of Pharmacology and Toxicology (SSPT), 2002-2010

Member of the Scientific Advisory Board, Society in Science: The Branco Weiss Fellowship, 2003-2009

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

Past-President of the Swiss Society of Experimental Pharmacology (SSEP)

Member of the Supervision commission “Medical Biology” within the Graduate School for Cellular and Biomedical Sciences of the University of Bern, 2005-2009

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

President, European Cell Death Society (ECDO), 2007-2009

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), since 2009

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

***Prof. Shida Yousefi***

Coordinator for radioactive work at the PKI

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

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

Coordinator for PC work at the PKI

***Prof. Uwe Zangemeister-Wittke***

Member of the examiHuman SwissMedic Expert Committee

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

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

Quality & Biosafety coach at the PKI

Informatics & Network Coordinator at the PKI

Member of the Editorial Board, Lung Cancer

***Zhaoyue He***

Deputy Coordinator for PC and Mac work at the PKI

# 6. Services

## 6.1. Confocal Microscopy

The facility belongs to the **Department of Clinical Research (DKF)** of the University of Bern. It hosts a new laser scanning microscope (LSM 5 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 2009 for approximately 709 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 30 different research groups. In 2009, the operator and her team spent for the facility more than 600 hours. In general, the usage of this facility has dramatically increased upon acquisition of the new LSM 5 Excitor instrument. Prof. S. Yousefi organizes practical courses for confocal microscopy and image analysis twice per year.

## 6.2. Flow Cytometry

A service is provided for analyzing potential pathogenic mechanisms of eosinophilic disorders 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

***Angelique Müller, Thun, Switzerland***
Vernissage: Nov. 26, 2009

***Lorenz Zala, Wabern, Switzerland***
Vernissage: Nov. 26, 2009

# 8. Sponsors

## 8.1. Research Grants

### *Dr. Sébastien Conus*

University of Bern, grant writing support
Novartis Foundation (formerly Ciba-Geigy-Jubilee Foundation), fellowship

### *Dr. Barbara Geering*

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

### *Dr. Stephan von Gunten*

CSL Behring Research Scholarship
European Academy of Allergy and Clinical Immunology (EAACI), scholarship
Novartis Stiftung für Medizinisch-Biologische Forschung

### *Prof. Andrea Huwiler*

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

### *Prof. Thomas Kaufmann*

Swiss National Science Foundation, SNF-Professorship (grant No. PP00A-119203/1)
Novartis Stiftung für Medizinisch-Biologische Forschung
Josephine Clark-Fonds der Medizinischen Fakultät
UniBern Forschungsstiftung

### *Dr. Nataliya Kotelevets*

Fellowship, Eidgenössische Stipendienkommission für ausländische Studierende (ESKAS)

### *Oleksandr Pastukhov, M.Sc.*

Fellowship, Eidgenössische Stipendienkommission für ausländische Studierende (ESKAS)

### *Prof. Hans-Uwe Simon*

Swiss National Science Foundation (grant No. 310000-107526)
CSL Behring AG, Bern

***Prof. Shida Yousefi***

Swiss National Science Foundation (grant No. 310000-112078 and 310030-127628/1)

***Prof. Uwe Zangemeister-Wittke***

Swiss National Science Foundation (grant No. 310030-119859)
Bernische Krebsliga
Sassella-Stiftung of the Zürcher Kantonalbank

## 8.2. Meetings

***8th III-International Summer School, Bönigen (CH), Aug. 9-11, 2009***

Allergopharma AG, Therwil
Becton Dickinson Biosciences, Allschwil
Carl Zeiss AG, Feldbach
ENZO Life Science, Lausen
Essex Chemie AG, Luzern
GlaxoSmithKline AG, Münchenbuchsee
Lucerna Chem AG, Luzern
PerkinElmer (Schweiz) AG, Schwerzenbach
Pfizer AG, Zurich
USGEB
Kontaktgruppe für Forschungsfragen (KFG), Basel
Graduate School of Cellular and Biomedical Science, University of Bern

## 8.3. Seminars „Progress in Pharmacology“

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

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

## 8.4. Seminars „Bern Immunology Club“

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

## 8.5. Travel Support

***Swiss Society of Pharmacology & Toxicology (SSPT)***
Support of Dr. Stephan von Gunten
Support of Dipak Maskey

***Union of the Swiss Societies for Experimental Biology (USGEB)***
Support of Dr. Christina Stöckle

***European Cell Death Organization (ECDO)***
Support of Cristina Mihalache

## 8.6. Other Support

***Bürgi Fonds*** Seminar series of the institute