Annual Report 2021

Institut für Pharmakologie (PKI)
der Universität Bern

Institute of Pharmacology
University of Bern

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1. Introduction

1.1. Vorwort

Dies ist der einundzwanzigste umfassende Jahresbericht des Instituts für Pharmakologie (PKI) der Universität Bern. Infolge der Corona-Pandemie hatten wir auch im Jahr 2021 neue Herausforderungen anzunehmen. Die Arbeiten im Institut erfolgten mit Hilfe eines Schutzkonzepts, welches wir erfolgreich umsetzen. So konnte die Verzögerung in den Forschungsprojekten in den meisten Fällen maximal reduziert werden. Lehre und ein Grossteil unserer Kommunikation erfolgte mit digitalen Mitteln. Wissenschaftliche Meetings waren nur teilweise möglich. Trotz dieser Umstände können wir mitteilen, dass das PKI auch im Jahr 2021 seine Aufgaben in Lehre und Forschung innerhalb der Medizinischen Fakultät vorbildlich erfüllt hat.

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 weiterzuentwickeln. 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. Das PKI bietet ein breites Spektrum an Labormethoden an und kann Erfahrungen von der *biologischen Grundlagen-* bis zur *klinischen Forschung*, beides Kernaufgaben der Pharmakologie, in neue Forschungsprojekte einbringen.

Neben unserer regulären Lehrtätigkeit im 3. und 6. Studienjahr Medizin sowie der Ausbildung der Zahnmediziner*innen sind einige Dozent*innen des Instituts zusätzlich in die Immunologieausbildung von Student*innen der Biologie (Naturwissenschaftliche Fakultät der Universität Bern) einbezogen. Weiterhin sind wir auch für die Pharmakologieausbildung in B.Sc.- und M.Sc.-Kursen für Biomedizin der Universität Bern verantwortlich. Ebenso führen wir seit September 2019 die Pharmakologieausbildung im 3. Studienjahr Pharmazie an unserer Universität, die seit 3 Jahren ein Vollstudium für Pharmazie anbietet, durch. Die Dozent*innen 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 zusätzliche Bildungsangebote in Form von Seminaren (Current Topics in Pharmacology and Theranostics; gemeinsam organisiert mit dem Zentrum für Labormedizin) und einer Summer School, die durch Prof. Simon organisiert wird. Diese Bildungsangebote werden weitgehend aus eigenen finanziellen Mitteln und Sponsorengeldern bestritten. Im Institut arbeiten gegenwärtig 23 Doktorand*innen, und 4 Doktorand*innen (PhD) haben im Berichtsjahr ihre Arbeiten erfolgreich abgeschlossen.

Die Mitarbeiter*innen des PKI (ohne Klinische Pharmakologie) publizierten im Jahr 2021 insgesamt 35 Originalarbeiten sowie 21 Übersichtsartikel in internationalen Fachzeitschriften (Summe der „impact factors“ >250). Mitarbeiter*innen des Instituts wurden trotz vieler Kongressabsagen zu insgesamt 20 Vorträgen bzw. Seminaren eingeladen. Mehrere Mitarbeiter*innen des PKI wurden mit Forschungspreisen ausgezeichnet. Gegenwärtig werden 8 Mitarbeiter*innen (ohne Klinische Pharmakologie) mit namhaften Beiträgen des Schweizerischen Nationalfonds unterstützt. Prof. Simon startete im Januar 2021 ein sogenanntes Mega-Grant - Projekt der Russischen Regierung in Kazan (Russland). Weiterhin ist unser Institut mit einem Projekt von Herrn Prof. von Gunten im interfakultären Berner Zentrum für Präzisionsmedizin vertreten. Prof. Kaufmann hat gemeinsam mit Prof. Tschan (Institut für Pathologie, Universität Bern) und Prof. Brunner (Lehrstuhl Biochemische Pharmakologie, Universität Konstanz, Deutschland) das „11th Swiss Apoptosis and Autophagy Meeting (SA^{2}M)“ (9.-10.9.2021) durchgeführt, welches, aufgrund der Corona-Lage, als Hybridveranstaltung mit 140 Teilnehmer*innen (davon 100 vor Ort) aus dem In- und Ausland ein grosser Erfolg war. Diese Aufzählung belegt den hohen Stellenwert, den die Forschung in unserem Institut besitzt.

Prof. Simon amtet seit Herbst 2021 als Präsident der Medizinischen Hochschule Brandenburg in Deutschland. Das Institut wird deshalb seit 1.10.2021 von Frau Prof. Huwiler geführt. Prof. Simon bleibt dem Institut erhalten und führt weiterhin seine Forschungsgruppe. Wir danken allen Mitarbeiterinnen und Mitarbeitern für ihren Einsatz, welcher auch im Jahr 2021 zu einer Bilanz beitrug, die internationalen Massstäben gerecht wird. Ebenso danken wir allen Sponsoren und Freunden des Instituts.

Prof. Dr. med. Dr. h.c. mult. Hans-Uwe Simon

Prof. Dr. Andrea Huwiler

Bern, Januar 2022

1.2. Foreword

This is the 21st comprehensive annual report of the Institute of Pharmacology (PKI) of the University of Bern. Owing to the Corona pandemic, we had to manage furthermore many challenges. We worked according to a safety concept, which we successfully implemented in our institute. This way, the delay of progress in our research project could be very much limited. Teaching and a large part of our communication was done by digital tools. Scientific meetings were often impossible to organize and cancelled. In spite of these circumstances, we fulfilled our tasks in teaching and research within the Faculty of Medicine 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”. The PKI 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. We offer a broad spectrum of laboratory methods and have experiences in both *clinical research* and *basic biological science*. 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. In September 2019, we also started 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, 23 PhD students work at the PKI, and in 2021, four PhD student successfully completed their 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 Laboratory Medicine) and the

Summer School (organized by Prof. Simon). Significantly, these additional events were financed exclusively by external sponsors.

Research is our other main activity. In 2021, staff members of the PKI (without Clinical Pharmacology) published 35 original and 21 review articles in international peer-reviewed journals (the sum of the “impact factors” is above 250). Despite of the cancellation of many congresses, co-workers of the institute were invited to present 20 lectures or seminars. Several PKI members received research prizes. The research projects of 8 co-workers (without Clinical Pharmacology) are currently supported by grants from the Swiss National Science Foundation. In January 2021, Prof. Simon started to work within a so-called “mega-grant” project from the Russian government. With a project of Prof. von Gunten, we are also integrated in the Interfaculty Center for Precision Medicine of the University of Bern. Prof. Kaufmann, together with Prof. Tschan (Institute of Pathology, University of Bern) and Prof. Brunner (Department of Biochemical Pharmacology, Univ. of Constance, Germany), have organized an international congress (11th Swiss Apoptosis and Autophagy Meeting; September 9-10, 2021), which, due to the Corona situation, was held as hybrid event. It was attended by 140 national and international scientists (100 on site) and overall a great success. In summary, we carry out research of a high standard which plays a very important role at the PKI.

Prof. Simon was appointed in fall 2021 as President of the Brandenburg Medical School in Germany. Therefore, Prof. Huwiler serves as director of the PKI since October 1, 2021. Prof. Simon continues to work as principal investigator and deputy director in the Institute. We thank all co-workers of the institute for their hard work. These efforts have contributed in an important way to the success of the PKI in 2021. We are grateful to all the sponsors and friends of the institute for their support.

