Annual Report 2018

Institut für Pharmakologie (PKI)
der Universität Bern

Institute of Pharmacology
University of Bern

Address: Inselspital, INO-F
CH-3010 Bern
Switzerland

Tel.: +41 31 632 3281
E-mail: debora.scherrer@pki.unibe.ch

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

Inhaltsverzeichnis

1. Introduction

1.1. Vorwort

Dies ist der achtzehnte umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Das PKI hat auch im Jahr 2018 seine Aufgaben in Lehre und Forschung innerhalb der Medizinischen Fakultät vorbildlich erfüllt. Nach unserem Umzug im Jahr 2015 bietet uns das INO-Gebäude des Inselspitals hervorragende Bedingungen für eine erfolgreiche Forschungstätigkeit. Mit dem Zentrum für Labormedizin teilen wir uns den Stock F und nutzen gemeinsam die vorhandene Infrastruktur. In Lehre und Forschung wurden inzwischen zahlreiche neue Projekte gestartet, mit dem Ziel die personalisierte Medizin weiter zu entwickeln. Im April 2017 startete Prof. Dr. Manuel Haschke mit seiner Forschungsgruppe für Klinische Pharmakologie in unser Institut und seine zwei aus Basel mitgebrachten Massenspektrometer sind installiert. Mit der Rekrutierung von Prof. Haschke haben sich neue Möglichkeiten der Zusammenarbeit eröffnet, sowohl in der *biologischen Grundlagen*- als auch in der *klinischen Forschung*, beides Kernaufgaben der Pharmakologie, bzw. klinischen Pharmakologie.

Das PKI arbeitet eng mit verschiedenen 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 2018 trugen wir dazu bei, die Kommunikation zwischen WissenschaftlerInnen und Öffentlichkeit zu fördern.

Neben unserer regulären Lehrtätigkeit im 3. und 6. Studienjahr Medizin sowie der Ausbildung der ZahnmedizinerInnen sind einige DozentInnen des Instituts zusätzlich in die Immunologie-Ausbildung von StudentInnen der Biologie (Naturwissenschaftliche Fakultät der Universität Bern) einbezogen. Weiterhin sind wir auch für die Pharmakologie-Ausbildung in B.Sc.- und M.Sc.-Kursen für Biomedizin der Universität Bern verantwortlich. Ebenso führen wir ab September 2019 die Pharmakologie-Ausbildung im 3. Studienjahr Pharmazie an unserer Universität durch, die neu ein Vollstudium für Pharmazie anbietet. Die DozentInnen des PKI sind ausserdem innerhalb der interfakultären Graduate School for Cellular and Biomedical Sciences der Universität Bern aktiv tätig. Prof. Kaufmann, Prof. von Gunten und Prof. Konstantinidou sind Mitglieder einer Betreuungskommission innerhalb dieses Ausbildungsprogramms für Doktorandinnen und Doktoranden. Dazu kommen zu-

sätzliche Bildungsangebote in Form von Seminaren (Current Topics in Pharmacology and Theranostics; gemeinsam organisiert mit dem Zentrum für Labormedizin) und einer Summer School, die durch mich organisiert wird. Diese Bildungsangebote werden weitgehend aus eigenen finanziellen Mitteln und Sponsorengeldern bestritten. Im Institut arbeiten gegenwärtig 16 DoktorandInnen (15 PhD/1 MD), und 1 Doktorand (PhD) hat im Berichtsjahr seine Arbeit erfolgreich abgeschlossen.

Die Mitarbeiter und Mitarbeiterinnen des PKI (ohne Klinische Pharmakologie) publizierten im Jahr 2018 insgesamt 31 Originalarbeiten sowie 20 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >200). MitarbeiterInnen des Instituts wurden zu insgesamt 39 Vorträgen bzw. Seminaren eingeladen. Mehrere MitarbeiterInnen des PKI wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 8 MitarbeiterInnen mit namhaften Beiträgen des Schweizerischen Nationalfonds unterstützt. Zahlreiche Persönlichkeiten besuchten das Institut und hielten Forschungsseminare. Prof. von Gunten war Mitorganisator des Jahreskongresses der Schweizerischen Gesellschaft für Pharmakologie und Toxikologie (SGPT). Prof. Kaufmann organisierte gemeinsam mit Prof. Tschan (Institut für Pathologie, Universität Bern) und Prof. Brunner (Lehrstuhl Biochemische Pharmakologie, Universität Konstanz, Deutschland) das „10th Swiss Apoptosis Meeting (SAM)“ (12.-14.9.2018), zu dem wir ca. 200 TeilnehmerInnen aus dem In- und Ausland empfingen. Seit 2014 ist das Institut für Pharmakologie Bestandteil eines Europäischen Netzwerks für Doktoranden innerhalb des EU-Programms für Forschung und Innovation „HORIZON 2020“. Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Ich bin gegenwärtig als Dekan der Medizinischen Fakultät der Universität Bern tätig. Zusätzlich nimmt das PKI auch ausserhalb der Universität wissenschaftspolitische Verantwortung für die Medizin und die Biowissenschaften wahr. Zum Beispiel amtet Prof. von Gunten als Präsident der Schweizerischen Gesellschaft für Experimentelle Pharmakologie (SGEP).

Ich danke allen Mitarbeiterinnen und Mitarbeitern für ihren Einsatz, welcher auch im Jahr 2018 zu einer Bilanz beitrug, die internationalen Massstäben gerecht wird. Ebenso danke ich allen Sponsoren und Freunden des Instituts.

Prof. Dr. med. Hans-Uwe Simon, PhD, Dr. h.c. Bern, Januar 2019
Direktor

1.2. Foreword

This is the eighteenth comprehensive annual report for our Institute of Pharmacology (PKI) of the University of Bern. We have worked hard to fulfil optimally our tasks in teaching and research within the Medical Faculty in the past year. After moving to the INO-building of the University Hospital (Inselspital) in 2015, we have enjoyed excellent conditions for successful research. We share floor F of the building with the Center for Laboratory Medicine and have jointly developed the available infrastructure. We organize multiple joint teaching and research projects with this Center to further accentuate the field of “Precision Medicine”. In April 2017, Prof. Manuel Haschke with his research group joined our institute and now facilitates our research in the field of Clinical Pharmacology. Two mass spectrometers of the Haschke group have been moved from Basel and are operating in our institute. The presence of his group opens up new opportunities for collaboration in both *clinical research* and *basic biological science*.

The PKI wants to succeed in both areas and, therefore, maintains close contacts with several clinics at the Inselspital as well as with other research institutes of the University. In doing so, we hope to strengthen both translational research and teaching in the Medical Faculty. In addition, we are very much interested in collaborating with industry on new developments. Finally, we have also made an effort to promote communication between scientists and the public in 2018. All our current activities are summarized here below.

Besides the regular teaching in the third and sixth year medical student curriculum and in the teaching of dental students, we are responsible for teaching Pharmacology in both B.Sc. and M.Sc. courses in Biomedicine. Some of the PKI staff are additionally involved in the Immunology M.Sc. programmes within the Natural Science Faculty of our university. Beginning in September 2019, we are also responsible for the teaching Pharmacology to students of Pharmacy of our University, which newly offers a full study in Pharmacy. Of course, we also actively participate in the graduate program for MD/PhD students of the University of Bern (Graduate School for Cellular and Biomedical Sciences). Prof. Kaufmann, Prof. von Gunten and Prof. Konstantinidou are members of the tutoring committee “Cell Biology” within that school. Currently, 15 PhD students and 1 MD student work at the PKI, and in 2018, one PhD student successfully completed his doctoral studies. Also important for the institute are additional teaching activities outside the medical curriculum, such as seminars (Current Topics in Pharmacology and Theranostics; jointly organized with the Center of La-

boratory Medicine) and the Summer School (organized by myself). Significantly, these additional events were financed exclusively by external sponsors.

Research is our other main activity. In 2018, staff members of the PKI (without Clinical Pharmacology) published 31 original and 20 review articles in international peer-reviewed journals (the sum of the “impact factors” is above 200). Co-workers of the institute were invited to present 39 lectures or seminars. Several PKI members received research prizes. The research projects of 8 co-workers are currently supported by grants from the Swiss National Science Foundation. Several internationally prominent researchers visited our institute to present seminars. Prof. von Gunten was a member of the organizing committee for the annual meeting of the Swiss Society of Pharmacology and Toxicology (SSPT). Prof. Kaufmann, together with Prof. Tschan (Institute of Pathology, University of Bern) and Prof. Brunner (Department of Biochemical Pharmacology, Univ. of Constance, Germany), organized an international congress (10th Swiss Apoptosis Meeting; September 12-14, 2018), which attracted approximately 200 scientists interested in the fields of “Cell Death and Autophagy”. Moreover, since 2014, the Institute of Pharmacology has been part of a Training Network for PhD students within the EU Framework Program for Research and Innovation „HORIZON 2020“. In summary, we carry out research of a high standard which plays a very important role at the PKI.

I am the Dean of the Medical Faculty of the University of Bern. Prof. von Gunten currently serves as president of the Swiss Society of Experimental Pharmacology (SSEP).

I thank all co-workers in the institute for their hard work. These efforts have contributed in an important way to the success of the PKI in 2018. I am grateful to all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD, Dr. h.c
Director

Bern, January 2019

2. Staff 2018

Director

Prof. Dr.	Simon, Hans Uwe	MD, PhD, Dr. h.c.

Deputy Director

Prof. Dr.	Huwiler, Andrea	PhD

Principal Investigators

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

Scientific Staff

Dr.	Adams, Olivia	Postdoctoral fellow* (since Aug 2017)
	Aeschlimann, Salome	Lab Technician (until Jan 2018)
	Bachmann, Daniel	Lab Technican
	Blanchard, Olivier	PhD student*
	Blümli, Natascha	M.Sc. pharm. student* (until June 2018)
	Brandl, Fabian	PhD student*
	Erhardt, Martin	PhD student
Dr.	Fernandez Marrero, Yuniel	Postdoctoral fellow*
	Frangez, Ziva	PhD student*
Dr.	Frias Boligan, Kayluz	Postdoctoral fellow*
	Germic, Nina	PhD student
	Gigon, Lea	M.Sc. student* (since Sep 2018)
	Glück, Angéline	M.Sc. biomed. student* (until Feb 2018)
	Graeter, Stefanie	PhD student*
	Haas, Quentin	PhD student*
Dr.	He, Zhaoyue	Postdoctoral fellow
	Karlen, Hélène	MD student*
	Klapan, Kim	PhD student*
	Kocher, Raphaela	M.Sc. pharm. student* (until June 2018)
	Kozlowski, Evelyne	Lab Technician
	Kremenovic, Mirela	M.Sc. student* (until Jan 2018)
	Künzli, Yves	M.Sc. student* (until Dec 2018)
Dr.	Liu, He	Postdoctoral fellow*
	Maillard-van Laer, Marianne	Lab Technician
	Maneva Timcheva, Tankica	Lab Technician* (since Jan 2018)
	Markov, Nikita	PhD student
	Moolan, Robin	M.Sc. student* (until June 2018)
	Muli, Kevin	M.Sc. biomed. student* (since Dec 2017)
	Naim, Samara	PhD student*
	Nasser, Riim	Lab Technician*
	Oberson, Kevin	Lab Technician

	Peng, Shuang	PhD student*
	Pozzato, Chiara	PhD student*
Dr.	Reinhart, Ramona	Postdoctoral fellow (until April 2018)
	Rossi Sebastiano, Matteo	PhD student
	Saliakoura, Maria	PhD student*
	Schnüriger, Noah	M.Sc. biomed. student*
	Schumacher Annik Mirja	M.Sc. pharm. student* (until June 2018)
	Stark, Manuel	PhD student (until Oct 2018)
	Stepanovska, Bisera	PhD student
Dr.	Stojkov, Darko	Postdoctoral fellow
	Verschoor, Daniëlle	Practicant (since Aug 2018)
	Von Gunten, Aldona	Technician (since May 2018)
Dr.	Wang, Xiaoliang	Postdoctoral fellow
	Zürcher, Marc	M.Sc. student* (until June 2018)

Principal Investigator – Clinical Pharmacology

Prof. Dr.	Haschke, Manuel	MD

Scientific Staff – Clinical Pharmacology

PD Dr.	Bohlender, Jürgen	MD
Dr.	Liakoni, Evangelia	MD
Dr.	Sandbaumhüter, Friederike	PhD, postdoctoral fellow (until Aug 2018)
Dr.	Geiling, Katharina	MD
	Scholz, Irene	med. pract.

External University Teachers

Dr.	Bürgi, Sibylle	PhD*
PD Dr.	Cachelin, Armand	MD, PhD*
Prof. Dr.	Mlinaric, Irena	PhD* (Adjunct Prof., Univ. of Ljubljana, Slovenia)

Guest Scientists

Prof. Dr.	Simon, Dagmar	MD*, Dept. Dermatology, Inselspital, Univ. Bern
Dr.	Sokollik, Christiane	MD*, Dept. Pediatrics, Inselspital, Univ. Bern
Dr.	Schwalm, Stephanie	PhD*, Dept. of Pharmacology, Univ. Frankfurt
PD Dr.	Spirk, David	MD*, Sanofi-Aventis AG
Dr.	Amirshahrokhi, Keyvan	MD*, Arbabil University of Medical Sciences, Iran
	Ardali, Razieh	PhD student*, Shiraz University, Shiraz, Iran
	Macrchand, Anthony	Visiting student*, EPFL
	Steinhoff, Julia	Training student, University of Bonn, Germany

Office

Berger, Jana	Secretary, 60% (until Sep 2018)
Cookman, Sabrina	Secretary, 60% (since Aug 2018)
Scherrer, Debora	Secretary, 70%

Workshop / House Keeping

Conforti, Isa

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

Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT)

Progress in Pharmacology, Treatment of Skin Diseases, Bern, January 24, 2018

Summer School

Members of the Institute of Pharmacology of the University of Bern together with participants of our International Summer School in Bönigen; July 29 - 31, 2018.