Prof. Hans-Uwe Simon, MD, PhD, Dr. h.c. mult. Prof. Andrea Huwiler, PhD

Bern, January 2022

2. Staff 2021

Director

Prof. Dr.	Simon, Hans-Uwe	MD, PhD, Dr. h.c. mult. (until Sept. 30, 2021)
Prof. Dr.	Huwiler, Andrea	PhD (ad interim since Oct. 1, 2021)

Deputy Director

Prof. Dr.	Huwiler, Andrea	PhD (until Sept. 30, 2021)
Prof. Dr.	Simon, Hans-Uwe	MD, PhD, Dr. h.c. mult. (since Oct. 1, 2021)

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 (until July 31, 2021)
PD Dr.	Späth, Peter	PhD*

Scientific Staff

	Aregger, Raphael Valentin	Bachelor student* (until July 2021)
	Arnold, Janine	Bachelor student*
	Bachmann, Daniel	Lab Technican
Dr.	Boros-Majewska, Joanna	Lab Technican (since Sept 2021)
	Chanwangpong, Apinya	M.Sc. pharm. student*
	Chen, Yihe	PhD student*
	Christen, Mira	Lab Technican*
	Claus, Mike	Lab Technican (until Aug 2021)
Dr.	Erhardt, Martin	PhD student (until Aug 2021)
	Falco, Simone	PhD student*
	Fettrelet, Timothée	PhD student* (since Oct 2021)
Dr.	Frangez, Ziva	Postdoctoral fellow* (until Feb 2021)
	Furer, Alexander	Technical Specialist*
Dr.	Germic, Nina	Postdoctoral fellow (until Feb 2021)
	Gigon, Lea	PhD student
	Hafizi, Redona	PhD student
Dr.	He, Zhaoyue	Postdoctoral fellow*
	Hevia Hernandez, Giselle	PhD student*
	Hosseini, Aref	PhD student
	Hugonnet Marjolaine, Claire	PhD student
Dr.	Imeri, Faik	Postdoctoral fellow* (until August 2021)
	Jazaeri, Ali	PhD student* (since Sept 2021)
	JeanRichard, Philippe	PhD student* (since Dec 2021)
	Kishavarz, Fatemeh	M.Sc. pharm. student* (until May 2021)
Dr.	Klapan, Kim	PhD student* (until June 2021)
	Kozlowski, Evelyne	Lab Technician
	Lakomy, Rebecca	M.Sc. pharm. student* (since August 2021)
	Lavrencic, Marusa	M.Sc. pharm. student* (Feb-August 2021)
	Leroux, Cédric	PhD student
	Markov, Nikita	PhD student

	Motta, Fabricio	M.Sc. student* (until July 2021)
	Mulaki, Jehona	M.Sc. student* (until Jan 2021)
	Mürner, Lukas	PhD student*
Dr.	Naim, Samara	PhD student* and Postdoc. Fellow* (Sept. 2021)
	Nasser, Riim	Lab Technician
	Nikdima Ioanna	PhD student* (since June 2021)
	Oberson, Kevin	Lab Technician
	Paschoud, Thierry	M.Sc. student* (until Feb 2021)
	Peng, Shuang	PhD student*
	Pozzato, Chiara	PhD student*
	Pulfer, Livia	M.Sc.pharm. student* (until July 2021)
Dr.	Saliakoura, Maria	Postdoctoral fellow*
	Singh, Pushpita	PhD student* (since Oct 2020)
Dr.	Stepanovska Tanturovska Bisera	Postdoctoral fellow
Dr.	Thapa, Asmita	Postdoctoral fellow (until Feb 2021)
	Toledo, Darien	PhD student
	Verschoor, Daniëlle	PhD student
	von Gunten, Aldona	Technical Specialist*
	Weiss, Fabian	PhD student*
	Wyss, Jacqueline	M.Sc. student* (until March 2021)
	Zahiroddini, Peymaneh	M.Sc. student* (until March 2021)

Principal Investigator – Clinical Pharmacology

Prof. Dr.	Haschke, Manuel	MD

Scientific Staff – Clinical Pharmacology

PD Dr.	Liakoni, Evangelia	MD
PD Dr.	Hammann, Felix	MD, PhD
Dr.	van der Velpen, Vera	PhD
Dr.	Rouholahnejad, Fereshteh	PhD
Dr.	Verena Schöning	PhD
	Charlotte Kern	PhD student

External University Teachers

Dr.	Bürgi, Sibylle	PhD*
PD Dr.	Cachelin, Armand	MD, PhD*
Prof. Dr.	Mlinarič-Raščan, Irena	PhD* (Adjunct Prof., Univ. of Ljubljana, Slovenia)
Prof. Dr.	Levi-Schaffer, Francesca	PhD* (Adjunct Prof., Hebrew Univ. Jerusalem, Israel)
Prof. Dr.	Shi, Yufang	PhD* (Adjunct Prof., Shanghai Jiaotong, PR China)

Guest Scientists

Prof. Dr.	Simon, Dagmar	MD*, Dept. Dermatology, Inselspital, Univ. Bern
Dr.	Schwalm, Stephanie	PhD*, Dept. of Pharmacology, Univ. Frankfurt
Prof. Dr.	Spirk, David	MD*, Sanofi-Aventis AG
Dr.	Stojkov, Darko	PhD*, University of Tübingen, Germany

Office	Scherrer, Debora	Secretary, 80% (since Nov 2021 10%)
	Joray, Celine	Secretary, 50%
	Wettstein, Valentina	Secretary, 70%
	Conforti, Isa	Workshop / house keeping, 50%

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

Summer School 2021

Members of the Institute of Pharmacology of the University of Bern together with participants of our International Summer School in Emmetten; July 4 – 6, 2021.

3. Teaching Activities

3.1. Lectures

Lectures for Medical Students: Pharmacology

Date	Lecturer	Titel of the lecture
Mar 09, 2021	Prof. Stephan von Gunten	Hormone aus pharmakol. Sicht (Teil 1)
Mar 09, 2021	Prof. Stephan von Gunten	Hormone aus pharmakol. Sicht (Teil 2)
Mar 15, 2021	Prof. Stephan von Gunten	Lipidsenker + Behandlung der Gicht
Mar 15, 2021	Prof. Stephan von Gunten	Antidiabetika
Mar 23, 2021	Prof. Andrea Huwiler	Therapie von M. Parkinson und Demenz
Mar 29, 2021	Prof. Andrea Huwiler	Lokalanästhetika
Apr 12, 2021	Prof. Andrea Huwiler	Antiepileptika
Apr 13, 2021	Prof. Huwiler/Prof. L.Theiler	Pharmakologie von Narkosemitteln und Muskelrelaxantien I
Apr 13, 2021	Prof. Huwiler/Prof. L.Theiler	Pharmakologie von Narkosemitteln und Muskelrelaxantien II
Apr 19, 2021	Prof. Andrea Huwiler	Psychopharmakologie
Apr 26, 2021	Prof. Andrea Huwiler	Antipsychotika und Stimmungsstabilisatoren
Apr 26, 2021	Prof. Andrea Huwiler	Antidepressiva, Anxiolytika, Sedativa
Apr 27, 2021	Prof. Manuel Haschke	Schmerz und Analgesiologie (Teil 1)
Apr 27, 2021	Prof. Manuel Haschke	Schmerz und Analgesiologie (Teil 2)
May 04, 2021	Prof. Hans-Uwe Simon	Immunmodulation
Sep 22, 2021	Prof. Hans-Uwe Simon	Pharmakodynamik (Teil 1)
Sep 22, 2021	Prof. Hans-Uwe Simon	Pharmakodynamik (Teil 2)
Sep 28, 2021	Prof. Hans-Uwe Simon	Entzündungshemmung
Sep 28, 2021	Prof. Hans-Uwe Simon	Einführung in die Toxikologie
Oct 04, 2021	Prof. Hans-Uwe Simon	Pharmakotherapie bei Lungenkrankheiten
Oct 26, 2021	Prof. David Spirk	Pharmakologie der Hämostase
Nov 02, 2021	Prof. T. Kaufmann	Pharmakologie des vegetativen Nervensystems
Nov 09, 2021	Prof. David Spirk	Behandlung der Herzinsuffizienz und Angina pectoris
Nov 09, 2021	Prof. Stephan von Gunten	Antihypertensiva
Nov 09, 2021	Prof. Stephan von Gunten	Antiarrhythmika
Nov 09, 2021	Prof. Stephan von Gunten	Diuretika (Teil 1)
Nov 09, 2021	Prof. Spephan von Gunten	Diuretika (Teil 2)

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

All lectures were recorded as a podcast.

Lectures for Medical Students: Cell Biology

Date	Lecturer	Titel of the lecture
Sep 30, 2021	Prof. Thomas Kaufmann	Entwicklung des Lebens
Oct 14, 2021	Prof. Thomas Kaufmann	Zellstoffwechsel
Nov 04, 2021	Prof. Thomas Kaufmann	Zelltod 2

Special seminars for Medical Students: Grundprinzipien lebender Systeme / Zellen und Organismen

Date	Lecturer	Titel of the lecture
Mar 15, 2021	Prof. U. Zangemeister-Wittke	Gezielte Tumortherapie mit Antikörpern und Immunkonjugaten
Mar 22, 2021	Prof. Thomas Kaufmann	Modulation des Zelltodes - aktueller Stand und neue Entwicklungen
Mar 15, 2021	Prof. Stephan von Gunten	Functional Glycomics - Neue Optionen für die Tumor- und Entzündungspharmakologie
Mar 22, 2021	Prof. Hans-Uwe Simon	Personalisierte Arzneimitteltherapie

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

Date	Lecturer	Title of the lecture
Feb 15, 2021	Prof. U. Zangemeister-Wittke	Einführung in die Pharmakokinetik
Feb 1, 2021	Prof. Hans-Uwe Simon	Rezeptoren, Dosis-Wirkungskurven,
Feb 1, 2021	Prof. Hans-Uwe Simon	Antagonisten, Applikationsarten
Feb 24, 2021	Prof. Thomas Kaufmann	Pharmakogenetik, Interaktionen
Feb 17, 2021	Prof. U. Zangemeister-Wittke	Pharmakologie des vegetativen Nervensystems
Mar 10, 2021	Prof. Andrea Huwiler	Narkose, Beruhigungsmittel
Mar 17, 2021	Prof. Andrea Huwiler	Pharmakologie der Atemwege
Mar 22, 2021	PD Dr. Armand Cachelin	Analgetika
Mar 24, 2021	Prof. Stephan von Gunten	Pharmakologie des Knochens
Mar 31, 2021	Prof. Stephan von Gunten	Magensäurehemmung
Apr 12, 2021	Prof. David Spirk	Herz-Kreislauf Medikamente, Antithrombotika
Apr 14, 2021	Dr. Sibylle Bürgi	Antidiabetika
Apr 21, 2021	Dr. Sibylle Bürgi	Lokalanästhetika
Apr 26, 2021	Dr. Sibylle Bürgi	Antibiotika

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

Lectures for Pharmacy Students: Pharmacology (Coordinators: Prof. Hans-Uwe Simon, Prof. Manuel Haschke)

Date	Lecturer	Title of the lecture
Mar 05, 2021	Prof. Andrea Huwiler	Depressionen (2 h)
Mar 11, 2021	Prof. Andrea Huwiler	Schlafstörungen (2 h)
Mar 12, 2021	Prof. Andrea Huwiler	Schizophrenie, Psychosen (2 h)
Mar 18, 2021	Prof. Andrea Huwiler	Demenz (2 h)
Mar 19, 2021	Prof. Andrea Huwiler	Allgemein- und Lokalanästhesie (2 h)
Apr 15, 2021	Prof. Stephan von Gunten	Knochenkrankheiten, Osteoporose, Gicht
Apr 16, 2021	Prof. Stephan von Gunten	Gelenkkranheiten, Arthrose
Apr 22, 2021	Prof. Stephan von Gunten	Arthritis
Mai 14, 2021	Prof. Andrea Huwiler	Epilepsien (2 h)
Mai 20, 2021	Prof. Andrea Huwiler	Parkinson (2 h)
May 27, 2021	Prof. Hans-Uwe Simon	Krankheiten des Immunsystems
May 21, 2021	Prof. Uwe Zangemeister	Prostataerkrankungen
Jun 03, 2021	Prof. Uwe Zangemeister	Tumorimmunologie
Sep 23, 2021	Prof. Hans-Uwe Simon	Pharmakodynamik 1
Sep 23, 2021	Prof. Hans-Uwe Simon	Pharmakodynamik 2
Sep 23, 2021	Prof. Hans-Uwe Simon	Pharmakodynamik 3
Sep 23, 2021	Prof. Hans-Uwe Simon	Arzneimittelallergien
Sep 27, 2021	Prof. Hans-Uwe Simon	Experimentelle Toxikologie 1
Sep 27, 2021	Prof. Hans-Uwe Simon	Experimentelle Toxikologie 2
Nov 18, 2021	Prof. Stephan von Gunten	Säureassoziierte KH / Erbrechen
Nov 23, 2021	Prof. Stephan von Gunten	Motilitätsstörungen / Entzündliche Darmerkrankungen
Nov 30, 2021	Prof. Georgia Konstantinidou	Zytostatika, Teil 1
Dec 02, 2021	Prof. Georgia Konstantinidou	Zytostatika, Teil 2
Dec 07, 2021	Prof. Thomas Kaufmann	Anämien
Dec 09, 2021	Prof. Thomas Kaufmann	Leukämien
Dec 14, 2021	Prof. Thomas Kaufmann	Lymphome

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

Date	Lecturer	Title of the lecture
Feb 25, 2021	Prof. Stephan von Gunten	Introduction
Feb 25, 2021	Prof. Stephan von Gunten	Glycoimmunology
Apr 29, 2021	Prof. Georgia Konstantinidou	Immunopharmacology

Written examination and oral tests: Prof. Stephan von Gunten

Lecture for Natural Sciences Faculty: Cellular and Molecular Immunology (Coordinator: Prof. Martin Bachmann)

Date	Lecturer	Title of the lecture
Sep 23, 2021	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
Apr 01, 2021	Prof. Georgia Konstantinidou	Lipid mediators in inflammation
May 20, 2021	Prof. Shida Yousefi	Inflammation - good or bad? Resolution of inflammation - apoptosis

Practical work for Natural Science Faculty: Immunology II

Date	Lecturer
Dec. 3, 9 Dec. 10, 16 Dec. 17, 23 (total 6 days)	Prof. Stephan von Gunten + Prof.Thomas Kaufmann

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 24, 2021	Prof. Stephan von Gunten	Gastrointestinal tract
Oct 01, 2021	Prof. David Spirk	Haemopoietic system and haemostasis
Oct 08, 2021	Prof. Stephan von Gunten	Heart and vascular system
Oct 15, 2021	Prof. Stephan von Gunten	Endocrine and reproductive system
Oct 22, 2021	Prof. Thomas Kaufmann	Immune system
Oct 29, 2021	Prof. Thomas Kaufmann	Antiinfectious therapy
Nov 05, 2021	Prof. Shida Yousefi	Lungs and kidneys
Nov 12, 2021	Dr. Bisera Stepanovska Tanturovska	Nervous system

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 03, 2021	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 16, 2021	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 29, 2021	Prof. Shida Yousefi	Laser scanning microscopy and specific applications (FRET, FRAP, spectral unmixing) and digital image restoration (Huygen and Imaris software)

Cell Biology tutorial "Happy Cell" 2019 (5.0 ECTS), CTS/KSL 7606"

Date	Lecturer	Title of the lecture
Nov 03, 2021 2 hours	Prof. Thomas Kaufmann	Chapter 15 (Cell signaling)

Online Lectures for Medical Students: Clinical Pharmacology (*switched to on-site lecture on April 27)

Date	Lecturer	Titel of the lecture
Feb 08, 2021	Prof. Manuel Haschke	Pharmakologie: Laxativa, Antidiarrhoika, Antiemetika
Feb 08, 2021	Prof. Manuel Haschke	Hemmung der Säuresekretion
Feb 15, 2021	PD Felix Hammann	Pharmakokinetik 3&4 (2 Lekt.)
Mar 09, 2021	PD Evangelia Liakoni	Analgetika
Mar 11, 2021	PD Evangelia Liakoni	Antikoagulantien & Thrombozytenhemmer
Mar 11, 2021	PD Evangelia Liakoni	Notfallmedikamente
Mar 29, 2021	PD Evangelia Liakoni	Arterielle Hypertonie u. Herzinsuffizienz
Mar 29, 2021	PD Evangelia Liakoni	Diabetes u. Dyslipidämie
Mar 29, 2021	Prof. Manuel Haschke	Antiinfektiva
*Apr 27, 2021	Prof. Manuel Haschke	Schmerzmittel 1&2 (2 Lekt.)
Sep 28, 2021	PD Felix Hammann	Pharmakokinetik 1&2 (2 Lekt.)
Oct 08, 2021	PD Evangelia Liakoni	Interaktionen
Oct 08, 2021	PD Evangelia Liakoni	Nebenwirkungen