3. Teaching Activities

3.1. Lectures

Lectures for Medical Students: Pharmacology

Date	Lecturer	Titel of the lecture
Mar 19, 2018	Prof. Stephan von Gunten	Hormone aus pharmakol. Sicht (Teil 1)
Mar 19, 2018	Prof. Stephan von Gunten	Hormone aus pharmakol. Sicht (Teil 2)
Mar 21, 2018	Prof. Stephan von Gunten	Lipidsenker + Behandlung der Gicht
Mar 21, 2018	Prof. Stephan von Gunten	Antidiabetika
Mar 28, 2018	Prof. Andrea Huwiler	Pharmakologie von Narkosemitteln und Muskelrelaxantien I
Mar 28, 2018	Prof. Andrea Huwiler	Pharmakologie von Narkosemitteln und Muskelrelaxantien II
Apr 16, 2018	Prof. Andrea Huwiler	Antiepileptika
Apr 25, 2018	Prof. Andrea Huwiler	Therapie von M. Parkinson und Demenz
Apr 25, 2018	Prof. Andrea Huwiler	Lokalanästhetika
Apr 25, 2018	Prof. Andrea Huwiler	Neurologie-Blocksynthese
Apr 30, 2018	Prof. Andrea Huwiler	Psychopharmakologie
May 07, 2018	Prof. Andrea Huwiler	Antidepressiva, Anxiolytika und Stimmungsstabilisatoren
May 07, 2018	Prof. Andrea Huwiler	Antipsychotika
May 09, 2018	Prof. Andrea Huwiler	Schmerz und Analgesiologie (Teil 1)
May 09, 2018	Prof. Andrea Huwiler	Schmerz und Analgesiologie (Teil 2)
May 31, 2018	Prof. Hans-Uwe Simon	Immunmodulation
Sep 17, 2018	Prof. Hans-Uwe Simon	Pharmakodynamik (Teil 1)
Sep 17, 2018	Prof. Hans-Uwe Simon	Pharmakodynamik (Teil 2)
Sep 25, 2018	Prof. Hans-Uwe Simon	Entzündungshemmung
Sep 25, 2018	Prof. Hans-Uwe Simon	Einführung in die Toxikologie
Oct 17, 2018	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Oct 30, 2018	Prof. U. Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Oct 30, 2018	Prof. U. Zangemeister-Wittke	Antihypertensiva
Oct 31, 2018	PD Dr. David Spirk	Pharmakologie der Hämostase
Nov 05, 2018	PD Dr. David Spirk	Behandlung der Herzinsuffizienz und Angina pectoris
Nov 14, 2018	Prof. U. Zangemeister-Wittke	Antiarrhythmika
Dec 10, 2018	Prof. U. Zangemeister-Wittke	Diuretika (Teil 1)
Dec 10, 2018	Prof. U. Zangemeister-Wittke	Diuretika (Teil 2)

All lecturers additionally participated in the “Wochensynthese” and “Blocksynthese”.

Lectures for Medical Students: Cell Biology

Date	Lecturer	Titel of the lecture
Sep 27, 2018	Prof. Thomas Kaufmann	Entwicklung des Lebens
Oct 11, 2018	Prof. Thomas Kaufmann	Zellstoffwechsel
Nov 1, 2018	Prof. Thomas Kaufmann	Zelltod 2

Seminars for Medical Students: Pharmacology

Date	Lecturer	Titel of the lecture
Apr 12, 2018	Prof. Stephan von Gunten	Functional Glycomics - Neue Optionen für die Tumor- und Entzündungspharmakologie
Apr 12, 2018	Prof. Hans-Uwe Simon	Personalisierte Arzneimitteltherapie
Apr 23, 2018	Prof. Thomas Kaufmann	Modulation des Zelltodes - aktueller Stand und neue Entwicklungen
Apr 23, 2018	Prof. U. Zangemeister-Wittke	Gezielte Tumortherapie mit Antikörpern und Immunkonjugaten

Lectures for Medical Students: Pathology

Date	Lecturer	Title of the lecture
Sep 19, 2018	Dr. Christina Merz-Stöckle	Adaptation und Zellschäden

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

Date	Lecturer	Title of the lecture
Feb 05, 2018	Prof. Hans-Uwe Simon	Rezeptoren, Dosis-Wirkungskurven,
Feb 05, 2018	Prof. Hans-Uwe Simon	Antagonisten, Applikationsarten
Feb 19, 2018	Prof. U. Zangemeister-Wittke	Einführung in die Pharmakokinetik
Feb 21, 2018	Prof. Andrea Huwiler	Narkose, Beruhigungsmittel
Feb 28, 2018	Prof. U. Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Mar 07, 2018	Prof. Andrea Huwiler	Pharmakologie der Atemwege
Mar 12, 2018	PD Dr. Armand Cachelin	Analgetika
Mar 28, 2018	Prof. Thomas Kaufmann	Pharmakogenetik, Interaktionen
Apr 11, 2018	Prof. Stephan von Gunten	Psychopharmaka

Apr 16, 2018	PD Dr. David Spirk	Pharmakologie der Herzerkrankungen
Apr 16, 2018	PD Dr. David Spirk	Pharmakologie der Hämostase
Apr 18, 2018	Dr. Sibylle Bürgi	Antidiabetika, Lokalanästhetika
Apr 30, 2018	Dr. Sibylle Bürgi	Antibiotika
May 02, 2018	Dr. Sibylle Bürgi	Antidiabetika
May 09, 2018	Prof. Stephan von Gunten	Magensäurehemmung

Oral examinations: Prof. Zangemeister-Wittke, Prof. Huwiler, Prof. von Gunten, Prof. Simon, Prof. Kaufmann

Lectures for Natural Sciences Faculty and Biomedical Sciences students: Clinical Immunology (Coordinator: Prof. Stephan von Gunten)

Date	Lecturer	Title of the lecture
Feb 22, 2018	Prof. Stephan von Gunten	Introduction
Feb 22, 2018	Prof. Stephan von Gunten	Glycoimmunology
May 24, 2018	Prof. Stephan von Gunten	Immunopharmacology

Written examination and oral tests: Prof. von Gunten

Lecture for Natural Sciences Faculty: Cellular and Molecular Immunology (Coordinator: Prof. Christoph Müller)

Date	Lecturer	Title of the lecture
Nov 01, 2018	Prof. Thomas Kaufmann	Cell death in the immune system

Lectures for Biomedical Sciences students (M.Sc. program, Bern) and Natural Sciences Faculty: Molecular Biology of Inflammation (Coordinator: Prof. Britta Engelhardt)

Date	Lecturer	Title of the lecture
April 12, 2018	Prof. Andrea Huwiler	Lipid mediators in inflammation
May 17, 2018	Prof. Shida Yousefi	Inflammation - good or bad? Resolution of inflammation - apoptosis

Practical work for Natural Science Faculty: Immunology II (Coordinator: Prof. Thomas Kaufmann)

Date	Lecturer	Title of the lecture
Dec 06, 2018	Prof. Shida Yousefi Prof. Stephan von Gunten Prof. Thomas Kaufmann	Immunological Methods (1 day)
Dec 07, 2018	Prof. Shida Yousefi Prof. Stephan von Gunten Prof. Thomas Kaufmann	Immunological Methods (1 day)
Dec 13, 2018	Prof. Shida Yousefi Prof. Stephan von Gunten Prof. Thomas Kaufmann	Immunological Methods (1 day)
Dec 14, 2018	Prof. Shida Yousefi Prof. Stephan von Gunten Prof. Thomas Kaufmann	Immunological Methods (1 day)
Dec 20, 2018	Prof. Shida Yousefi Prof. Stephan von Gunten Prof. Thomas Kaufmann	Immunological Methods (1 day)
Dec 21, 2018	Prof. Shida Yousefi Prof. Stephan von Gunten Prof. Thomas Kaufmann	Evaluation (4 h)

Lectures for Biomedical Sciences Students (M.Sc. program, Bern) and Graduate School for Cellular and Biomedical Sciences: Pharmacology of Major Organ Systems (Coordinator: Prof. Thomas Kaufmann)

Date	Lecturer	Title of the lecture
Sep 21, 2018	Prof. Stephan von Gunten	Gastrointestinal tract
Oct 12, 2018	Prof. Stephan von Gunten	Endocrine and reproductive system
Sep 28, 2018	PD Dr. David Spirk	Haemopoietic system and haemostasis
Oct 06, 2018	Prof. Thomas Kaufmann	Antiinfectious therapy
Oct 19, 2018	Prof. Georgia Konstantinidou	Immune system
Nov 02, 2018	Prof. Andrea Huwiler	Nervous system
Nov 16, 2018	Prof. U. Zangemeister-Wittke	Heart and vascular system
Oct 26, 2018	Prof. Shida Yousefi	Lungs and kidneys

Lecture for Biomedical Sciences Students (M.Sc. program, Bern) and Graduate School for Cellular and Biomedical Sciences: Topics in Tumor Biology (Coordinator: Prof. Deborah Stroka)

Date	Lecturer	Title of the lecture
Feb 28, 2018	Prof. Georgia Konstantinidou	Oncogenes – how to target them

Lecture for Natural Sciences Faculty and Biomedical Sciences students (M.Sc. program, Cell Biology, Bern) and Graduate School for Cellular and Biomedical Sciences: General Pathology & Histology (Coordinator: PD Dr. Philippe Krebs)

Date	Lecturer	Title of the lecture
Nov 13, 2018	Prof. Thomas Kaufmann	Cell damage

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

Date	Lecturer	Title of the lecture
Oct 19, 2018	Prof. Shida Yousefi	Laser scanning microscopy and specific applications (FRET, FRAP, spectral unmixing) and digital image restoration (Huygen and Imaris software)

External teaching activities: University of Zurich (Molecular Medicine)

Date	Lecturer	Title of the lecture
May 2018	Prof. U. Zangemeister-Wittke	Seminars in Molecular Cell Biology for students of human and dental medicine (1st year)
Nov 2018	Porf. U. Zangemeister-Wittke	Seminars in cardiovascular diseases for students of human medicine (2nd year)
(total 12h)		

Lectures for Medical Students: Clinical Pharmacology

Date	Lecturer	Titel of the lecture
Feb 26, 2018	Prof. Manuel Haschke	Pharmakokinetik
Feb 27, 2018	Prof. Manuel Haschke	Analgetika
Feb 27, 2018	Prof. Manuel Haschke	Antiinfektiva
Feb 27, 2018	PD Dr. Jürgen Bohlender	Arterielle Hypertonie u. Herzinsuffizienz
Feb 27, 2018	PD Dr. Jürgen Bohlender	Diabetes u. Dyslipidämie
Mar 01, 2018	Prof. Manuel Haschke	Notfallmedikamente
Mar 01, 2018	PD Dr. Jürgen Bohlender	Antikoagulantien
Mar 21, 2018	PD Dr. Jürgen Bohlender	Drug-Disease Interaktionen
Apr 25, 2018	PD Dr. Jürgen Bohlender	Resistente Hypertonie
Sep 26, 2018	Prof. Manuel Haschke	Pharmakokinetik
Nov 14, 2018	Prof. Manuel Haschke	Interaktionen
Nov 14, 2018	Prof. Manuel Haschke	Unerwünschte Arzneimittelwirkungen

Lectures for Dental Medicine Students: Clinical Pharmacology

Date	Lecturer	Titel of the lecture
Nov 07, 2018	PD Dr. Jürgen Bohlender	Pat. mit akuten med. Problemen
Nov 14, 2018	PD Jürgen Bohlender	Pat. mit chron. med. Problemen
Nov 21, 2018	Dr. Katharina Geiling	UAW im Mund
Nov 28, 2018	Prof. Manuel Haschke	Analgetika
Dec 12, 2018	Irene Scholz	Antikoagulation
Dec 19, 2018	Prof. Manuel Haschke	Antibiotika

Clinical Pharmacology Lectures: University Hospital/Inselspital Bern

Date	Lecturer	Titel of the lecture
Jan 09, 2018	Prof. Manuel Haschke	Paracetamol 1 (TS)
Jan 30, 2018	Prof. Manuel Haschke	Paracetamol 2 (TS)
Feb 06, 2018	Prof. Manuel Haschke	NSAR (TS)
March 08, 2018	Haschke/Bohlender/Geiling	Arzneimittel-Interaktionen (Skills Training)
Mar 16, 2018	Prof. Manuel Haschke	Coxibe (TS)
Mar 22, 2018	Prof. Manuel Haschke	Arzneimittel-Intoxikationen (DTS)
Apr 04, 2018	Prof. Manuel Haschke	Metamizol (TS)
May 25, 2018	Prof. Manuel Haschke	Opioide 1 (TS)
Jun 06, 2018	Prof. Manuel Haschke	Opioide 2 (TS)
Jul 03, 2018	Prof. Manuel Haschke	Opioide 3 (TS)
Aug 03, 2018	Prof. Manuel Haschke	Coumarine (TS)
Okt 23, 2018	Prof. Manuel Haschke	Pharmakogenetik Coumarine (TS)
Nov 02, 2018	Prof. Manuel Haschke	DOACs 1 (TS)
Nov 15, 2018	Haschke/Bohlender/Geiling	Dosisanpassung (Skills Training)
Nov 16, 2018	Prof. Manuel Haschke	DOACs 2 (TS)
Nov 22, 2018	Prof. Manuel Haschke	Interaktionen DOACs (DTS)

External Lectures: Clinical Pharmacology

Date	Lecturer	Titel of the lecture
May 30, 2018	Prof. Manuel Haschke	Polypharmazie (SGAIM)
Jun 28, 2018	Prof. Manuel Haschke	Co-/Analgetika (CAS Basel)
Jul 04, 2018	Prof. Manuel Haschke	Polypharmazie (MediWeek Davos)
Sep 06, 2018	Prof. Manuel Haschke	Pharmacogenomics (NCCR Kidney, Bern)
Nov 22, 2018	Prof. Manuel Haschke	PK orale Antibiotika (Berner Infektiologie-Symposium)

3.2. Coordination PBL Medical Students, 3rd year (2018/2019)

Core group member:
Prof. Andrea Huwiler

Representatives of Pharmacology for teaching blocks:
Prof. Hans-Uwe Simon (blocks I, II, and IX)
Prof. Uwe Zangemeister-Wittke (blocks IV and V)
Prof. Stephan von Gunten (block V)
Prof. Andrea Huwiler (blocks VI, VII and VIII)

3.3. Tutorials (study year 2018/2019)

For Medical students 3rd year:
Prof. Georgia Konstantinidou
Dr. Zhaoyue He
Prof. Thomas Kaufmann
Kim Klapan
Dr. Darko Stojkov
Stefanie Graeter, M.Sc.
Dr. Christina Merz-Stöckle

For PhD students,
Graduate School for Cellular and Biomedical Sciences, course "Happy Cell":
Prof. Shida Yousefi
Prof. Thomas Kaufmann

Graduate School for Cellular and Biomedical Sciences, Training course on "Concepts and Methods in Programmed Cell Death and Autophagy"
Prof. Thomas Kaufmann

3.4. Elective Module Supervision

For Biomedical Sciences students:
Marjolaine Hugonnet (Prof. Thomas Kaufmann)