Lectures for Dental Medicine Students: Clinical Pharmacology

Date	Lecturer	Titel of the lecture
Oct 27, 2021	Prof. Manuel Haschke	Pat. mit akuten med. Problemen
Nov 03, 2021	PD Felix Hammann	Pat. mit chronischen med. Problem
Nov 10, 2021	Prof. Manuel Haschke	Antibiotika 1
Nov 17, 2021	PD Evangelia Liakoni	Antikoagulation
Nov 24, 2021	Prof. Manuel Haschke	Antibiotika 2
Dec 01, 2021	Vanessa Bütler	Analgetika 1
Dec 08, 2021	Vanessa Bütler	Analgetika 2
Dec 15, 2021	Prof. Manuel Haschke	UAW im Mund

Lectures for Pharmacy Students (Bachelor): Clinical Pharmacology (*switched to on-site lecture on Sept 30)

Date	Lecturer	Titel of the lecture
Feb 23, 2021	PD Felix Hammann	Biopharmazie
Feb 25, 2021	PD Evangelia Liakoni	Asthma, COPD, Pneumonien
Feb 26, 2021	PD Evangelia Liakoni	Asthma, COPD, Pneumonien
Mar 02, 2021	Verena Schöning	Biopharmazie
Mar 09, 2021	PD Felix Hammann	Biopharmazie
Mar16, 2021	PD Felix Hammann	Biopharmazie
Mar 23, 2021	PD Felix Hammann	Biopharmazie
Mar 25, 2021	Prof. Manuel Haschke	Opioidanalgetika
Mar 26, 2021	PD Evangelia Liakoni	Nicht-opioid Analgetika

Mar 30, 2021	Prof. Manuel Haschke	Biopharmazie
Apr 01, 2021	PD Evangelia Liakoni	Schmerz, neuropathisch
Apr 01, 2021	Prof. Manuel Haschke	Kopfschmerzen, Migräne
Apr 13, 2021	PD Felix Hammann	Biopharmazie
Apr 20, 2021	PD Felix Hammann	Biopharmazie
Apr 23, 2021	Prof. Stephan Krähenbühl	Schilddrüsenkrankheiten
Apr 27, 2021	Prof. Carlo Largiadèr	Biopharmazie
Apr 29, 2021	Prof. Manuel Haschke	Hypophysäre Störungen
Apr 30, 2021	PD Evangelia Liakoni	Dyslipidämie
May 04, 2021	Prof. Carlo Largiadèr	Biopharmazie
May 06, 2021	Prof. Manuel Haschke	Diabetes
May 07, 2021	Prof. Stephan Krähenbühl	Geschlechtshormone, Kontrazeptiva
May 11, 2021	Prof. Manuel Haschke	Biopharmazie
May 18, 2021	PD Evangelia Liakoni	Biopharmazie
May 25, 2021	Dr. Vera van der Velpen	Biopharmazie
Jun 01, 2021	PD Felix Hammann	Biopharmazie
Jun 04, 2021	Prof. Manuel Haschke	Polypharmazie
*Sep 30, 2021	Sarah Banholzer	drug safety/adverse events/pharmacovigilance
Oct 05, 2021	PD Stefan Weiler	Pharmakokinetik I & II
Oct 07, 2021	PD Stefan Weiler	Pharmakokinetik III
Oct 19, 2021	Prof. Stephan Krähenbühl	Venöse KH
Oct 21, 2021	PD Felix Hammann	Herzinsuffizienz, Rhythmusstörungen
Oct 26, 2021	Prof. Stephan Krähenbühl	Arterielle KH
Oct 28, 2021	PD Felix Hammann	Hypertonie
Nov 02, 2021	PD Stefan Weiler	Virale und retrovirale KH
Nov 04, 2021	PD Stefan Weiler	Pilzerkrankungen Mycobacterielle KH
Nov 09, 2021	Prof. Manuel Haschke	Bakterielle Infektionen I & II
Nov 11, 2021	Prof. Manuel Haschke	Bakterielle Infektionen III & IV
Nov 16, 2021	Prof. Manuel Haschke	Parasiten / Malaria
Dec 16, 2021	PD Felix Hammann	Nierenkrankheiten, Dialyse, Dosisanpsung Nieren-/Lebererkrankungen
Dec 21, 2021	PD Felix Hammann	HWI, Inkontinenz
Dec 23, 2021	PD Evangelia Liakoni	Klinische Toxikologie

Lectures for Pharmacy Students (Master): Clinical Pharmacology

Date	**Lecturer**	**Titel of the lecture**
Sep 21, 2021	Sarah Banholzer	Arzneimittelsicherheit: Pharmakovigilanz – Vertiefung

3.2. Coordination PBL Medical Students, 3rd year (2021/2022)

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 2021/2022)

For Medical students 3rd year:
Prof. Georgia Konstantinidou
Dr. Zhaoyue He
Dr. Bisera Stepanovska Tanturovska
Dr. Darko Stojkov
Prof. Thomas Kaufmann
Marjolaine Claire Hugonnet
Samara Naim

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:
Angèle Clerc (Daniel Bachmann & Thomas Kaufmann)
Widad Hassan (Daniel Bachmann & Thomas Kaufmann)

3.5. Seminars of Invited Speakers

Date	Teacher	Title of the seminar	Host
June 17, 2021	Prof. Dr. Wolfram Hötzenecker, Klinik für Dermatologie und Venerologie, Johannes-Kepler-Universität Linz, Österreich	Covid-19 in Allergologie und Dermatologie	H.-U. Simon
June 30, 2021	BIC: Prof. Dr. Christian Münz, Institute of Experimental Immunology, University of Zurich	Modulation of virus-induced pathogenesis by genetic variability and co-infections	H.-U. Simon
July 13, 2021	Dr. Dasha Nelidova, Institute of Molecular and Clinical Ophthalmology, Basel	Restoring light sensitivity using tunable near-infrared sensors	H.-U. Simon
July 21, 2021	Prof. Dr. Stephan Krähenbühl, Clinical Pharmacology & Toxicology, University Hospital Basel	Drug-induced mitochondrial toxicity	H.-U. Simon
Oct 27, 2021	Prof. Dr. med. Josef Pfeilschifter, Pharmazentrum Frankfurt/ZAFES, Universitätsklinikum, Goethe University Frankfurt am Main	The role of gastrotransmitters in glomerular diseases	A. Huwiler
Dec 15, 2021	Prof. Dr. Roland H. Wenger, Institute of Physiology, University of Zürich	Origin and fate of renal erythropoietin-producing cells	A. Huwiler

3.6. Academic Degrees

Klapan Kim, PhD, University of Bern
Thesis: Evidence for Lysosomal Dysfunction Within Epidermis in Psoriasis and Atopic Dermatitis (June 2021)
Supervisors: Prof. Hans-Uwe Simon, Prof. Dagmar Simon

Erhardt Martin, PhD, University of Bern
Thesis: The Role of Ceramide Kinase and Phospholipase A2 in In Vitro Models of Inflammation and Migration Associated Disorders (Aug 2021)
Supervisors: Prof. Zangemeister-Wittke and Prof. Andrea Huwiler

Naim Samara, PhD, University of Bern
Thesis: Towards Understanding the Physiological and Pathophysiological Roles of the BCL-2 Family Member BOK (Aug 2021)
Supervisor: Prof. Thomas Kaufmann

Peng Shuang, PhD, University of Bern
Thesis: Role of RHOH in Neutrophil Effector Functions (Nov 2021)
Supervisor: Prof. Hans-Uwe Simon

Paschoud Thierry, M.Sc., University of Bern
Thesis: Lipid metabolism mediated vulnerabilities in non-small cell lung cancer (Febr 2021)
Supervisor: Prof. Georgia Konstantinidou

Wyss Jacqueline, M.Sc., University of Bern
Thesis: Integrative Analysis of LncRNAs to Discover New Potential Biomarkers and Therapeutic Targets in Eosinophil-Related Disorders (March 2021)
Supervisor: Prof. Hans-Uwe Simon

Motta Fabrizio, M.Sc., University of Bern
Thesis: Towards Exploiting BOK as a Therapeutic Target (July 2021)
Supervisor: Prof. Thomas Kaufmann

Kishavarz, Fatemeh, M.Sc.pharm., University of Basel
Thesis: Drug-Mediated By-Passing of the NADPH Oxidase in Neutrophils (July 2021)
Supervisor: Prof. Hans-Uwe Simon, Dr. Darko Stojkov

Aregger Raphael Valentin, M.Sc.pharm., University of Bern
Thesis: The effects of ACSL3 inhibition in KRAS and PI3K mutated cell lines (July 2021)
Supervisor: Prof. Georgia Konstantinidou

Timothée Louis Fettrelet, M.Sc., University of Lausanne
Thesis: Single-Cell Characterization of Eosinophils (Aug 2021)
Supervisor: Prof. Hans-Uwe Simon

Pulfer Livia, M.Sc.pharm., University of Bern
Thesis: The Role of XIAP in the Regulation of GM-CSF Signaling and Effector Functions of Mouse Neutrophils (Aug 2021)
Supervisor: Prof. Thomas Kaufmann

Lavrencic Marusa, M.Sc.pharm., University of Ljubljana
Thesis: Molecular Interactions Between Eosinophil Major Basic Protein and DNA (Sept 2021)
Supervisor: Prof. Hans-Uwe Simon

4. Research Activities

4.1. Research Projects and Publications

Group Prof. Andrea Huwiler

Group members: Riim Nasser, Lab Technician[1]
Dr. Faik Imeri, postdoctoral fellow[1]
Dr. Bisera Stepanovska Tanturovska, postdoctoral fellow [1]
Redona Hafizi, PhD student[1]
Jehona Mulaki, M.sc. student[1] (until Jan 2021)
Rebecca Lakomy, M.sc. pharm. student (Basel)
Helen Broughton. M.med. student[1]
Isolde Römer, Technician[2]
Stephanie Schwalm, Dr., postdoctoral fellow[2]

[1]Institute of Pharmacology, University of Bern
[2]Institut für Allgemeine Pharmakologie und Toxikologie, Universität Frankfurt/Main

Our research is focused on sphingolipids and their contribution to physiological 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 growth.

S1P Stimulates Erythropoietin Production in Mouse Renal Interstitial Fibroblasts by S1P 1 and S1P 3 Receptor Activation and HIF-2α Stabilization
Hafizi R*, Imeri F*, Wenger RH, Huwiler A
Erythropoietin (Epo) is the critical hormone for erythropoiesis. In adults, Epo is mainly produced by a subset of interstitial fibroblasts in the kidney, with minor amounts being produced in the liver and the brain. In this study, we used the immortalized renal interstitial fibroblast cell line FAIK F3-5 to investigate the ability of the bioactive sphingolipid sphingosine 1-phosphate (S1P) to stimulate Epo production and to reveal the mechanism involved. Stimulation of cells with exogenous S1P under normoxic conditions (21% O_2) led to a dose-dependent increase in Epo mRNA and protein levels and subsequent release of Epo into the medium. S1P also enhanced the stabilization of HIF-2α, a key transcription factor for Epo expression. S1P-stimulated Epo mRNA and protein expression was abolished by HIF-2α mRNA knockdown or by the HIF-2 inhibitor compound 2. Furthermore, the approved S1P receptor modulator FTY720, and its active form FTY720-phosphate, both exerted a similar

effect on Epo expression as S1P. The effect of S1P on Epo was antagonized by the selective $S1P_1$ and $S1P_3$ antagonists NIBR-0213 and TY-52156, but not by the $S1P_2$ antagonist JTE-013. Moreover, inhibitors of the classical MAPK/ERK, the p38-MAPK, and inhibitors of protein kinase (PK) C and D all blocked the effect of S1P on Epo expression. Finally, the S1P and FTY720 effects were recapitulated in the Epo-producing human neuroblastoma cell line Kelly, suggesting that S1P receptor-dependent Epo synthesis is of general relevance and not species-specific. In summary, these data suggest that, in renal interstitial fibroblasts, which are the primary source of plasma Epo, $S1P_{1 \text{ and } 3}$ receptor activation upregulates Epo under normoxic conditions. This may have a therapeutic impact on disease situations such as chronic kidney disease, where Epo production is impaired, causing anemia, but it may also have therapeutic value as Epo can mediate additional tissue-protective effects in various organs. (* equal contribution)
See original publication No 1

ST-2191, an anellated bismorpholino derivative of oxy-fingolimod, shows selective S1P1 agonist and functional antagonist potency in vitro and in vivo
Stepanovska Tanturovska B, Zivkovic A, Imeri F, Homann T, Kleuser B, Stark H, Huwiler A
Sphingosine 1-phosphate (S1P) is an extensively studied signaling molecule that contributes to cell proliferation, survival, migration and other functions through binding to specific S1P receptors. The cycle of $S1P_1$ internalization upon S1P binding and recycling to the cell surface when local S1P concentrations are low drives T cell trafficking. $S1P_1$ modulators, such as fingolimod, disrupt this recycling by inducing persistent $S1P_1$ internalization and receptor degradation, which results in blocked egress of T cells from the secondary lymphoid tissues. The approval of these compounds for the treatment of multiple sclerosis has placed the development of S1PR modulators in the focus of pharmacological research, mostly for autoimmune indications. Here, we report on a novel anellated bismorpholino derivative of oxy-fingolimod, named ST-2191, which exerts selective $S1P_1$ agonist and functional antagonist potency. ST-2191 is also effective in reducing the lymphocyte number in mice, and this effect is not dependent on phosphorylation by sphingosine kinase 2 for activity. These data show that ST-2191 is a novel $S1P_1$ modulator, but further experiments are needed to analyze the therapeutic impact of ST-2191 in animal models of autoimmune diseases.
See original publication No 2

Loss of sphingosine kinase 2 enhances Wilm's tumor suppressor gene 1 and nephrin expression in podocytes and protects from streptozotocin-induced podocytopathy and albuminuria in mice
Imeri F, Stepanovska Tanturovska B, Schwalm S, Saha S, Zeng-Brouwers J, Pavenstädt H, Pfeilschifter J, Schaefer L, Huwiler A
The sphingosine 1-phosphate (S1P) is a bioactive sphingolipid that is now appreciated as key regulatory factor for various cellular functions in the kidney, including matrix remodeling. It is generated by two sphingosine kinases (Sphk), Sphk1 and Sphk2, which are ubiquitously expressed, but have distinct enzymatic activities and subcellular localizations. In this study, we have investigated the role of Sphk2 in podocyte function and its contribution to diabetic nephropathy. We show that streptozotocin (STZ)-induced nephropathy and albuminuria in mice is prevented by genetic depletion of Sphk2. This protection correlated with an increased protein expression of the transcription factor Wilm's tumor suppressor gene 1 (WT1) and its target gene nephrin, and a reduced macrophage infiltration in immunohistochemical renal sections of STZ-treated $Sphk2^{-/-}$ mice compared to STZ-treated wildtype mice. To investigate changes on the cellular level, we used an immortalized human podocyte cell line and generated a stable knockdown of Sphk2 (Sphk2-kd) by a lentiviral transduction method. These Sphk2-kd cells accumulated sphingosine as a consequence of the knockdown and showed enhanced nephrin and WT1 mRNA and protein expressions similar to the finding in Sphk2