3.5. Seminars of Invited Speakers

Date	Teacher	Title of the seminar	Host
Jan 19, 2018	Prof. Dr. Daniel Hoessli, Panjwani Center for Molecular Medicine and Drug Design, University of Karachi, Pakistan	Modulation of resistance to tyrosine kinase inhibitors	H.-U. Simon
Feb 14, 2018	PD Dr. Remo Perozzo, School of Pharmaceutical Sciences, University of Geneva	Development of a novel bacterial three-hybrid system: A feasibility study	H.-U. Simon
Feb 28, 2018	Dr. Isabelle Arnold, Institute of Molecular Cancer Research, University of Zurich	Eosinophils suppress Th1 responses and restrict bacterially induced gastrointestinal inflammation	H.-U. Simon
Mar 13, 2018	Prof. Dr. Guy Gorochov, CIMI Research Centre, Paris, France	Metagenome-wide analysis of gut microbiota in human IgA deficiency	S. von Gunten
Mar 21, 2018	Dr. Melita Irving, Department of Oncology UNIL CHUV, Ludwig Institute for Cancer Research, Lausanne	T-cell engineering approaches for improving cancer immunotherapy	S. von Gunten
Mar 28, 2018	Prof. Dr. Jan Hendrik Niess, Universitätsspital Basel, Gastroenterologie und Hepatologie	IL-20 cytokines in intestinal diseases	H.-U. Simon
April 18, 2018	Prof. Dr. Richard Cummings, Harvard Medical School, Boston, USA	Glycosylation is required for leukocyte trafficking and function in immune recognition	S. von Gunten
May 16, 2018	Prof. Dr. Csaba Szabo, Department of Pharmacology, University of Fribourg	The vascular roles of H2S in health and disease	A. Huwiler
May 30, 2018	Dr. Christoph Esslinger, CEO Memo Therapeutics AG	MemoMAB: Gateway to human antibody repertoires	S. von Gunten

June 15, 2018	Prof. Dr. Mojgan Masoodi, Departement of Nutritional Sciences, Faculty of Medicine, University of Toronto, and Nestlé Institute of Health Sciences, Lausanne, Switzerland	The role of lipid metabolism in metabolic disorders: From biomarker discovery to nutritional intervention	C. Largiadèr
July 18, 2018	Prof. em. Dr. Urs Rüegg, Department of Pharmacology, University of Geneva	Tamoxifen: a potential drug for treatment of Duchenne muscular dystrophy	A. Huwiler
Sep 19, 2018	Prof. Dr. Robbie Joseph Loewith, Department of Molecular Biology, University of Geneva, Switzerland	Growth control by TORC1 and TORC2, opposite sides of the same coin	G. Konstantinidou
Sep 26, 2018	Dr. Alexander Lämmle, Universitätsklinik für Kinderheilkunde und Universitätsinstitut für Kinische Chemie, Inselspital, University of Bern	Liver disease modeling using iPSC-derived hepatocytes	H.-U. Simon
Nov 7, 2018	Prof. Dr. Boris Turk, Jozef Stefan Institute, Department of Biochemistry and Molecular and Structural Biology, Ljubljana, Slovenia	Extracellular cysteine cathepsins: targets for diagnostics and targeted drug delivery	H.-U. Simon
Nov 21, 2018	Prof. Dr. Edward Pearce, Max Planck Institute of Immunobiology and Epigenetics and University of Freiburg, Freiburg, Germany	Metabolic compensation for self-inflicted damage during macrophage activation	H.-U. Simon
Nov 28, 2018	Prof. Dr. Inti Zlobec, Institut für Pathology, Universität Bern	Digital pathology in translational research	S. von Gunten
Dec 21, 2018	Dr. Sébastien Herzig, The Salk Institute, San Diego, CA, USA	Exploring the interplay between mitochondria, metabolism and energy-sensing signaling pathways	H.-U. Simon

3.6. Academic Degrees

David Spirk, Titularprofessor, University of Bern
(Sep 2018)

Blanchard Olivier, PhD, University of Bern
Thesis: The role of sphingosine-1-phosphate in human proximal tubular epithelial cell inflammation and fibrosis (Mai 2018)
Supervisor: Prof. Andrea Huwiler

Kremenovic Mirela, M.Sc., University of Bern
Thesis: Blocking of sialyltransferases inhibits the expression of Siglec-7 and -9 ligands on cancer cells (Jan 2018)
Supervisors: Prof. Stephan von Gunten, Dr. Kayluz Frias Boligan

Muli Kevin, M.Sc., University of Bern
Thesis: Mechanisms of Regulation of the Profibrotic Connective Tissue Growth Factor (CTGF) by Protein Kinase C in Fibroblast Cultures (Sep 2018)
Supervisors: Prof. Andrea Huwiler, Prof. Uwe Zangemeister-Wittke

Zürcher Marc, M.Sc., University of Bern
Thesis: Purification and characterization of cancer cell line-derived exosomes (July 2018)
Supervisors: Prof. Stephan von Gunten, Dr. Kayluz Frias Boligan

Glück Angéline, M.Sc., University of Bern
Thesis: Role of autophagy in intestinal epithelial cells: The effect of ATG5 on proliferation (Feb 2018)
Supervisors: Prof. Hans-Uwe Simon, Dr. Christiane Sokollik

Blümli Natascha, M. Sc. pharm., University of Basel
Thesis: Characterization of the inflammatory cell and cytokine expression pattern in eosinophilic esophagitis-like disease (June 2018)
Supervisors: Prof. Hans-Uwe Simon, Prof. Dagmar Simon

Kocher Raphaela, M. Sc. pharm., University of Basel
Thesis: Eosinophilic esophagitis (EoE)-like disease (June 2018)
Supervisors: Prof. Hans-Uwe Simon, Prof. Dagmar Simon

Schumacher Annik Mirja, M. Sc. pharm., University of Basel
Thesis: The influence of the mitochondrial membrane potential on neuronal differentiation (June 2018)
Supervisors: Prof. Hans-Uwe Simon, Dr. He Liu

Robin Moolan, M. Drug Sc., University of Basel
Thesis: The functional role of the BK_{Ca} channel in NET formation and NLRP3 inflammasome activation in human and mouse neutrophils (June 2018)
Supervisors: Prof. Hans-Uwe Simon, Dr. Darko Stojkov

Yves Künzli, M.Sc., University of Bern
Thesis: Evidence for a role of NRD1 in the regulation of autophagy (Dec 2018)
Supervisors: Prof. Hans-Uwe Simon, Dr. Zhaoyue He

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

Group members: Olivier Blanchard, PhD student[1]
Fabian Burkhard, M.Sc. student[1]
Tankica Maneva Timcheva, Lab Technician[1]
Kevin Muli, M.Sc. student[1]
Manuel Stark, PhD student[1]
Marianne Maillard-van Laer, Lab Technician[1]
Isolde Römer, Technician[2]
Stephanie Schwalm, Dr., Postdoc[1,2]
Bisera Stepanovska, PhD student[1]

[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 and patho-physiological processes that regulate diseases such as cancer, inflammation and fibrosis. A special focus we have put on those sphingolipid species that build the cellular “rheostat”, i.e. ceramide, sphingosine, sphingosine 1-phosphate (S1P), and ceramide 1-phosphate (C1P). We are studying the regulation of the critical sphingolipid-generating and -degrading enzymes including ceramidases, sphingosine kinases, and the ceramide kinase 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 growrh.

Downregulation of the S1P Transporter Spinster Homology Protein 2 (Spns2) Exerts an Anti-Fibrotic and Anti-Inflammatory Effect in Human Renal Proximal Tubular Epithelial Cells

Blanchard O, Stepanovska B, Starck M, Erhardt M, Römer I, Meyer Zu Heringdorf D, Pfeilschifter J, Zangemeister-Wittke U, Huwiler A

Sphingosine kinase (SK) catalyses the formation of sphingosine 1-phosphate (S1P), which acts as a key regulator of inflammatory and fibrotic reactions, mainly via S1P receptor activation. Here, we show that in the human renal proximal tubular epithelial cell line HK2, the pro-fibrotic mediator transforming growth factor β (TGFβ) induces SK-1 mRNA and protein expression, and in parallel, it also upregulates the expression of the fibrotic markers connective tissue growth factor (CTGF) and fibronectin. Stable downregulation of SK-1 by RNAi resulted in the increased expression of CTGF, suggesting a suppressive effect of SK-1-derived intracellular S1P in the fibrotic process, which is lost when SK-1 is downregulated. In a further approach, the S1P transporter Spns2, which is known to export S1P and thereby reduces intracellular S1P levels, was stably downregulated in HK2 cells by RNAi. This treatment de-

creased TGFβ-induced CTGF and fibronectin expression, and it abolished the strong induction of the monocyte chemotactic protein 1 (MCP-1) by the pro-inflammatory cytokines tumor necrosis factor (TNF)α and interleukin (IL)-1β. Moreover, it enhanced the expression of aquaporin 1, which is an important water channel that is expressed in the proximal tubules, and reverted aquaporin 1 downregulation induced by IL-1β/TNFα. On the other hand, overexpression of a Spns2-GFP construct increased S1P secretion and it resulted in enhanced TGFβ-induced CTGF expression. In summary, our data demonstrate that in human renal proximal tubular epithelial cells, SK-1 downregulation accelerates an inflammatory and fibrotic reaction, whereas Spns2 downregulation has an opposite effect. We conclude that Spns2 represents a promising new target for the treatment of tubulointerstitial inflammation and fibrosis.

See publication No 1

Renal Mesangial Cells Isolated from Sphingosine Kinase 2 Transgenic Mice Show Reduced Proliferation and are More Sensitive to Stress-Induced Apoptosis

Beyer S, Schwalm S, Pfeilschifter J, Huwiler A

Sphingosine 1-phosphate (S1P) is considered as a key molecule regulating various cell functions including cell growth and death. It is produced by two sphingosine kinases (SK) denoted as SK-1 and SK-2. Whereas SK-1 has been extensively studied and has been appointed a role in promoting cell growth, the function of SK-2 is controversial, and both pro-proliferative and pro-apoptotic functions have been suggested. In this study we investigated whether renal mesangial cells isolated from transgenic mice overexpressing the human Sphk2 gene (hSK2-tg) showed an altered cell response towards growth-inducing and apoptotic stimuli.

hSK2-tg mice were generated by using a Quick KnockinR strategy. Renal mesangial cells were isolated by a differential sieving method and further cultivated in vitro. Lipids were quantified by mass spectrometry. Protein expression was determined by Western blot analysis, cell proliferation was determined by 3H-thymidine incorporation, and apoptosis was determined by a DNA fragmentation ELISA.

We show here that kidneys and mesangial cells from hSK2-tg mice express the hSK2 as well as the endogenous mouse mSK2. hSK2 and mSK2 predominantly resided in the cytosol of quiescent transgenic cells. However, S1P accumulated strongly in the nucleus and only minimally in the cytosol of transgenic cells. Functionally, hSK2-tg cells proliferated less than control cells under normal growth conditions and were also more sensitive towards stress-induced apoptosis. On the molecular level, this was reflected by reduced ERK and Akt/PKB activation, and upon staurosporine treatment, by a sensitized mitochondrial pathway as manifested by reduced anti-apoptotic Bcl-XL expression and increased cleavage of caspase-9, downstream caspase-3 and PARP-1.

Altogether, these data demonstrate that SK-2 exerts an antiproliferative and apoptosis-sensitizing effect in renal mesangial cells which suggests that selective inhibitors of SK-2 may promote proliferation and reduce apoptosis and this may have impact on the outcome of proliferation-associated diseases such as mesangioproliferative glomerulonephritis.

See publication No 2

Original publications

1. Blanchard O, Stepanovska B, Starck M, Erhardt M, Römer I, Meyer Zu Heringdorf D, Pfeilschifter J, Zangemeister-Wittke U, **Huwiler A**: Downregulation of the S1P Transporter Spinster Homology Protein 2 (Spns2) Exerts an Anti-Fibrotic and Anti-Inflammatory Effect in Human Renal Proximal Tubular Epithelial Cells. Int J Mol Sci. 19 (2018), 1498; doi:10.3390/ijms19051498

2. Beyer S, Schwalm S, Pfeilschifter J, **Huwiler A**: Renal Mesangial Cells Isolated from Sphingosine Kinase 2 Transgenic Mice Show Reduced Proliferation and are More Sensitive to Stress-Induced Apoptosis. Cell Physiol Biochem. 47 (2018), 2522-2533.

3. Vasilakaki S, Pastukhov O, Mavromoustakos TM, **Huwiler A**, Kokotos G: Small peptides able to suppress prostaglandin E2 generation in renal mesangial cells. Molecules 23 (2018), 158; doi:10.3390/molecules23010158

4. Eresch J, Stumpf M1, Koch A, Vutukuri R1, Ferreirós N, Schreiber Y, Schröder K, Devraj K, Popp R, **Huwiler A**, Hattenbach LO, Pfeilschifter J, Pfeilschifter W: Sphingosine Kinase 2 Modulates Retinal Neovascularization in the Mouse Model of Oxygen-Induced Retinopathy. Invest Ophthalmol Vis Sci. 59 (2018), 653-661.

5. Evangelopoulos ME, Miclea A, Schrewe L, Briner M, Salmen A, Engelhardt B, **Huwiler A**, Chan A, Hoepner R: Frequency and clinical characteristics of Multiple Sclerosis rebounds after withdrawal of Fingolimod. CNS Neurosci Ther. 24 (2018), 984-986. doi: 10.1111/cns.12992

Review articles

1. **Huwiler A**, Zangemeister-Wittke U: The sphingosine 1-phosphate receptor modulator fingolimod as a therapeutic agent: recent findings and new perspectives. Pharmacol Ther.17 185 (2018), 34-49.

2. **Huwiler A**, Pfeilschifter J: Sphingolipid signaling in renal fibrosis. Matrix Biol. 68-69 (2018), 230-247.

Group Prof. Thomas Kaufmann

Group members: Dr. Ramona Reinhart, postdoctoral fellow
Dr. Yuniel Fernandez Marrero, postdoctoral fellow
Samara Naim, PhD student
Noah Schnüriger, M.Sc. student
Anthony Marchand, visiting student (EPFL)
Daniel Bachmann, Lab Technician

Our group is interested in the molecular mechanisms of programmed cell death (PCD), in particular apoptosis and necroptosis, and the link between cell death and innate immune signaling. A focus in the latter lies on myeloid cells, in particular granulocytes (neutrophils and basophils) and mast cells, which are central players of innate immunity. Apoptosis is recognized as the most relevant (patho-) physiological form of PCD, whereas the physiological role of necroptosis is less well understood. Given the fact that apoptosis suppresses necroptosis, the latter is hypothesized to serve as a backup, proinflammatory form of PCD upon infection with pathogens that actively block apoptosis.

Granulocytes isolated from mice can only be obtained in low numbers, which makes biochemical analyses difficult, and – in the case of basophils – almost impossible. We have established a protocol to generate conditionally immortalized progenitor cells (“Hoxb8 cells”) that are committed to the macrophage/neutrophil- or the basophil lineages. Those cells can be differentiated in vitro into mature granulocytes in nearly unlimited numbers. An advantage of “Hoxb8” cells over primary granulocytes lies in the straightforward possibility of further genetic manipulation, such as overexpression of genes of interest reconstitution of gene deficient cells lines with particular mutants of that same gene. Regarding basophils and mast cells, we are interested how cytokines, such as IL-3, or binding of IgE and subsequent cross-linking of the high affinity IgE receptor by antigen, activate these cells, and if/how those stimuli increase cellular viability. On the other hand, selective killing of activated basophils or mast cells (or activated immune cells in general) is an intriguing concept to target immunological disorders, including allergies. Newly developed drugs aiming at inducing apoptosis in cancer cells (so called BH3-mimetics) are tested in our lab for their potential to kill activated leukocyte populations selectively.

Currently of great interest to our group is the pro-apoptotic family member BOK. BOK has raised much interest recently, as it is deleted in human cancers with surprisingly high frequency. Several cancer models with our newly developed *Bok*-deficient mouse strain are ongoing in our lab and in collaboration with others to test the potential tumour suppressor potential of BOK. Our recent data indicate that BOK may have a previously non-recognized

tumor-suppressor function in non-small-cell lung cancer and that BOK is a crucial mediator of liver damage and carcinogenesis induced by chemical carcinogens. Other BOK related projects focus on the molecular function of this still rather enigmatic protein. So far, we have demonstrated that BOK is much more widely expressed than previously reported and, intriguingly, we found that although it has the potential to induce apoptosis when highly expressed, BOK localizes preferentially to the membranes of the ER and Golgi apparatus rather than to mitochondria. The subcellular localization of BOK correlates with its association with IP3 receptors (Ca^{2+} channels on the ER) and a deregulated ER stress response of *Bok*-deficient cells. Interestingly, BOK is prominently also found in nuclear fractions and we observed that BOK modulates cellular proliferation. We are currently investigating mechanism regulating BOK stability and the role of BOK in cancer development and maintenance.

BH3 mimetics efficiently induce apoptosis in mouse basophils and mast cells
Reinhart R, Rohner L, Wicki S, Fux M, Kaufmann T
Basophil granulocytes and mast cells are recognized for their roles in immunity and are central effectors of diverse immunological disorders. Despite their similarities, there is emerging evidence for non-redundant roles of the circulating yet scarce basophils and tissue-resident mast cells, respectively. Because of their importance in allergic pathogenesis, specific induction of apoptosis in basophils and mast cells may represent an interesting novel treatment strategy. The pro-inflammatory cytokine interleukin-3 serves as a key factor for basophil and mouse mast cell survival. Interleukin-3 increases the expression of anti-apoptotic BCL-2 family members, such as BCL-2, BCL-XL or MCL-1; however, little is known how strongly these individual proteins contribute to basophil survival. Here, we were applying small molecule inhibitors called BH3 mimetics, some of which show remarkable success in cancer treatments, to neutralize the function of anti-apoptotic BCL-2 family members. We observed that expression levels of anti-apoptotic BCL-2 proteins do not necessarily correlate with their respective importance for basophil survival. Whereas naive in vitro-differentiated mouse basophils efficiently died upon BCL-2 or BCL-XL inhibition, interleukin-3 priming rendered the cells highly resistant toward apoptosis, and this could only be overcome upon combined targeting of BCL-2 and BCL-XL. Of note, human basophils differed from mouse basophils as they depended on BCL-2 and MCL-1, but not on BCL-XL, for their survival at steady state. On the other hand, and in contrast to mouse basophils, MCL-1 proved critical in mediating survival of interleukin-3 stimulated mouse mast cells, whereas BCL-XL seemed dispensable. Taken together, our results indicate that by choosing the right combination of BH3 mimetic compounds, basophils and mast cells can be efficiently killed, even after stimulation with potent pro-survival cytokines such as interleukin-3. Because of the tolerable side effects of BH3 mimetics, targeting basophils or mast cells for apoptosis opens interesting possibilities for novel treatment approaches.
See publication No 1

BOK promotes chemical-induced hepatocarcinogenesis in mice
Rabachini T, Fernandez-Marrero Y, Montani M, Loforese G, Sladky V, He Z, Bachmann D, Wicki S, Villunger A, Stroka D, Kaufmann T
BCL-2-related ovarian killer (BOK) is a conserved and widely expressed BCL-2 family member with sequence homology to pro-apoptotic BAX and BAK, but with poorly understood pathophysiological function. Since several members of the BCL-2 family are critically involved

in the regulation of hepatocellular apoptosis and carcinogenesis we aimed to establish whether loss of BOK affects diethylnitrosamine (DEN)-induced hepatocarcinogenesis in mice. Short-term exposure to DEN lead to upregulation of BOK mRNA and protein in the liver. Of note, induction of CHOP and the pro-apoptotic BH3-only proteins PUMA and BIM by DEN was strongly reduced in the absence of BOK. Accordingly, Bok -/- mice were significantly protected from DEN-induced acute hepatocellular apoptosis and associated inflammation. As a consequence, Bok -/- animals were partially protected against chemical-induced hepatocarcinogenesis showing fewer and, surprisingly, also smaller tumors than WT controls. Gene expression profiling revealed that downregulation of BOK results in upregulation of genes involved in cell cycle arrest. Bok -/- hepatocellular carcinoma (HCC) displayed higher expression levels of the cyclin kinase inhibitors p19INK4d and p21cip1. Accordingly, hepatocellular carcinoma in Bok -/- animals, BOK-deficient human HCC cell lines, as well as non-transformed cells, showed significantly less proliferation than BOK-proficient controls. We conclude that BOK is induced by DEN, contributes to DEN-induced hepatocellular apoptosis and resulting hepatocarcinogenesis. In line with its previously reported predominant localization at the endoplasmic reticulum, our findings support a role of BOK that links the cell cycle and cell death machineries upstream of mitochondrial damage.
See publication No 2

Loss of BID Delays FASL-Induced Cell Death of Mouse Neutrophils and Aggravates DSS-Induced Weight Loss

Wicki S, Gurzeler U, Corazza N, Genitsch V, Wong WW, Kaufmann T

Neutrophils are key players in the early defense against invading pathogens. Due to their potent effector functions, programmed cell death of activated neutrophils has to be tightly controlled; however, its underlying mechanisms remain unclear. Fas ligand (FASL/CD95L) has been shown to induce neutrophil apoptosis, which is accelerated by the processing of the BH3-only protein BH3 interacting domain death agonist (BID) to trigger mitochondrial apoptotic events, and been attributed a regulatory role during viral and bacterial infections. Here, we show that, in accordance with previous works, mouse neutrophils underwent caspase-dependent apoptosis in response to FASL, and that this cell death was significantly delayed upon loss of BID. However, pan-caspase inhibition failed to protect mouse neutrophils from FASL-induced apoptosis and caused a switch to RIPK3-dependent necroptotic cell death. Intriguingly, such a switch was less evident in the absence of BID, particularly under inflammatory conditions. Delayed neutrophil apoptosis has been implicated in several auto-inflammatory diseases, including inflammatory bowel disease. We show that neutrophil and macrophage driven acute dextran sulfate sodium (DSS) induced colitis was slightly more aggravated in BID-deficient mice, based on significantly increased weight loss compared to wild-type controls. Taken together, our data support a central role for FASL > FAS and BID in mouse neutrophil cell death and further underline the anti-inflammatory role of BID.
See publication No 3

IL-4 enhances survival of in vitro-differentiated mouse basophils through transcription-independent signaling downstream of PI3K

Reinhart R, Kaufmann T

Interleukin 4 (IL-4) is a critical cytokine implicated with T_H2 immune reactions, which are linked to pathologic conditions of allergic diseases. In that context, the initiation of T_H2 responses can critically depend on early basophil-derived IL-4 to activate T-cell responses, which then amplify IL-4 secretion. As a pleiotropic cytokine, IL-4 acts on a broad variety of hematopoietic and non-hematopoietic cells. However, the effect of IL-4 on basophils themselves, which are emerging as relevant players in allergic as well as autoimmune diseases, was only scarcely addressed so far. Here we used in vitro-differentiated mouse basophils to investigate the direct effects of IL-4 on cellular viability and surface expression of the high-

affinity receptor for IgE, FcεRI. We observed that IL-4 elicits pronounced pro-survival signaling in basophils, delaying spontaneous apoptosis in vitro to a degree comparable to the known pro-survival effects of IL-3. Our data indicate that IL-4-mediated survival depends on PI3K/AKT signaling and—in contrast to IL-3—seems to be largely independent of transcriptional changes but effectuated by post-translational mechanisms affecting BCL-2 family members among others. Additionally, we found that IL-4 signaling has a stabilizing effect on the surface expression levels of the critical basophil activation receptor FcεRI. In summary, our findings indicate an important regulatory role of IL-4 on in vitro-differentiated mouse basophils enhancing their survival and stabilizing FcεRI receptor expression through PI3K-dependent signaling. A better understanding of the regulation of basophil survival will help to define promising targets and consequently treatment strategies in basophil-driven diseases.
See publication No 4

Negative Regulation of BOK Expression by Recruitment of TRIM28 to Regulatory Elements in Its 3' Untranslated Region
Fernandez-Marrero Y, Bachmann D, Lauber E, Kaufmann T
BCL-2-related ovarian killer (BOK) is a pro-apoptotic BAX-like member of the BCL-2 family with suggested tumor suppressor activity. The molecular mechanisms regulating BOK expression are poorly understood and fail to explain a frequent lack of concordance between protein and transcript levels. Here, we describe a potent post-transcriptional mechanism that negatively regulates BOK expression mediated by conserved (AU/U)-rich elements within its 3' UTR. Using proteomics approaches we identified TRIM28 as a key component associating with U-rich elements in the human BOK 3' UTR, resulting in a dramatic reduction of BOK expression. TRIM28 is overexpressed in several cancers, correlating with poor patient outcome, whereas the BOK locus is frequently deleted or its expression downregulated in human cancers. Data mining indicated that, for certain cancers, high TRIM28 and low BOK expression are significantly correlated in the stratum of patients with the worst survival, suggesting that this mechanism might be of potential therapeutic value.
See publication No 5

Original publications

1. Reinhart R, Rohner L, Wicki S, Fux M, **Kaufmann T**: BH3 mimetics efficiently induce apoptosis in mouse basophils and mast cells. Cell Death Differ. 25 (2018), 204-216.

2. Rabachini T, Fernandez-Marrero Y, Montani M, Loforese G, Sladky V, He Z, Bachmann D, Wicki S, Villunger A, Stroka D, **Kaufmann T**: BOK promotes chemical-induced hepatocarcinogenesis in mice. Cell Death Differ. 25 (2018), 706-718

3. Wicki S, Gurzeler U, Corazza N, Genitsch V, Wong WW, **Kaufmann T**: Loss of BID Delays FASL-Induced Cell Death of Mouse Neutrophils and Aggravates DSS-Induced Weight Loss. Int J Mol Sci. 19 (2018), 684.

4. Reinhart R, **Kaufmann T**: IL-4 enhances survival of in vitro-differentiated mouse basophils through transcription-independent signaling downstream of PI3K. Cell Death Dis. 9 (2018), 713.

5. Fernandez-Marrero Y, Bachmann D, Lauber E, **Kaufmann T**: Negative Regulation of BOK Expression by Recruitment of TRIM28 to Regulatory Elements in Its 3' Untranslated Region. iScience 9 (2018), 461-474.

6. Rohner L, Reinhart R, Hagmann B, Odermatt A, Babirye A, **Kaufmann T**, Fux M: FcεRI cross-linking and IL-3 protect human basophils from intrinsic apoptotic stress. J Allergy Clin Immunol. 142 (2018), 1647-1650.

Review article

1. Galluzzi L,… **Kaufmann T**,…Kroemer G: Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 25 (2018), 486-541.

Group Prof. Georgia Konstantinidou

Group members: Chiara Pozzato, PhD student
Matteo Rossi Sebastiano, PhD student
Maria Saliakoura, PhD student

Cancer cells undergo oncogene-directed reprogramming in order to meet the energetic and biosynthetic challenges of cell survival, growth and proliferation. Our lab aims at identifying vulnerabilities of cancer cells in order to reveal targets for the development of innovative therapeutic strategies. In particular, we focus on the signaling and lipid metabolic alterations in KRAS-induced lung and pancreatic cancer. We work on cell lines (using a combination of techniques in molecular biology, cell biology and biochemistry), mouse models of lung and pancreatic cancer and human specimens.

Group Prof. Hans-Uwe Simon

Group members:
Salome Aeschlimann, Technician*
Kevin Oberson, Technician*
Evelyne Kozlowski, Technician*
Riim Naser, Technician*,**
Dr. Zhaoyue He, Postdoc
Dr. He Liu, Postdoc
Dr. Darko Stojkov, Postdoc*
Dr. Xiaoliang Wang, Postdoc
Ziva Frangez, PhD student
Nina Germic, PhD student
Kim Klapan, PhD student**
Peng Shuang, PhD student*
Nikita Markov, PhD student*
Yves Künzli, M.Sc. student
Robin Moolan, M.Sc. student*
Angéline Glück, M.Sc. student***
Hélène Karlen, MD student**
Natascha Blümli, M.Sc. pharm. student*,**
Raphaela Kocher, M.Sc. pharm. student*,**
Annik Mirja Schumacher, M.Sc. pharm. student*,**
Razieh Ardali, Adjunct PhD student
Keyvan Amirshahrokhi, Adjunct Professor

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

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, bullous pemphigoid and malignant melanoma. Our research goal is the identification of new drug targets for future therapeutic approaches in these diseases. Besides research into pathogenesis, 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 can be seen in the following abstracts, which briefly describe our research activities in 2018.

Neutrophil extracellular trap formation requires OPA1-dependent glycolytic ATP production

Amini P, Stojkov D, Felser A, Jackson CB, Courage C, Schaller A, Gelman L, Soriano ME, Nuoffer JM, Scorrano L, Benarafa C, Yousefi S, Simon HU

Optic atrophy 1 (OPA1) is a mitochondrial inner membrane protein that has an important role in mitochondrial fusion and structural integrity. Dysfunctional OPA1 mutations cause atrophy of the optic nerve leading to blindness. Here, we show that OPA1 has an important role in the innate immune system. Using conditional knockout mice lacking Opa1 in neutrophils ($Opa1^{N\Delta}$), we report that lack of OPA1 reduces the activity of mitochondrial electron transport complex I in neutrophils. This then causes a decline in adenosine-triphosphate (ATP) production through glycolysis due to lowered NAD^+ availability. Additionally, we show that OPA1-dependent ATP production in these cells is required for microtubule network assembly and for the formation of neutrophil extracellular traps. Finally, we show that $Opa1^{N\Delta}$ mice exhibit a reduced antibacterial defense capability against Pseudomonas aeruginosa.