knockout mice. Treatment of wildtype podocytes with the highly selective Sphk2 inhibitor SLM6031434 caused a similar upregulation of nephrin and WT1 expression. Furthermore, exposing cells to the profibrotic mediator transforming growth factor β (TGFβ) resulted on the one side in reduced nephrin and WT1 expression, but on the other side, in upregulation of various profibrotic marker proteins, including connective tissue growth factor (CTGF), fibronectin (FN) and plasminogen activator inhibitor (PAI) 1. All these effects were reverted by Sphk2-kd and SLM6031434. Mechanistically, the protection by Sphk2-kd may depend on accumulated sphingosine and inhibited PKC activity, since treatment of cells with exogenous sphingosine not only reduced the phosphorylation pattern of PKC substrates, but also increased WT1 protein expression. Moreover, the selective stable knockdown of PKCδ increased WT1 expression, suggesting the involvement of this PKC isoenzyme in WT1 regulation. The glucocorticoid dexamethasone, which is a treatment option in many glomerular diseases and is known to mediate a nephroprotection, not only downregulated Sphk2 and enhanced cellular sphingosine, but also enhanced WT1 and nephrin expressions, thus, suggesting that parts of the nephroprotective effect of dexamethasone is mediated by Sphk2 downregulation. Altogether, our data demonstrated that loss of Sphk2 is protective in diabetes-induced podocytopathy and can prevent proteinuria, which is a hallmark of many glomerular diseases. Thus, Sphk2 could serve as a new attractive pharmacological target to treat proteinuric kidney diseases.

See original publication No 3

Novel compounds with dual S1P receptor agonist and histamine H3 receptor antagonist activities act protective in a mouse model of multiple sclerosis

Imeri F, Stepanovska Tanturovska B, Zivkovic A, Enzmann G, Schwalm S, Pfeilschifter J, Homann T, Kleuser B, Engelhardt B, Stark H, Huwiler A

The sphingosine 1-phosphate (S1P) receptor 1 ($S1P_1$) has emerged as a therapeutic target for the treatment of multiple sclerosis (MS). Fingolimod (FTY720) is the first functional antagonist of $S1P_1$ that has been approved for oral treatment of MS. Previously, we have developed novel butterfly derivatives of FTY720 that acted similar to FTY720 in reducing disease symptoms in a mouse model of experimental autoimmune encephalomyelitis (EAE). In this study, we have synthesized a piperidine derivative of the oxazolo-oxazole compounds, denoted ST-1505, and its ring-opened analogue ST-1478, and characterised their in-vitro and in-vivo functions. Notably, the 3-piperidinopropyloxy moiety resembles a structural motif of pitolisant, a drug with histamine H_3R antagonistic/inverse agonist activity approved for the treatment of narcolepsy. Both novel compounds exerted H_3R affinities, and in addition, ST-1505 was characterised as a dual $S1P_{1+3}$ agonist, whereas ST-1478 was a dual $S1P_{1+5}$ agonist. Both multitargeting compounds were also active in mice and reduced the lymphocyte numbers as well as diminished disease symptoms in the mouse model of MS. The effect of ST-1478 was dependent on SK-2 activity suggesting that it is a prodrug like FTY720, but with a more selective S1P receptor activation profile, whereas ST-1505 is a fully active drug even in the absence of SK-2. In summary, these data suggest that the well soluble piperidine derivatives ST-1505 and ST-1478 hold promise as novel drugs for the treatment of MS and other autoimmune or inflammatory diseases, and by their H_3R antagonist potency, they might additionally improve cognitive impairment during disease.

See original publication No 4

Original publications

1. Hafizi R, Imeri F, Wenger RH, **Huwiler A:** S1P Stimulates Erythropoietin Production in Mouse Renal Interstitial Fibroblasts by S1P1 and S1P3 Receptor Activation and HIF-2α Stabilization. Int J Mol Sci. 22 (2021), 9467.

2. Stepanovska Tanturovska B, Zivkovic A, Imeri F, Homann T, Kleuser B, Stark H, **Huwiler A:** ST-2191, an Anellated Bismorpholino Derivative of Oxy-Fingolimod, Shows Selective S1P1 Agonist and Functional Antagonist Potency In Vitro and In Vivo . Molecules. 26 (2021), 5134.

3. Imeri F, Stepanovska Tanturovska B, Schwalm S, Saha S, Zeng-Brouwers J, Pavenstädt H, Pfeilschifter J, Schaefer L, **Huwiler A:** Loss of sphingosine kinase 2 enhances Wilm's tumor suppressor gene 1 and nephrin expression in podocytes and protects from streptozotocin-induced podocytopathy and albuminuria in mice. Matrix Biol. 98 (2021), 32-48.

4. Imeri F, Stepanovska Tanturovska B, Zivkovic A, Enzmann G, Schwalm S, Pfeilschifter J, Homann T, Kleuser B, Engelhardt B, Stark H, **Huwiler A:** Novel compounds with dual S1P receptor agonist and histamine H3 receptor antagonist activities act protective in a mouse model of multiple sclerosis . Neuropharmacol. 186 (2021), 108464.

5. Psarra A, Theodoropoulou MA, Erhardt M, Mertiri M, Mantzourani C, Vasilakaki S, Magrioti V, **Huwiler A**, Kokotos G: α-Ketoheterocycles Able to Inhibit the Generation of Prostaglandin E2 (PGE2) in Rat Mesangial Cells. Biomolecules.11, 275.

6. Schwalm S, Beyer S, Hafizi R, Trautmann S, Geisslinger G, Adams DR, Pyne S, Pyne N, Schaefer L, **Huwiler A***, Pfeilschifter J*: Validation of highly selective sphingosine kinase 2 inhibitors SLM6031434 and HWG-35D as effective anti-fibrotic treatment options in a mouse model of tubulointerstitial fibrosis. Cell Signal. 79 (2021)109881.
   * (shared senior authorship)

Review article

1. **Huwiler A**, Pfeilschifter J: Recuperation of Vascular Homeostasis. Circ Res. 129 (2021), 237-239. (Editorial)

Group Prof. Thomas Kaufmann

Group members: Samara Naim, PhD student
Ali Jazaeri, PhD student
Philippe JeanRichard, PhD student
Livia Pulfer, M.Sc.pharm, student
Fabrizio Motta, M.Sc. student
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, as well as its role in cancer development and maintenance. Regarding the latter, we have recently identified a novel function of BOK, linking this cell death regulator to nucleotide metabolism, mitochondrial morphology and functions, cellular proliferation and malignant transformation of cancer cells.

A novel functional mast cell assay for the detection of allergies

Zbären N, Brigger D, Bachmann D, Helbling A, Jörg L, Horn MP, Schmid JM, Hoffmann HJ, Kinet JP, Kaufmann T*, Eggel A*

Background: Clinical management of allergic diseases has been hampered by the lack of safe and convenient tests to reliably identify culprit allergens and to closely follow changes in disease activity over time. Because allergy diagnosis is a complex and laborious multistep procedure, there is an urgent need for simpler but still functionally accurate ex vivo assays allowing objective diagnosis, substantiating treatment choices, and quantifying therapeutic responses. Objective: In this study, we sought to develop a novel functional cell-based assay that relies on passive sensitization of allergic effector cells with patient serum, circumventing current limitations in allergy diagnosis. Methods: We genetically engineered a conditional homeobox B8 (Hoxb8)-immortalized progenitor line from the bone marrow of mice that are transgenic for the human high-affinity IgE receptor (FcεRIa). These cells can be reproducibly differentiated into mature Hoxb8 mast cells within 5 days of culture in virtually unlimited numbers. Results: We demonstrate that the established Hoxb8 mast cell assay can be used to accurately measure total IgE levels, identify culprit allergens, longitudinally monitor allergen-specific immunotherapy, and potentially determine the time point of tolerance induction upon allergen-specific immunotherapy in patients with allergy. To facilitate the analysis of large testing volumes, we demonstrate a proof-of-concept for a high-throughput screening application based on fluorescent cell barcoding using the engineered Hoxb8 mast cells.