See publication No. 1

Biochemical re-programming of human dermal stem cells to neurons by increasing mitochondrial membrane potential

Liu H, He Z, Leonhard April S, Trefny MP, Rougier JS, Salemi S, Olariu R, Widmer HR, Simon HU

Stem cells are generally believed to contain a small number of mitochondria, thus accounting for their glycolytic phenotype. We demonstrate here, however, that despite an indispensable glucose dependency, human dermal stem cells (hDSCs) contain very numerous mitochondria. Interestingly, these stem cells segregate into two distinct subpopulations. One exhibits high, the other low-mitochondrial membrane potentials (Δψm). We have made the same observations with mouse neural stem cells (mNSCs) which serve here as a complementary model to hDSCs. Strikingly, pharmacologic inhibition of phosphoinositide 3-kinase (PI3K) increased the overall Δψm, decreased the dependency on glycolysis and led to formation of TUJ1 positive, electrophysiologically functional neuron-like cells in both mNSCs and hDSCs, even in the absence of any neuronal growth factors. Furthermore, of the two, it was the Δψm-high subpopulation which produced more mitochondrial reactive oxygen species (ROS) and showed an enhanced neuronal differentiation capacity as compared to the Δψm-low subpopulation. These data suggest that the Δψm-low stem cells may function as the dormant stem cell population to sustain future neuronal differentiation by avoiding excessive ROS production. Thus, chemical modulation of PI3K activity, switching the metabotype of hDSCs to neurons, may have potential as an autologous transplantation strategy for neurodegenerative diseases.

See publication No. 2

Evidence of an abnormal epithelial barrier in active, untreated and corticosteroid-treated eosinophilic esophagitis

Simon D, Page B, Vogel M, Bussmann C, Blanchard C, Straumann A, Simon HU

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated disease characterized by symptoms related to esophageal dysfunction and an eosinophil-predominant inflammation. This study has aimed to investigate whether the recently observed sensitization to Candida albicans in EoE patients is owing to pre-existing disease and its underlying abnormal epithelial barrier or, alternatively, is linked to corticosteroid (CS) therapy. Medical histories, as well as serum and tissue samples of 60 EoE patients (15 CS-naive, 45 with current or previous CS therapy) and 20 controls, stored in the Swiss Eosinophilic Esophagitis Database (SEED) and Biobank, were analyzed. We applied ImmunoCAP to measure IgE levels and immunofluorescence techniques to examine epithelial barrier components. EoE patients had higher total IgE levels and were more frequently sensitized to Candida albicans than controls.

In EoE tissue specimens, increased numbers of eosinophils and mast cells, a higher expression levels of thymic stromal lymphopoietin (TSLP), cathelicidin, proteases, i.e. the kallikreins (KLK)-5 and KLK-7, were observed as compared with controls, while reduced expression of lympho-epithelial Kazal-type-related inhibitor (LEKTI), filaggrin, E-cadherin, claudin, occludin, demoglein-1 was found, independent of CS therapy. In CS-treated EoE, significantly lower numbers of CD1a+ cells and cathelicidin expression were noted as compared to CS-naive EoE. This study provides further evidence that EoE is associated with an abnormal epithelial barrier and postulates that CS therapy, by reducing innate immune mechanisms, may promote Candida albicans colonization and likely subsequent sensitization.
See original publication No 3

Monocytes enhance neutrophil-induced blister formation in an ex vivo model of bullous pemphigoid

de Graauw E, Sitaru C, Horn MP, Borradori L, Yousefi S, Simon D, Simon HU

Lesions of bullous pemphigoid (BP), an autoimmune subepidermal blistering disease characterized by the presence of tissue-bound and circulating autoantibodies to hemidesmosomal antigens, harbor a mixed inflammatory cellular infiltrate. In various models, neutrophils, eosinophils, mast cells, monocytes as well as B and T cells have been shown to be involved in the pathogenesis of BP. However, their interactions with and effective role in blister formation remain uncertain. This study was aimed at investigating the effect of monocyte/neutrophil interaction on blister formation in an ex vivo BP model. Skin cryosections were incubated with purified human neutrophils and monocytes, in the presence or absence of BP autoantibodies. Production of reactive oxygen species (ROS), degranulation, mediator release (neutrophil elastase [NE], myeloperoxidase [MPO], matrix metalloproteinase-9 [MMP-9]), binding of Fcγ receptor (CD16, CD32, CD64), and cell adhesion (CD18, ICAM-1) was investigated using appropriate inhibitors. Dermal-epidermal separation (DES) was assessed by light microscopy and quantified by Fiji software. Monocytes and neutrophils synergistically interact resulting in a significantly higher DES compared to either monocytes or neutrophils separately ($P < .0001$). Monocyte/neutrophil-induced DES was associated with increased ROS production and was dependent on adhesion and FcγRIII binding. Upon stimulation by the granule-poor fraction of monocyte supernatants, neutrophils increased their release of MMP-9, thereby also DES at the dermal-epidermal junction of skin cryosections. Our observations suggest that the interaction of cells, as shown here for monocytes and neutrophils, enhances mediator release resulting in an increased subepidermal blister formation. Thus, blocking intercellular cross talk promises a new therapeutic approach for blocking tissue damage in BP.
See original publication No 4

Downregulation of autophagy-related proteins 1, 5, and 16 in testicular germ cell tumors parallels lowered LC3B and elevated p62 levels, suggesting reduced basal autophagy

Liu H, He Z, Bode P, Moch H, Simon HU

Autophagy is a cellular "self-digestion" process known to be essential for various physiological and pathological pathways, including cancer, where its role appears to be context-dependent. In this work, we aimed to investigate the level of autophagy by evaluating the expression of key autophagy-related proteins (ATGs) in testicular germ cell tumors (TGCT) for which autophagy has been rarely investigated. We decided to use an immunohistochemical (IHC) staining approach employing a tissue microarray (TMA). Software-based evaluation of the integrated optical densities (IODs) of these proteins indicated a significant downregulation of ATG1, ATG5, and ATG16L1. Accordingly, reduced levels of microtubule-associated proteins 1A/1B light chain 3B (LC3B) were found to parallel increases in sequestosome-1 (SQSTM1 or p62), a protein normally degraded via autophagy, suggesting an in vivo reduction in autophagy with TGCT. Thus, our work provides evidence for a tumor suppressive

function of autophagy in the development of TGCT and supports the concept of a context-dependent role of autophagy in tumorigenesis which is tumor type-dependent.
See publication No 5

Original publications

1. Amini P, Stojkov D, Felser A, Jackson CB, Courage C, Schaller A, Gelman L, Soriano ME, Nuoffer JM, Scorrano L, Benarafa C, Yousefi S, **Simon HU**: Neutrophil extracellular trap formation requires OPA1-dependent glycolytic ATP production. Nat Commun. 9 (2018), 2958.

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5. Liu H, He Z, Bode P, Moch H, **Simon HU**: Downregulation of autophagy-related proteins 1, 5, and 16 in testicular germ cell tumors parallels lowered LC3B and elevated p62 levels, suggesting reduced basal autophagy. Front Oncol. 8 (2018), 366.

6. Prince R, Bologna L, Manetti M, Melchiorre D, Rosa I, Dewarrat N, Suardi S, Amini P, Fernández JA, Burnier L, Quarroz C, Reina Caro MD, Matsumura Y, Kremer Hovinga JA, Griffin JH, **Simon HU**, Ibba-Manneschi L, Saller F, Calzavarini S, Angelillo-Scherrer A: Targeting anticoagulant protein S to improve hemostasis in hemophilia. Blood 131 (2018), 1360-1371.

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10. Jin J, Britschgi A, Schläfli AM, Humbert M, Shan-Krauer D, Batliner J, Federzoni EA, Ernst M, Torbett BE, Yousefi S, **Simon HU**, Tschan MP: Low Autophagy (ATG) Gene Expression Is Associated with an Immature AML Blast Cell Phenotype and Can Be Restored during AML Differentiation Therapy. Oxid Med Cell Longev. (2018), 1482795.

11. Eberli D, Horst M, Mortezavi A, Andersson KE, Gobet R, Sulser T, **Simon HU**, Salemi S: Increased autophagy contributes to impaired smooth muscle function in neurogenic lower urinary tract dysfunction. Neurourol Urodyn. 37 (2018), 2414-2424.

12. Seyed Jafari SM, Wiedmer C, Cazzaniga S, Frangež Ž, Shafighi M, Beltraminelli H, Weber B, **Simon HU**, Hunger RE: Correlation of Vascular Endothelial Growth Factor subtypes and their receptors with melanoma progression: A next-generation Tissue Microarray (ngTMA) automated analysis. PLoS One. 13 (2018), e0207019.

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Book chapter

1. Simon D, Radonjic-Hösli S, Straumann A, Yousefi S, **Simon HU**: Epithelial barrier defects and eosinophil extracellular trap formation in active eosinophilic esophagitis. In: Towards precision diagnosis and targeted intervention in allergic disease (Eds. B.S. Bochner and P.S. Creticos); Pacini Editore S.p.A., Pisa, 2018, p. 45-47.

Group Prof. Stephan von Gunten

Group members: Dr. Kayluz Frias Boligan, Postdoc
Dr. Olivia Adams, Postdoc
Stefanie Graeter, PhD student
Quentin Haas, PhD student
Daniëlle Verschoor, Practicant
Aldona von Gunten, Technical specialist
Marc Zürcher, M.Sc. student
Mirela Kremenovic, M.Sc. student

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

Original publications

1. Stanczak MA, Siddiqui SS, Trefny MP, Thommen DS, Boligan KF, **von Gunten S**, Tzankov A, Tietze L, Lardinois D, Heinzelmann-Schwarz V, von Bergwelt-Baildon MS, Zhang W, Lenz HJ, Han Y, Amos CI, Syedbasha M, Egli A, Stenner F, Speiser DE, Varki A, Zippelius A, Läubli H: Self-associated molecular patterns mediate cancer immune evasion by engaging Siglecs on T cells. J Clin Invest. 128 (2018), 4912-4923.

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Review articles/Editorials

1. Haas Q, Simillion C, **von Gunten S**: A cartography of Siglecs and sialyltransferases in gynecologic malignancies: Is there a road towards a sweet future? Front Oncol. 8 (2018), 68.

2. Adams OJ, Stanczak MA, **von Gunten S**, Läubli H: Targeting sialic acid-Siglec interactions to reverse immune suppression in cancer. Glycobiology 28 (2018), 640-647.

3. Adams OJ, **von Gunten S**: Recent advances in experimental allergy. Int Arch Allergy Immunol. 177 (2018), 281-289.

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Book chapter

1. Vassilev TL, Kostov V, **von Gunten S**, Pashov AD (2018) Basics of immunoglobulins as effector molecules and drugs. In: Imbach, P. (ed) Antibody Therapy : Substitution - Immunomodulation - Monclonal Therapy. Springer, Cham, Switzerland, pp 133-150.

Group Prof. Shida Yousefi

Group members: Salome Aeschlimann, Technician*
Meike Claus, Technician*
Evelyne Kozlowski, Technician*
Riim Nasser, Technician*
Kevin Oberson, Technician*
Dr. Darko Stojkov, Postdoc*
Shuang Peng, PhD student*
Robin Moolan, M.Sc. student*

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

We are interested in mechanisms regulating granulocyte functions, such as the release of inflammatory mediators and anti-microbial defense mechanisms. Extracellular DNA trap formation by granulocytes is a newly defined anti-microbial mechanism. Previous reports from our group revealed that extracellular DNA trap formation by neutrophils, eosinophils, and basophils does not require their death, and that DNA traps are composed of mitochondrial DNA and granule proteins. Our aim is to investigate mouse and human neutrophils with respect to their extracellular DNA trap formation and the molecular events required.

Oxidative damage of SP-D abolishes control of eosinophil extracellular DNA trap formation.
Yousefi S, Sharma SK, Stojkov D, Germic N, Aeschlimann S, Ge MQ, Flayer CH, Larson ED, Redai IG, Zhang S, Koziol-White CJ, Karikó K, Simon HU, Haczku A.
The asthmatic airways are highly susceptible to inflammatory injury by air pollutants such as ozone (O3), characterized by enhanced activation of eosinophilic granulocytes and a failure of immune protective mechanisms. Eosinophil activation during asthma exacerbation contributes to the proinflammatory oxidative stress by high levels of nitric oxide (NO) production and extracellular DNA release. Surfactant protein-D (SP-D), an epithelial cell product of the airways, is a critical immune regulatory molecule with a multimeric structure susceptible to oxidative modifications. Using recombinant proteins and confocal imaging, we demonstrate here that SP-D directly bound to the membrane and inhibited extracellular DNA trap formation by human and murine eosinophils in a concentration and carbohydrate-dependent manner. Combined allergic airway sensitization and O3 exposure heightened eosinophilia and nos2 mRNA (iNOS) activation in the lung tissue and S-nitrosylation related de-oligomerisation of SP-D in the airways. In vitro reproduction of the iNOS action led to similar effects on SP-D. Importantly, S-nitrosylation abolished the ability of SP-D to block extracellular DNA trap formation. Thus, the homeostatic negative regulatory feedback between SP-D and eosinophils is destroyed by the NO-rich oxidative lung tissue environment in asthma exacerbations.
See publication No 1

Original publications

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4. de Graauw E, Sitaru C, Horn MP, Borradori L, **Yousefi S**, Simon D, Simon HU: Monocytes enhance neutrophil-induced blister formation in an ex vivo model of bullous pemphigoid. Allergy 73 (2018), 1119-1130.

5. Jin J, Britschgi A, Schläfli AM, Humbert M, Shan-Krauer D, Batliner J, Federzoni EA, Ernst M, Torbett BE, **Yousefi S**, Simon HU, Tschan MP: Low autophagy (ATG) gene expression is associated with an immature AML blast cell phenotype and can be restored during AML differentiation therapy. Oxid Med Cell Longev. (2018), 1482795.

Review articles/Correspondences

1. Wang X, **Yousefi S**, Simon HU: Necroptosis and neutrophil-associated disorders. Cell Death Dis. 9 (2018), 111.

2. Gevaert E, **Yousefi S**, Bachert C, Simon HU: Extracellular eosinophil traps - Reply. J. Allergy Clin Immunol. 141 (2018), 1164-1165.

3. Boeltz S, … **Yousefi S**, … Herrmann M: To NET or not to NET: current opinions and state of the science regarding the formation of neutrophil extracellular traps. Cell Death Differ. 2019, in press.

Book chapter

1. Simon D, Radonjic-Hösli S, Straumann A, **Yousefi S**, Simon HU: Epithelial barrier defects and eosinophil extracellular trap formation in active eosinophilic esophagitis. In: Towards precision diagnosis and targeted intervention in allergic disease (Eds. B.S. Bochner and P.S. Creticos); Pacini Editore S.p.A., Pisa, 2018, p. 45-47.

Group Prof. Uwe Zangemeister-Wittke

Group members: Fabian Brandl, PhD student
Hannes Merten, PhD student[1]
Martin Erhardt, PhD student

[1]Institute of Biochemistry, University of Zürich

We are interested in translational aspects of molecular oncology, biomarker validation and tumor targeting with rationally engineered and pharmacologically improved protein-drug conjugates. For tumor targeting we use Designed Ankyrin Repeat Proteins (DARPins), as highly stable non-IgG scaffold proteins, for site-specific and orthogonal conjugation, to generate drug conjugates of defined stoichiometry and optimized pharmacokinetics. The affinity-maturated DARPins were genetically modified and expressed in in a special E. coli strain to obtain protein carrying both a thiol and an azide group for thiol-maleimide conjugation and strain-promoted azide-alkyne cycloaddition (click chemistry). Based on this technology, we have generated nanomedicines payloaded with cytotoxins of various origins, including domain I-truncated Pseudomonas Aeruginosa Exotoxin A engineered to a prodrug activated by specific enzymes in tumor-tissues, and the antimitotic agent Monomethyl Auristatin F (MMAF). To quantitatively improve tumor localization, the serum half-life of the bioconjugates was extended by site-specific conjugation with serum albumin or the synthetic unstructured polypeptides PAS or XTEN with variable length. In addition, in collaboration with A. Huwiler (see project description above) we use well-defined human tumor cell lines from primary tumors and from metastases of different sites to investigate the role of various components of the sphingolipid signaling pathway in malignant progression and metastasis.

Original publication

1. Blanchard O, Stepanovska B, Starck M, Erhardt M, Römer I, Meyer Zu Heringdorf D, Pfeilschifter J, **Zangemeister-Wittke U**, Huwiler A: Downregulation of the S1P transporter spinster homology protein 2 (Spns2) exerts an anti-fibrotic and anti-inflammatory effect in human renal proximal tubular epithelial cells. Int J Mol Sci. 19 (2018), 1498-1517.

Review article

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Book chapter

1. Merten A, Schaefer JV, Brandl F, **Zangemeister-Wittke U**, Plückthun A: Facile site-specific multi-conjugation strategies in recombinant proteins produced in bacteria. Methods Mol Biol, in press

Group Prof. Manuel Haschke (Clinical Pharmacology)

Group members: Friederike Sandbaumhüter, PhD
Jürgen Bohlender, MD
Evangelia Liakoni, MD
Katharina Geiling, MD
Irene Scholz, med pract

We are interested in mechanisms of drug toxicity and factors responsible for variations of drug metabolism. Exogenous and endogenous compounds used as biomarkers for toxicity or drug metabolism are characterized and quantified using liquid chromatography tandem mass spectrometry (LC-MS/MS) systems. We use a previously developed low-dose cocktail to phenotype phase I drug metabolizing enzymes. Quantitative analysis of renin-angiotensin system peptides are investigated as adherence markers for drugs acting on the RAS. The systems are also used to quantifiy drug concentrations in samples from clinical phase I studies.

In addition to our research activities we provide clinical services to the University Hospital Bern to improve efficacy and safety in the clinical use of drugs. This includes a consiliary service (>250 reports/year), systematic evaluation of patients with drug-related problems (adverse drug effects, pharmacogenetics, phenotyping) or difficult to treat arterial hypertension in the outpatient clinics and regular drug safety screenings of inpatients on medical wards. In our regional pharmacovigilance center we evaluate reports on adverse drug events (>280/year), which then are fed into the national (Swiss Regulatory Authority) and international (WHO) adverse drug event databases. Short descriptions of the different projects are given below.

Mechanisms and Genetics of Metamizole-induced Agranulocytosis (MH)
In this SNF-project, we compare patients after metamizole-induced agranulocytosis (MIA) with metamizole tolerant patients and never-exposed subjects in a genome-wide association study (collaboration with U. Amstutz, Clinical Chemistry, Inselspital Bern). In addition, direct toxocitiy mechanisms (collaboration with S. Krähenbühl, Clin.Pharm Basel) as well as immune mediated mechanisms (collaboration D. Yerli, Immunology, Inselspital Bern) are investigated.

Phenotyping of phase I drug metabolism (MH)
To determine activity of major drug metabolizing cytochrome P450 enzymes we use a recently developed low dose phenotyping cocktail. A new combination capsule (CombiCap) containing mini-tablet formulations of all six probe drugs facilitates clinical application. This CombiCap is now ready to characterize phase I drug metabolism in patients with different diseases (e.g. liver cirrhosis).

Renin-Angiotensin-System (RAS) peptide profiles (MH)
Angiotensin I and II are degraded by ACE and other peptidases to smaller peptide fragments, which can be quantified using LC-MS/MS. Cardiovascular drugs such as ACE-inhibitors or angiotensin receptor blockers lead to characteristic changes in RAS peptide profiles. These profiles have been characterized in clinical trials with healthy subjects as well as in patients with newly diagnosed or difficult to control arterial hypertension. In conjunction with cardiovascular drug concentrations (also quantified by LC-MS/MS) we will test, whether these profiles allow a better discrimination between adherence-related problems and true drug-related problems in patients with difficult to treat arterial hypertension.

Pharmacokinetic analysis models for improving drug adherence screening (JB)
In this project, we explored ways to improve qualitative plasma drug screening by pharmacokinetic analysis of drug concentrations measured by LC-MS/MS. We developed analytical tools to improve the precision of adherence screening and tested these in a sample of patients.

Medication adherence during laboratory workup for secondary hypertension (JB)
In this project, we investigated potential drug bias and the validity of laboratory results during routine workup for secondary hypertension by measuring plasma drug concentrations using LC-MS/MS.

Tissue angiotensins and the angiotensinergic innervation of the heart, kidney and vessels (JB)
This project investigates the role of tissue angiotensins and of the angiotensinergic autonomic innervation of the heart, kidney and vessels of different species by angiotensin profiling. Peptides and catecholamines are quantified by LC-MS/MS. The cellular distribution of peptides and proteins is analysed using immunocytochemistry and monoclonal antibodies against angiotensin II, various neuropeptides such as calcitonin gene-related peptide, substance P or bradykinin, and enzymes of the catecholamine pathway. Neuronal and cellular co-expression and phenotypes are investigated and related to putative functional roles to clarify the interaction of the autonomic nervous system with its target cells in the cardiovascular system.

Effect of P-gp and CYP3A4-induction on PK and PD of Rivaroxaban (EL, IS)
In this open-label, sequential clinical study we will investigate the influence of the combined P-gp and CYP3A4 inducer hypericum perforatum (St. John's wort) on the pharmacokinetics and pharmacodynamics of the direct oral factor Xa inhibitor rivaroxaban in 12 healthy volunteers. CYP activity will be phenotyped at the start of each session using oral fexofenadine and midazolam. Primary outcomes include Cmax, tmax, ke, t1/2, and AUC of rivaroxaban (PK evaluation) and factor Xa activity (PD evaluation).

Epidemiological study of statin intolerance and risk of myopathy (EL)
Propensity score (PS) matched sequential cohort research project using the Clinical Practice Research Datalink (CPRD) to assess the risk of myopathy and the risk of unspecified statin intolerance associated with hydrophilic statin use, when compared with lipophilic statin use.

Participation to the European Drug Emergency Network (EuroDEN) (EL, IS)
Our department is part of the European Drug Emergencies Network (Euro-DEN) which collects data on acute recreational drug toxicity from 31 centres in 21 countries across Europe. This data contributes to the current knowledge of acute drug toxicity and the potential harms of novel psychoactive substances, thus helping to optimize patient treatment and preventive measures. The findings of the project are published regularly in form of descriptive studies,

case reports and subanalyses of special interest (e.g. recreational use of prescription and over the counter drugs, presentations associated with particular medical problems (e.g. psychosis) or substances (e.g. GHB)).

Original publications

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Am J Hypertens. 31 (2018), 188-196.

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6. Liakoni E, Edwards KC, St.Helen G, Nardone N, Dempsey DA, Tyndale RF, Benowitz NL: Effects of nicotine metabolic rate on withdrawal symptoms and response to cigarette smoking following abstinence. Clin Pharmacol Ther. 2018; doi: 10.1002/cpt.1238. [Epub ahead of print]

7. Liakoni E, Gugelmann H, Dempsey DA, Wiegand TJ, Havel C, Jacob P, Benowitz NL: Butanediol conversion to gamma-hydroxybutyrate markedly reduced by the alcohol dehydrogenase blocker fomepizole. Clin Pharmacol Ther. 2018; doi: 10.1002/cpt.1306. [Epub ahead of print]

8. Liakoni E, Dempsey DA, Meyers M, Myrphy NG, Fiorentino D, Havel C, Haller C, Benowitz NL: Effect of gamma-hydroxybutyrate (GHB) on driving as measured by a driving simulator. Psychopharmacology (Berl). 235 (2018), 3223-3232.

9. Liakoni E, Yates C, Dines AM, Dargan PI, Heyerdahl F, Hovda KE, Wood DM, Eyer F, Liechti ME, Euro-DEN Research Group - Corporate Authors: Anand JS, Barcelo B, Chevillard L, Galicia M, Giraudon I, Jürgens G, Kabata PM, Mégarbane B, Miró O, Moughty A, O'Connor N, O'Donohoe P, Paasma R, Pedersen CB, Persett PS, Põld K, Puiguriguer J, Rabe C, Stenzel J, Vallersnes OM, Waring WS, Yeung S: Acute recreational drug toxicity: comparison of self-reports and results of immunoassay and additional analytical methods in a multi-center European case series. Medicine (Baltimore). 97 (2018), e9784.

10. Liakoni E, Gartwyl F, Ricklin M, Exadaktylos AK, Krähenbühl S: Psychoactive substances and violent offences: A retrospective analysis of presentations to an urban emergency department in Switzerland. PloS One. 13 (2018), e0195234.

11. Leuppi-Taegtmeyer A, Duthaler U, Hammann F, Schmid Y, Dickenmann M, Amico P, Jehle AW, Kalbermatter S, Lenherr C, Meyer Zu Schwabedissen HE, **Haschke M**, Liechti ME, Krähenbühl S: Pharmacokinetics of oxycodone/naloxone and its metabolites in patients with end-stage renal disease during and between haemodialysis sessions. Nephrol Dial Transplant. (2018); doi: 10.1093/ndt/gfy285.

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14. Miró Ò, Yates C, Dines AM, Wood DM, Dargan P, Galán I, Jerez A, Puiguriguer J, Waring WS, Moughty A, O'Connor N, Heyerdahl F, Hodva KE, Vallersnes OM, Paasma R, Põld K, Jürgens G, Megarbane B, Anand JS, Liakoni E, Liechti ME, Eyer F, Zacharov S, Caganova B, Giraudon I, Galicia M: Comparación de las urgencias atendidas por drogas de abuso en dos servicios de urgencias españoles con las atendidas en tres áreas europeas distintas. EMERGENCIAS 2018, in press

15. Miró Ò, Dargan P, Wood DM, Dines AM, Yates C, Heyerdahl F, Hovda KE, Giraudon I, Euro-DEN Research Group, Galicia M: Epidemiology, clinical features and management of patients presenting to European emergency departments with acute cocaine toxicity: Comparison between powder cocaine and crack cocaine cases. Clin Toxicol 2018, in press.

16. Rickli A, Liakoni E, Hoener MC, Liechti ME: Opioid-induced inhibition of the human serotonin and norepinephrine transporters in vitro: link to clinical reports of serotonin syndrome. Br J Pharmacol. 175 (2018), 532-543.

17. Sandbaumhüter FA, **Haschke M**, Vogt B, Bohlender JM: Medication adherence during laboratory workup for primary aldosteronism: pilot study. Patient Prefer Adherence 12 (2018), 2449-2455.

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19. Sandbaumhüter FA, Vimercati S, Thormann W, Mevissen M: Role of the equine CYP3A94, CYP3A95 and CYP3A97 in ketamine metabolism in presence of medetomidine, diazepam and methadone studied by enantioselective capillary electrophoresis. Toxicol In Vitro. 50 (2018), 242-248.

20. Sandbaumhüter FA, Thormann W: Enantioselective capillary electrophoresis provides insight into the phase II metabolism of ketamine and its metabolites in vivo and in vitro. Electrophoresis 39 (2018), 1478-1481.

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23. Yamamoto T, Dargan PI, Dines A, Yates C, Heyerdahl F, Hovda KE, Giraudon I, Sedefov R, Wood DM; Euro-DEN Research Group: Chevillard L, Eyer F, Galicia M, Homar C, Jürgens G, Kabata PM, Liakoni E, Liechti ME, Markey G, Mégarbane B, Miro O, Moughty A, O' Connor N, Paasma P, Persett PS, Pold K, Puiguriguer J, Shields G, Vallersnes OM, Waring WS, Waldman W, Yeung SJ: Concurrent Use of Benzodiazepine by Heroin Users - What Are the Prevalence and the Risks Associated with This Pattern of Use? J Med Toxicol. 2018; doi: 10.1007/s13181-018-0674-4. [Epub ahead of print]

Review articles/Case reports

1. Bohlender JM, Nussberger J, Leuenberger S, **Haschke M**: Resistente Hypertonie. Swiss Med Forum. 50 (2018), 1059-1065.

2. Liakoni E, **Haschke M**: Dosisanpassung bei Niereninsuffizienz. Prim Hosp Care Allg Inn Med. 18 (2018), 122-124.

3. Liakoni E, **Haschke M**: Dosisanpassung bei Leberinsuffizienz. Prim Hosp Care Allg Inn Med. 18 (2018), 134-136.

4. Müller S, Nussbaumer S, Plitzko G, Ludwig R, Weinmann W, Krähenbühl S, Liakoni E: “Recreational use of carfentanil – a case report with laboratory confirmation”. Clin Toxicol (Phila). 56 (2018), 151-152.

5. Scholz I et al. Lithiumintoxikation: Kleines Kation, grosse Wirkung – gerade im Alter. Swiss Med Forum 18 (2018), 670-671.

Additional Publications by PKI Members

Original publications

Sebastian T, Hakki LO, **Spirk D**, Baumann FA, Périard D, Banyai M, Spescha RS, Kucher N, Engelberger RP: Rivaroxaban or vitamin-K antagonists following early endovascular thrombus removal and stent placement for acute iliofemoral deep vein thrombosis. Thromb Res. 172 (2018), 86-93.