See original publication No 1

Loss of BOK has a minor impact on acetaminophen overdose-induced liver damage in mice

Naim S, Fernandez-Marrero Y, de Brot S, Bachmann D, Kaufmann T

Acetaminophen (APAP) is one of the most commonly used analgesic and anti-pyretic drugs, and APAP intoxication is one of the main reasons for liver transplantation following liver failure in the Western world. While APAP poisoning ultimately leads to liver necrosis, various programmed cell death modalities have been implicated, including ER stress-triggered apoptosis. The BCL-2 family member BOK (BCL-2-related ovarian killer) has been described to modulate the unfolded protein response and to promote chemical-induced liver injury. We therefore investigated the impact of the loss of BOK following APAP overdosing in mice. Surprisingly, we observed sex-dependent differences in the activation of the unfolded protein response (UPR) in both wildtype (WT) and *Bok*$^{-/-}$ mice, with increased activation of JNK in females compared with males. Loss of BOK led to a decrease in JNK activation and a reduced percentage of centrilobular necrosis in both sexes after APAP treatment; however, this protection was more pronounced in *Bok*$^{-/-}$ females. Nevertheless, serum ALT and AST levels of *Bok*$^{-/-}$ and WT mice were comparable, indicating that there was no major difference in the overall outcome of liver injury. We conclude that after APAP overdosing, loss of BOK affects initiating signaling steps linked to ER stress but has a more minor impact on the outcome of

liver necrosis. Furthermore, we observed sex-dependent differences that might be worthwhile to investigate.
See original publication No 2

Original publications

1. Zbären N, Brigger D, Bachmann D, Helbling A, Jörg L, Horn MP, Schmid JM, Hoffmann HJ, Kinet JP, **Kaufmann T***, Eggel A*: A novel functional mast cell assay for the detection of allergies. J Allergy Clin Immunol. 21 (2021), article in press.

2. Naim S, Fernandez-Marrero Y, de Brot S, Bachmann D, **Kaufmann T**: Loss of BOK has a minor impact on acetaminophen overdose-induced liver damage in mice. Int J Mol Sci. 22 (2021), doi: 10.3390/ijms22063281

3. Burgener SS, Brügger M, Sollberger S, Basilico P, **Kaufmann T**, Bird PI, Benarafa C. Granule leakage induces cell-intrinsic, granzyme B-mediated apoptosis in mast cells. Front Cell Dev Biol (2021), 9:630166.

4. Meinhardt A, Munkhbaatar E, Höckendorf U, Dietzen M, Dechant M, Anton M, Jacob A, Steiger K, Weichert W, Brcic L, McGranahan N, Branca C, **Kaufmann T**, Dengler MA, Jost PJ. The BCL-2 family member BOK promotes KRAS-driven lung cancer progression in a p53-dependent manner. Oncogene, in press.

Group Prof. Georgia Konstantinidou

Group members: Dr. Maria Saliakoura, Postdoc
Dr. Asmita Thapa, Postdoc (until Febr. 2021)
Chiara Pozzato, PhD student
Cédric Leroux, PhD student
Simone Falco, PhD student
Ioanna Nikdima, PhD student (since June 2021)
Thierry Paschoud, M.Sc. student (until Febr. 2021)
Raphael V. Aregger, M.Sc.pharm. student (until July 2021)

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.

Restriction of extracellular lipids renders pancreatic cancer dependent on autophagy
Maria Saliakoura, Matteo Rossi Sebastiano, Ioanna Nikdima, Chiara Pozzato, Georgia Konstantinidou
KRAS is the predominant oncogene mutated in pancreatic ductal adenocarcinoma (PDAC), the fourth cause of cancer-related deaths worldwide. Mutant KRAS-driven tumors are metabolically rewired to support their growth and survival, which can be used to identify metabolic vulnerabilities. Here we show that depletion of extracellularly derived lipids either by lipid restriction or suppression of the fatty acid activator, acyl-CoA synthetase long chain 3 (ACSL3), triggers autophagy, a process that protects PDAC cells from the reduction of bioenergetic intermediates. Combined extracellular lipid deprivation and autophagy inhibition exhibits antiproliferative and pro-apoptotic effects against PDAC cell lines *in vitro* and promotes suppression of xenografted human cancer cell-derived tumors in mice. Therefore, we propose lipid deprivation and autophagy blockade as a potential co-targeting strategy for PDAC treatment.
See original publication No 1

Original publications

1. Saliakoura M, Sebastiano MR, Nikdima I, Pozzato C, **Konstantinidou G**: Restriction of extracellular lipids renders pancreatic cancer dependent on autophagy. J Exp Clin Cancer Res, in press.

2. Yang Z, Liang SQ, Saliakoura M, Yang H, Vassella E, **Konstantinidou G**, Tschan M, Hegedüs B, Zhao L, Gao Y, Xu D, Deng H, Marti TM, Kocher GJ, Wang W, Schmid RA, Peng RW: Synergistic effects of FGFR1 and PLK1 inhibitors target a metabolic liability in KRAS-mutant cancer. EMBO Mol Med. 13 (2021), e13193.

Review article

1. Leroux C, **Konstantinidou G:** Targeted Therapies for Pancreatic Cancer: Overview of Current Treatments and New Opportunities for Personalized Oncology. Cancers (Basel) 13 (2021), 799.

Group Prof. Hans-Uwe Simon

Group members:
Kevin Oberson, Lab Technician*
Meike Claus, Lab Technician* (until Aug 2021)
Dr. Joanna Boros-Majewska, Lab Technician* (since Sept 2021)
Evelyne Kozlowski, Lab Technician*
Dr. Zhaoyue He, Postdoctoral fellow
Dr. Darko Stojkov, Postdoctoral fellow
Dr. Ziva Frangez, Postdoctoral fellow (until Feb 2021)
Dr. Nina Germic, Postdoctoral fellow* (until Feb 2021)
Dr. Kim Klapan, PhD student** (until June 2021)
Shuang Peng, PhD student*
Nikita Markov, PhD student
Lea Gigon, PhD student*
Yihe Chen, PhD student*
Aref Hosseini, PhD student*
Jacqueline Wyss, M.Sc. student (unil March 2021)
Timothée Fettrelet, M.Sc. student* (until Aug 2021)
Timothée Fettrelet, PhD student* (since Oct 2021)
Apinya Chanwangpong, M.Sc. pharm. student**
Lavrencic, Marusa, M.Sc. pharm. student* (Feb-Aug 2021)
Kishavarz, Fatemeh, M.Sc. pharm. student* (until May 2021)

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

We are interested in the role of apoptosis and autophagy in inflammatory diseases and cancer. Several diseases serve as models to study such processes. In particular, we investigate pathogenic mechanisms of the following diseases: Atopic dermatitis, hypereosinophilic syndromes, eosinophilic esophagitis, 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 Faculty of Medicine of the University of Bern. Results of these collaborative interactions can be seen in the following abstracts, which briefly describe our research activities in 2021.