Miserez AR, Martin FJ, **Spirk D**: DIAgnosis and Management Of familial hypercholesterolemia in a Nationwide Design (DIAMOND-FH): Prevalence in Switzerland, clinical characteristics and the diagnostic value of clinical scores. Atherosclerosis. 277 (2018), 282-288.

Spirk D, Noll S, Burnier M, Rimoldi S, Noll G, Sudano I: Effect of Home Blood Pressure Monitoring on Patient's Awareness and Goal Attainment Under Antihypertensive Therapy: The Factors Influencing Results in Anti-HypertenSive Treatment (FIRST) Study. Kidney Blood Press Res. 43 (2018), 979-86.

Sebastian T, Dopheide JF, Engelberger RP, **Spirk D**, Kucher N: Outcomes of endovascular reconstruction of the inferior vena cava with self-expanding nitinol stents. J Vasc Surg Venous and Lymphat Disord. 6 (2018), 312-20.

Blondon M, **Spirk D**, Kucher N, Aujesky D, Hayoz D, Beer JH, Husmann M, Frauchiger B, Korte W, Wuillemin WA, Bounameaux H, Righini M, Nendaz M: Comparative performance of clinical risk assessment models for hospital-acquired venous thromboembolism in medical patients. Thromb Haemost 118 (2018), 82-9.

Book chapters / Guidelines

Wahn V, **Späth P**: Antibody Therapy. Historical Aspects of Polyclonal igG Preparations. Springer Int. Publ. (2018), 121-132.

Späth PJ: Antibody Therapy. Essentials of the Production of Safe and Efficacious State-of-the-Art Polyclonal IgG Concentrates. Springer Int. Publ. (2018), 151-173.

Späth P: Antibody Therapy. Current IgG Products and Future Perspectives. Springer Int. Publ. (2018), 175-202.

The European Medicines Agency (EMA) through its bodies the Committee for Medicinal Products for Human Use (CHMP) and the Blood Product Working Party (BPWP) has adopted the drafts in form of guidelines as of 28 June 2018:
-Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)
-Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)

4.2. Congress Invitations

Prof. Hans-Uwe Simon
Gordon Research Conference, Mechanisms, prevention of, and emerging therapies for food allergy, Ventura (CA, USA); Jan. 7-12, 2018;
The role of eosinophils in eosinophilic esophagitis.

International Network of Universities for Molecular Allergology & Immunology (INUNIMAI), Vienna (A); Febr. 21-23, 2018;
Precision medicine in patients with allergic diseases.

World Immune Regulation Meeting XII, Davos (CH); March 14-17, 2018;
Neutrophil extracellular trap formation requires OPA1-regulated glycolytic ATP production.

International Union of Immunological Societies (IUIS): Advanced Course of Immunotherapy, Teheran (Iran); April 23-25, 2018;
Precision medicine in patients with allergic diseases.

14th International Congress of Immunology and Allergy (ICIA 2018), Teheran (Iran);
April 26-28, 2018;
Eosinophil extracellular traps and cytolysis.

Annual Meeting of the European Allergy and Clinical Immunology (EAACI),
Munich (Germany), May 26-30, 2018;
Pathogenesis of eosinophilic gastrointestinal disorders: At the cross road of allergy and autoimmunity.

Regional BioCamp 2018, Ljubljana (Slovenia), May 27-29, 2018;
Mitochondrial DNA in antibacterial defense.

67th Annual Meeting of the Japanese Society of Allergology, Chiba (Japan), June 22-24, 2018;
Eosinophils in allergic diseases: cytolysis, DNA traps and beyond.

Workshop on “Cell Death and Disease”, Villa Vigoni, Loveno di Menaggio, Como (I);
June 27-30, 2018;
A critical role for OPA1 in NET formation.

5th European Congress of Immunology, Amsterdam (NL), Sept. 2-5, 2018;
Extracellular DNA traps: Neutrophils, eosinophils, basophils.

32nd Symposium of the Collegium Internationale Allergologicum, Mallorca (Spain),
Sept. 30 – Oct. 5, 2018;
Neutrophil extracellular trap formation requires OPA1-regulated glycolytic ATP production.

10th Dermatological Meeting in Ticino: From the bench to the clinic,
Bellinzona (CH); Nov. 29, 2018;
PI3K inhibition and biochemical re-programming of dermal stem cells.

Prof. Thomas Kaufmann
LS2 (Life Science Switzerland) Annual Meeting 2018, Metabolism & Signaling in the Life Sciences, Lausanne (CH), Feb 12 – 13 2018;
A new player in the field: apoptosis regulation by the BCL-2 family member BOK.

11th European Work Shop on Cell Death (EWCD), May 6-11 2018, Fiuggi (IT);
Role of BOK in cancer.

Prof. Stephan von Gunten
Immunotherapy (IT) 2018 Congress, Havana (CU), Oct 29-Nov 2, 2018;
Tumor surface glycosylation: biological implications and opportunities.

Research conference, Biomedical Research Center (BMFZ), University of Marburg, Marburg (G), September 24, 2018;
Novel opportunities for inflammatory disorders and cancer offered by glycoimmunology.

Colloquium in pharmacology, Paracelsus Medical University (PMU), Salzburg, Austria, June 21, 2018;
Sweet but powerful - the impact of carbohydrate metabolism on the immunotherapy of inflammation and cancer.

Prof. Shida Yousefi
RIA Immunology Lunch Meeting, Bern (CH), October 3, 2018;
Mitochondrial DNA traps as antibacterial defense mechanism.

MIC training course, Bern (CH); Jan. 15, 2018: Imaris, basic and advanced.

Prof. Georgia Konstantinidou
Research conference, Biomedical Research Center (BMFZ), University of Marburg, Marburg (G), September 24, 2018;
Role of lipid metabolism in pancreatic cancer progression.

Dr. Yuniel Fernandez Marrero
Annual Meeting 2018 of the Swiss Society for Pharmacology and Toxicology, Bern (CH), April 21, 2018;
Negative regulation of BOK expression by recruitment of TRIM28 to U-rich elemnts in its 3' untranslated region.

Dr. He Liu
Annual Meeting 2018 of the Swiss Society for Pharmacology and Toxicology, Bern (CH), April 21, 2018;
ATG12 deficiency leads to tumor cell oncosis due to diminished mitochondrial biogenesis and reduced cellular bioenergetics.

Nina Germic
Annual Meeting 2018 of the Swiss Society for Pharmacology and Toxicology, Bern (CH), April 21, 2018;
ATG5 regulates eosinophil hematopoiesis.

Kim Klapan
The 7th European MD/Pharma-PhD Conference, Paris (F), June 29 – July 1, 2018;
The role of the p73-ATG5 axis in regulating autophagy in atopic dermatitis and psoriasis.

Matteo Rossi
Annual Meeting 2018 of the Swiss Society for Pharmacology and Toxicology, Bern (CH), April 21, 2018;
ACSL3 inhibition renders pancreatic tumors responsive to therapy.

Bisera Stepanovska
MS (Multiple sclerosis) Researcher Meeting, Luzern (CH), Jan 26, 2018;
A novel oxazolo-oxazole compound ST-1505 and its ring-opened analog ST-1478 differentially activate S1P receptor subtypes and act protective in experimental autoimmune encephalomyelitis in mice.

Annual Meeting 2018 of the Swiss Society of Pharmacology and Toxicology, Bern (CH), April 21, 2018;
Validation of novel fingolimod derivatives for EAE therapy.

BIOACTIVE LIPIDS Conference 2018, Athens (Greece), March 29 – 31, 2018;
A novel oxazolo-oxazole compound ST-1505 and its ring-opened analog ST-1478 differentially activate S1P receptor subtypes and act protective in experimental autoimmune encephalomyelitis in mice.

4.3. Seminar Invitations

Prof. Hans-Uwe Simon
National Institutes of Health (NIH), Bethesda (MD, USA); Jan 10, 2018;
guest of Dr. Amy Klion:
Eosinophils and neutrophils in disease: extracellular DNA trap formation and cytolysis.

Klinik für Klinische Immunologie, Universitätsspital Zürich, Zürich (CH); March 3, 2018;
guest of Prof. Onur Boyman:
The multifunctional role of eosinophils in inflammatory responses.

Klinik für Rheumatologie, Allergologie und Immunologie, Universitätsspital Bern, Inselspital, Bern (CH); March 14, 2018; guest of Prof. Martin Bachmann:
The mechanism of eosinophil cytolysis.

Akademie für Pneumologen, Eosinophile: «Morgenröte der Genesung» oder irregeleitete Entzündungszellen? Stuttgart (D); June 6, 2018; guest of Dr. Rainer Ehmann:
Eosinophile im Fokus: Braucht man sie, und wenn ja wieviele? Wann und warum können sie schaden?

Klinik für Innere Medizin I – Medizinische Universität Wien, Ludwig Boltzmann Cluster Oncology and SFB F47-B20, Wien (A); July 6, 2018; guest of Prof. Peter Valent:
Role of eosinophils in HES and related conditions: Update 2018.

Prof. Stephan von Gunten
Radbout University Medical Center, Nijmengen (NL), Jan 24, 2018; guest of Prof. Thomas Boltje:
Glycoimmunology – novel insights into immunodeficiency, autoimmune disease and cancer.

Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (USA), March 27, 2018; guest of Prof. Richard D. Cummings:
Novel insights on humoral and cellular glycoimmunology.

Palleon Pharmaceuticals Inc., Waltham MA (USA), March 27, 2018:
Understanding glycoimmunology – novel opportunities for cancer immunotherapy.

Palleon Pharmaceuticals Inc., Waltham MA (USA), March 26, 2018:
Sialoglycans and Siglecs in immune escape.

Seminar, Johns Hopkins Asthma & Allergy Center, The Johns Hopkins University, Baltimore MD (USA), April 4, 2018; guest of Prof. Marian Kollarik:
Novel insights on the human carbohydrate-specific IgG repertoire in health and disease.

Biomedical Research Center (BMFZ), University of Marburg, Marburg (G), June 11, 2018; guest of Prof. Magdalena Huber:
Novel opportunities for inflammatory disorders and cancer offered by glycoimmunology.

Prof. Georgia Konstantinidou
7th Faculty & Staff Retreat of the Swiss Cancer Center Lausanne (EPFL), Lausanne (CH), November 6, 2018:
Regulation of lipid metabolism in lung adenocarcinomas.

Dr. He Liu
Departement of Pulmonary Medicine, University Hospital Bern, Bern (CH), Feb 13, 2018; guest of Stem cell lunch seminar:
Differentiation of human dermal stem cells to neurons by altering stem cell metabolism.

PD Dr. Peter Späth
23. Tagung der Deutschen Gesellschaft für Angioödeme, Hautklinik Mainz, Mainz (DE), Nov 21, 2018:
Immunologische und genetische Parameter in der Diagnostik des HAE.

4.4. Organization of Meetings and Courses

Prof. Hans-Uwe Simon
Symposium of the Swiss Society of Pharmacology and Toxicology (together with task force SSPT): Progress in Pharmacology - Barrieredefekte der Haut und Schleimhäute;
Bern (CH), Jan. 24, 2018

Workshop on “Cell Death and Disease” (together with C. Brancolini, K.-M. Debatin and P.H. Krammer), Villa Vigoni, Loveno di Menaggio, Como (I), June 27-30, 2018

17th III-Bern International Summer School,
Bönigen (CH), July 29-31, 2018

Prof. Thomas Kaufmann
Co-organizer 10th Swiss Apoptosis Meeting, Bern (CH), Sep 12-14, 2018

Prof. Stephan von Gunten
Annual Meeting 2018 of the Swiss Society for Pharmacology and Toxicology (together with task force SSPT), Bern (CH), April 21, 2018

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon

Symposium of the Swiss Society of Pharmacology and Toxicology:
Progress in Pharmacology – Barrieredefekte der Haut und Schleimhäute, Morning session;
Bern (CH), Jan 24, 2018

World Immune Regulation Meeting XII; Session: Regulation of innate immunity;
Davos (CH), March 14-17, 2018.

Spring Meeting of the Swiss Society of Pharmacology and Toxicology (SSPT);
Session III; Bern (CH), April 19, 2018.

14th International Congress of Immunology and Allergy (ICIA 2018);
Morning session of April 27, 2018; Teheran (Iran), April 26-28, 2018.

Workshop on “Cell Death and Disease”; Session 2;
Villa Vigoni, Loveno di Menaggio, Como (I), June 27-30, 2018.

5th European Congress of Immunology; Guided poster session: Innate control
of inflammation and repair (P.C6.03); Amsterdam (NL), Sept. 2-5, 2018.

10th Swiss Apoptosis Meeting; Session II: Autophagy; Bern (CH), Sept. 12-14, 2018.

26th Conference of the European Cell Death Organisation (ECDO) - Cell Death in Disease:
From Small Molecules to Translational Medicine; Session IV: Never say never again:
cell death and cancer therapy; St. Petersburg (RU), Oct. 10-12, 2018.

Prof. Thomas Kaufmann

11th European Work Shop on Cell Death (EWCD), oral presentation, ‘Game changing science, session II’; Fiuggi (IT), May 6-11, 2018.

Prof. Stephan von Gunten
Immunotherapy (IT) 2018 Congress, Havana (CU), Oct 29-Nov 2, 2018.

Annual Meeting 2018 of the Swiss Society for Pharmacology and Toxicology, Bern (CH),
April 21, 2018.

4.6. Referee Work for Peer-Reviewed Journals

Dr. Zhaoyue He

Allergy
Cell Death Differ.
Cell Death Dis.

Prof. Andrea Huwiler

Biochem. Pharmacol.
Biochim. Biophys. Acta
Br. J. Pharmacol.
Cellular signaling
Frontiers in Pharmacology
Hormone Metabol. Res.
J. Cell. Biochem.
J. Exp. Pharmacol. Ther.

Cell. Physiol. Biochem
Clin. Chem. Lab. Med.
Diabetologica
Eur. J. Pharmacol.
Kidney and Blood Pressure Research
Kidney Int.
Naunyn Schmiedeb. Arch. Pharmacol.

Prof. Thomas Kaufmann

Acta Tropica
Advances in Medicine
Apoptosis
Allergy
BioEssays
Cell Communication and Signaling
Cell Death Differ.
Cell Death Dis.
Cellular & Molecular Immunology
Eur. J. Immunol.
FEBS Letter
FEBS Journal
Frontiers in Molecular and Cellular Oncology
Future Oncology
Hepatology
Immunology and Cell Biology
International Archives of Allergy and Immunologie
International Review of Cell and Molecular Biology
J. Hepatology
J. Molecular Cell Biology
J. Neuroscience
Methods
Molecular Cancer Therapeutics
Mol. Cell. Oncology
Oncogene
PLoS One
Scientific Reports
Trends in Cell Biology

Prof. Georgia Konstantinidou

Cell Death Dis.

Dr. He Liu

Allergy
Cell Death Dis.
Cell Death Differ.
Frontiers in Oncology

Prof. Hans-Uwe Simon

Allergy
Apoptosis
Autophagy
Blood
J. Cell Cycle
EMBO Reports
Eur. J. Immunol.
Cell Death Differ.
Cell Death Dis.
Gut
J. Allergy Clin. Immunol.
J. Exp. Med.
J. Immunol.
J. Leukoc. Biol.
Frontiers Oncology
Mol. Cell. Oncology
N. Engl. J. Med.
Cell Reports

PD Dr. Peter Späth

Clin. Exp. Allergy
Immunotherapy

Prof. Stephan von Gunten

ACS Chemical Biology
ACS Omega
Allergy
Am. J. Respir. Cell Mol. Biol.
Ann. Sports Med. Res.
Arthritis Res. Ther.
Blood
BMC Biotech.
Immunol. Cell Biol.
Immunol. Lett.
Int Arch Allergy Immunol
Int. Immunopharm.
J. Allergy Clin. Immunol.
J. Clin. Invest.
J. Immunol.
J. Immunotox.

Cell Death Differ.
Cell Death Dis.
Comput Biol Chem
Curr. Med. Chem.
Frontiers Oncology
Frontiers Pediatrics
Gene Therapy
Glycoconj J
Glycobiol.
Med. Inflamm.
Respiration
Oncotarget
Pathobiology
PLoS Pathogens
PLoS One
Respi. Res.
Tuberculosis
Tumor biology

Prof. Shida Yousefi
Cell Biol. Int.
Cell Biochem. Biophys.
Cell Death Differ.
Cell Death Dis.
Frontiers of Immunology
Eur. J. Immunol.
Exp. Lung Res.
Int. J. Mol. Sci.
Immunology
J. Vasc. Intervent. Radiol.
Respir. Res.
Scientific Reports
Int. J. Biochem. Cell Biol.
Thorax

Prof. Uwe Zangemeister-Wittke
Bioconjug. Chem.
J. Cell Physiol.
J. Control. Release
Expert Opin. Drug Delivery
Mol. Cell. Biol.
Proteins
J. Exp. Pharmacol. Ther.

Prof. Manuel Haschke
Analytical Chemistry
Bioanalysis
Clinical Pharmacokinetics
Eur J Clin Pharmacol
Rapid Comm Mass Spec
Swiss Med Forum
Swiss Medical Weekly
Xenobiotica

PD Dr. Jürgen Bohlender
J Am Soc Hypertens
Ther Clin Risk Manag
J Hypertens
Swiss Med Forum

Dr. Evangelia Liakoni
Ann Intern Med
Case Rep Emerg Med
J Anal Toxicol

4.7. Referee Work for Grant Bodies

Dr. Zhaoyue He
Swiss Cancer League

Prof. Andrea Huwiler
Deutsche Forschungsgemeinschaft (DFG)
Swiss National Science Foundadtion (SNF)

Prof. Thomas Kaufmann
Agence Nationale de la Recherche (ANR)
Austrian Science Fund (FWF)
National Science Centre Poland
Swiss Cancer League

German Research Foundation (DFG)
Swiss National Science Foundation (SNF)
L'Oréal Österreich

Dr. He Liu
Swiss Cancer League

Prof. Hans-Uwe Simon
Swiss National Science Foundation (SNF)
Swiss Cancer League
Italian Association for Cancer Res.
Novartis Foundation

Prof. Stephan von Gunten
Canadian Glycomics Network
Dutch Cancer Society (DCS)
Best Cancer Now

Prof. Uwe Zangemeister-Wittke
Swiss National Science Foundation
La Caixa Foundation, Barcelona
Swiss Cancer League
Qatar National Research Fund (QNRF)

4.8. Awards

Quentin Haas

Poster Price at the Immunotherapy Meeting 2018 in La Havana, Cuba
Immunotherapy Meeting, La Havana (Cuba), October 29 – November 2, 2018

Darko Stojkov

Prize «Best paper 2017»
Bern Immunology Club (BIC), Bern (CH), June 27, 2018

Quentin Haas

Prize of the best poster, Swiss Society of Experimental Pharmacology (SSEP)
LS2 meeting (Life Science Switzerland), Lausanne (CH), February 12-13, 2018

Quentin Haas

Novartis Institutes for Biomedical Research Prize for the best oral presentation
SSPT Spring Meeting, Bern (CH), April 19, 2018

PD Dr. Jürgen Bohlender

Servier-Research Award 2018. Swiss Society of Hypertension (SHG)

Best Poster Award of the 27th Scientific Meeting of the International Society of Hypertension (ISH)
27th Scientific Meeting of the International Society of Hypertension (ISH);
Peking (China), Sept. 20-23, 2018

5. Administrative, Advisory, and Honorary Posts

Dr. Zhaoyue He
Coordinator for PC work at the PKI
Webmaster at the PKI

Prof. Andrea Huwiler
President of the Ernennungs- und Habilitationskommission (EHK), Medical Faculty, University of Bern

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

Member of the Editorial Board of Cellular and Molecular Neurobiology

Member of the Editorial Board of Experimental Pharmacology and Drug Discovery, Frontiers in Pharmacology

Prof. Thomas Kaufmann
Member of the Supervision commission "Cell Biology" within the Graduate School for Cellular and Biomedical Sciences of the University of Bern, since 2009

Member of the Editorial Board, Cell Death and Disease
Member of the Editorial Board, Frontiers in Molecular and Cellular Oncology

Member of the World Allergy Organization (WAO) Special Committee on Eosinophils, Mast Cells & Basophils

Coordinator for FACS, Fluorescence Microscope, and Chemicals at the PKI

Coordinator FPLC (Äkta)

Prof. Georgia Konstantinidou
Member of the Supervision commission "Cell Biology" within the Graduate School for Cellular and Biomedical Sciences of the University of Bern.

Member of the doctorate course of Molecular Medicine (role: lecturer from foreign University) at the University of Ferrara, Italy.

Prof. Hans-Uwe Simon
Dean, Medical Faculty, University of Bern

President, Collegium of the Deans of the Swiss Faculties of Medicine

Vorstandsmitglied, Universitäre Medizin Schweiz

Mitglied der Geschäftsleitung, Insel Gruppe AG

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

Member of the Swiss Academy of Medical Sciences (SAMW)

President of the Novartis Foundation for Biomedical Research

Swiss-EU mobility program, Coordinator Pharmacology/Pharmacy, University of Bern

Editor-in-Chief, Cell Death & Disease

Editor-in-Chief, International Archives of Allergy and Immunology

Visiting-Professor, Medical University of Moscow – Department of Clinical Immunology and Allergology, Sechenov University, Moscow (Russia)

PD Dr. Peter Späth
Member of the Kreuth Immunoglobulin Working Group 'European Consensus Proposal for Immunoglobulin Therapies'; member of the expert group drafting an update of the 'core Summary of Product Characteristics' for human immunoglobulin preparations

Member of German speaking experts on Hereditary Angioedma in the Pedatric Population

Prof. Stephan von Gunten
President of the Swiss Society of Experimental Pharmacology (SSEP)

Board Member of the Swiss Society of Pharmacology and Toxicology (SSPT)

Participating Investigator of the US National Institutes of Health (NIH)-funded "Consortium for Functional Glycomics" (CFG; www. functionalglycomics.org)

Editor of "Literature Highlights", Immunopharmacology Section, International Union of Basic and Clinical Pharmacology (IUPHAR)

Editorial Board Member of "Allergy", European Journal of Allergy and Clinical Immunology

Topic Editor, Frontiers Oncology

Coordinator library at the PKI

Prof. Shida Yousefi
Coordinator for Radioactive Work, Confocal Microscopy and Imaging Analysis at the PKI

Prof. Uwe Zangemeister-Wittke
Consultant of the Human SwissMedic Expert Committee

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

Review Editor, Frontiers in Molecular and Cellular Oncology

Prof. Manuel Haschke
Head, Drug and Therapeutics Committee, Inselgruppe Bern

PD Jürgen Bohlender
Expert Member, Advisory Board Repatha® (Evolocumab) and Swiss Lipid Academy (28. Juni 2018), Amgen Corp.

Member, Inselspital Commission on Drug Safety (Hospital Pharmacy)

Member, Critical Incident Reporting System (CIRS) Commission, University Hospital of General Internal Medicine

Expert consultant European Society of Hypertension, 29th European Meeting on Hypertension and Cardiovascular Protection, Milan (Italy), June 21- 24, 2019

Dr. Evangelia Liakoni
Board member of the Swiss Society of Clinical Pharmacology and Toxicology (SSCPT)

Board member of the Working Group Medication and Patient Safety, Inselspital, University Hospital

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

6. Services

6.1. Confocal Microscopy

The facility hosts three laser scanning microscopes (LSM 5 Exciter, LSM 510 and LSM 700, Carl Zeiss Microimaging GmbH, Jena), which may be used by members of the Medical Faculty at a small charge (CHF 50 per h). The facility for confocal microscopy and image analysis in our institute is part of the Microscopy Imaging Center (MIC) of the University of Bern and operated by Prof. S. Yousefi.

6.2. Flow Cytometry

The Institute of Pharmacology is equipped with Becton-Dickinson FACSCalibur (4 color), and FACSVerse 8 color Flow Cytometer instruments and FACSLyric able to detect up to 12 colors. 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

Art Exhibition

Evelyne Kozlowski

Vernissage: Aug 30, 2018
Welcome: Prof. H.-U. Simon / Prof. M. Fiedler
Duration of the exhibition: Aug 30 – Sep 30, 2018

More information:

http://www.pki.unibe.ch/ueber_uns/aktivitaeten/vernissages/index_ger.html

8. Sponsors

8.1. Research Grants

Prof. Andrea Huwiler
Swiss National Science Foundation (grant No. 310030-153346/1)

Prof. Thomas Kaufmann
Swiss National Science Foundation, project grant No 31003A_173006
Novartis Foundation for Biological-Medical Research, Novartis, Basel (CH)

Prof. Georgia Konstantinidou
Swiss National Science Foundation, SNF-Professorship (grant No. PP00P3_163929)
Novartis Foundation for Biological-Medical Research, Novartis, Basel (CH)

Prof. Hans-Uwe Simon
Swiss National Science Foundation (grant No. 310030-166473)
Swiss Cancer League (KFS-3703-08-2015)
Novartis Foundation for Biological-Medical Research, Novartis, Basel (CH)
HORIZON 2020, Marie Sklodowska-Curie Actions, MEL-PLEX

Prof. Stephan von Gunten
Swiss National Science Foundation (SNSF) Grant Nr. 310030_162552
Swiss Cancer League (KFS-3941-08-2016)
Palleon Pharmaceuticals Inc., Waltham MA (USA)
Mizutani Foundation for Glycoscience (Japan)

Prof. Shida Yousefi
Swiss National Science Foundation (grant No. 310030-173215)

Prof. Uwe Zangemeister-Wittke
Swiss National Science Foundation (grant No. 31003A-170134)
Sassella-Stiftung of the Zürcher Kantonalbank

Prof. Manuel Haschke
Swiss National Science Foundation (31003A_160206 / 32003B_179346)

8.2. Meetings

Swiss Society of Pharmacology and Toxicology (SSPT): Progress in Pharmacology – Treatment of Skin Diseases, Bern, Jan 24, 2018

A. Menarini AG, Zürich
Alcina AG, Muttenz
Sanofi-Aventis AG, Vernier
Sanofi-Gezyme AG, Vernier
Novartis Pharma Schweiz AG, Rotkreuz
GlaxoSmithKline AG, Münchenbuchsee
Eli Lilly, Vernier
La Roche-Posay, Cosmetique Avtive SA, Vernier
Almirall AG, Wallisellen
Galderma Schweiz AG, Egerkingen
MEDA Pharma GmbH, Wangen ZH
Merz Pharma GmbH, Allschwil
Celgene GmbH, Zürich
Pierre Fabre Dermo-Cosmétique, Allschwil
Ultrasun AG, Zürich
Swiss Industry Science Fund (SISF), Basel

17th III-Bern International Summer School
Seehotel La Terrasse, CH 3806 - Bönigen, July 29 – 31, 2018

AstraZeneca AG, Zug
Carl Zeiss AG, Feldbach
BD Biosciences, Allschwil
Grogg Chemie AG, Stettlen-Deisswil
Mycrosynth AG, Balgach
PerkinElmer, Rodgau (DE)
Pfizer AG, Zürich
Zentrum für Labormedizin, Inselspital Bern
Graduate School for Cellular and Biomedical Sciences, Universität Bern

8.3. Seminar Series

„Current topics in Pharmacology and Theranostics“ (organized together with the Center of Laboratory Medicine and Division of Clinical Pharmacology, University Hospital Bern, Inselspital)

Astellas Pharma AG, Wallisellen
Pfizer AG, Zürich

8.4. Travel Support

Nikita Markov
European Cell Death Organisation (ECDO)
(ECDO conference 2018, St. Petersburg (Russia), October 10-12, 2018)

Quentin Haas
The Graduate School for Cellular and Biomedical Sciences (GCB) of the University of Bern
(Immunotherapy Meeting 2018, La Havana (Cuba), October 29 – November 2, 2018)

Swiss Society of Pharmacology and Toxicology (SSPT)
(San Diego Glycobiology Symposium 2018, San Diego, CA (USA), March 8 -10, 2018)

Kim Klapan
The Graduate School for Cellular and Biomedical Sciences (GCB) of the University of Bern
(7th European MD/PhD conference, Paris (France), June 29 - July 01, 2018)

Stefanie Graeter
The Graduate School for Cellular and Biomedical Sciences (GCB) of the University of Bern
(Neutrophil conference 2018, Québec (Canada) from June 02-05, 2018)

Swiss Society of Experimental Pharmacology (SSEP)
(Neutrophil conference 2018, Québec (Canada) from June 02-05, 2018)

Boehringer Ingelheim Foundation
(Research Internship (2 months) under the supervision of Prof. Jane C. Burns at the Kawasaki Disease Research Center at University of California, San Diego (UCSD) from March 1 – April 30, 2018)

Samara Naim
Swiss Society of Pharmacology and Toxicology (SSPT)
(11th European Work Shop on Cell Death (EWCD), Fiuggi (IT), May 6-11, 2018)

Bisera Stepanovska
Swiss Society of Pharmacology and Toxicology (SSPT)
(Bioactive Lipids Conference, Athens, (Greece), January 5, 2018)

8.5. Other Support

Bürgi Fonds Seminar series of the institute