ATG5 promotes eosinopoiesis but inhibits eosinophil effector functions
Germic N, Hosseini A, Stojkov D, Oberson K, Claus M, Benarafa C, Calzavarini S, Angelillo-Scherrer A, Arnold IC, Müller A, Riether C, Yousefi S, Simon HU
Eosinophils are white blood cells that contribute to the regulation of immunity and are involved in the pathogenesis of numerous inflammatory diseases. In contrast to other cells of the immune system, no information is available regarding the role of autophagy in eosinophil differentiation and functions. To study the autophagic pathway in eosinophils, we generated conditional knockout mice in which Atg5 is deleted within the eosinophil lineage only (desig-

nated Atg5eoΔ mice). Eosinophilia was provoked by crossbreeding Atg5eoΔ mice with Il5 (IL-5) overexpressing transgenic mice (designated Atg5eoΔIl5tg mice). Deletion of Atg5 in eosinophils resulted in a dramatic reduction in the number of mature eosinophils in blood and an increase of immature eosinophils in the bone marrow. Atg5-knockout eosinophil precursors exhibited reduced proliferation under both in vitro and in vivo conditions but no increased cell death. Moreover, reduced differentiation of eosinophils in the absence of Atg5 was also observed in mouse and human models of chronic eosinophilic leukemia. Atg5-knockout blood eosinophils exhibited augmented levels of degranulation and bacterial killing in vitro. Moreover, in an experimental in vivo model, we observed that Atg5eoΔ mice achieve better clearance of the local and systemic bacterial infection with Citrobacter rodentium. Evidence for increased degranulation of ATG5low-expressing human eosinophils was also obtained in both tissues and blood. Taken together, mouse and human eosinophil hematopoiesis and effector functions are regulated by ATG5, which controls the amplitude of overall antibacterial eosinophil immune responses.
See original publication No 1

ATG5 and ATG7 expression levels are reduced in cutaneous melanoma and regulated by NRF1
Frangež Ž, Gérard D, He Z, Gavriil M, Fernández-Marrero Y, Seyed Jafari SM, Hunger RE, Lucarelli P, Yousefi S, Sauter T, Sinkkonen L, Simon HU
Autophagy is a highly conserved cellular process in which intracellular proteins and organelles are sequestered and degraded after the fusion of double-membrane vesicles known as autophagosomes with lysosomes. The process of autophagy is dependent on autophagy-related (ATG) proteins. The role of autophagy in cancer is very complex and still elusive. We investigated the expression of ATG proteins in benign nevi, primary and metastatic melanoma tissues using customized tissue microarrays (TMA). Results from immunohistochemistry show that the expression of ATG5 and ATG7 is significantly reduced in melanoma tissues compared to benign nevi. This reduction correlated with changes in the expression of autophagic activity markers, suggesting decreased basal levels of autophagy in primary and metastatic melanomas. Furthermore, the analysis of survival data of melanoma patients revealed an association between reduced ATG5 and ATG7 levels with an unfavourable clinical outcome. Currently, the mechanisms regulating ATG expression levels in human melanoma remains unknown. Using bioinformatic predictions of transcription factor (TF) binding motifs in accessible chromatin of primary melanocytes, we identified new TFs involved in the regulation of core ATGs. We then show that nuclear respiratory factor 1 (NRF1) stimulates the production of mRNA and protein as well as the promoter activity of *ATG5* and *ATG7*. Moreover, NRF1 deficiency increased *in vitro* migration of melanoma cells. Our results support the concept that reduced autophagic activity contributes to melanoma development and progression, and identifies NRF1 as a novel TF involved in the regulation of both *ATG5* and *ATG7* genes.
See original publication No 2

Evidence for lysosomal dysfunction within the epidermis in psoriasis and atopic dermatitis
Klapan K, Frangež Ž, Markov N, Yousefi S, Simon D, Simon HU
Atopic dermatitis and psoriasis are frequent chronic inflammatory skin diseases. Autophagy plays a substantial role in the homeostasis of an organism. Loss or impairment of autophagy is associated with multiple diseases. To investigate the possibility that autophagy plays a role in atopic dermatitis and psoriasis, we investigated the levels of key ATG proteins in human skin specimens as well as in primary human epidermal keratinocytes exposed to inflammatory stimuli in vitro. Although TNF-α facilitated the induction of autophagy in an initial phase, it reduced the levels and enzymatic activities of lysosomal cathepsins in later time periods, resulting in autophagy inhibition. Therefore, TNF-α appears to play a dual role in the regulation

of autophagy. The relevance of these in vitro findings was supported by the observation that the protein levels of cathepsins D and L are decreased in both psoriasis and atopic dermatitis skin specimens. Taken together, this study suggests that TNF-α blocks autophagy in keratinocytes after long-term exposure, a mechanism that may contribute to the chronicity of inflammatory diseases of the skin and, perhaps, of other organs.
See original publication No 3

A putative serine protease is required to initiate the RIPK3-MLKL-mediated necroptotic death pathway in neutrophils
Wang X, Avsec D, Obreza A, Yousefi S, Mlinarič-Raščan I, Simon HU
Adhesion receptors, such as CD44, have been shown to activate receptor interacting protein kinase-3 (RIPK3)-mixed lineage kinase-like (MLKL) signaling, leading to a non-apoptotic cell death in human granulocyte/macrophage colony-stimulating factor (GM-CSF) - primed neutrophils. The signaling events of this necroptotic pathway, however, remain to be investigated. In the present study, we report the design, synthesis, and characterization of a series of novel serine protease inhibitors. Two of these inhibitors, compounds 1 and 3, were able to block CD44-triggered necroptosis in GM-CSF-primed neutrophils. Both inhibitors prevented the activation of MLKL, p38 mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3'-kinase (PI3K), hence blocking the increased levels of reactive oxygen species (ROS) required for cell death. Although compounds one and three partially inhibited isolated human neutrophil elastase (HNE) activity, we obtained no pharmacological evidence that HNE is involved in the initiation of this death pathway within a cellular context. Interestingly, neither serine protease inhibitor had any effect on FAS receptor-mediated apoptosis. Taken together, these results suggest that a serine protease is involved in non-apoptotic CD44-triggered RIPK3-MLKL-dependent neutrophil cell death, but not FAS receptor-mediated caspase-dependent apoptosis. Thus, a pharmacological block on serine proteases might be beneficial for preventing exacerbation of disease in neutrophilic inflammatory responses.
See original publication No 4

Characterization of eosinophilic esophagitis variants by clinical, histological and molecular analyses: a cross-sectional multi-center study
Greuter T, Straumann A, Fernandez-Marrero Y, Germic N, Hosseini A, Yousefi S, Simon D, Collins MH, Bussmann C, Chehade M, Dellon ES, Furuta GT, Gonsalves N, Hirano I, Moawad FJ, Biedermann L, Safroneeva E, Schoepfer AM, Simon HU
OBJECTIVE: Physicians are increasingly confronted with patients presenting with symptoms of esophageal dysfunction resembling eosinophilic esophagitis (EoE), but absence of significant esophageal eosinophilia. The purpose of this study was to characterize and classify this group of EoE variants.
DESIGN: Patients from six EoE-centers with symptoms of esophageal dysfunction, but peak eosinophil counts of <60/mm^2 (<15/hpf) in esophageal biopsies and absence of gastroesophageal reflux disease (GERD) were included. Clinical, endoscopic, (immuno)-histological and molecular features were determined and compared with EoE, GERD and healthy controls.
RESULTS: We included 69 patients with EoE variants. Endoscopic abnormalities were found in 53.6%. We identified three histological subtypes: *EoE-like esophagitis* (36/69, 52.2%), *lymphocytic esophagitis* (14/69, 20.3%) and *non-specific esophagitis* (19/69, 27.5%). Immunohistochemistry revealed – in contrast to EoE – no significant increase in inflammatory cell infiltrates compared to GERD and healthy controls, except for lymphocytes in lymphocytic esophagitis. EoE-typical Th2-response was absent in all EoE variants. However, considerable structural changes were detected based on histology and protein expression. Using next generation mRNA sequencing, we found the three EoE variants to have distinct molecular fingerprints partially sharing pronounced traits of EoE. Sample clustering of RNA sequencing

data confirmed the presence of an EoE-like (characterized by eotaxin-3 expression), non-specific and lymphocytic variant cluster (characterized by CD3 cells and TSLP expression). CONCLUSION: All EoE variants are clinically and histologically active conditions despite the absence of esophageal eosinophilia. EoE variants appear to be part of a disease spectrum, where classical EoE represents the most common and apparent phenotype.
See original publication No 5

Original publications

1. Germic N, Hosseini A, Stojkov D, Oberson K, Claus M, Benarafa C, Calzavarini S, Angelillo-Scherrer A, Arnold IC, Müller A, Riether C, Yousefi S, **Simon HU**: ATG5 promotes eosinopoiesis but inhibits eosinophil effector functions. Blood. 137 (2021), 2958-2969.

2. Frangež Ž, Gérard D, He Z, Gavriil M, Fernández-Marrero Y, Seyed Jafari SM, Hunger RE, Lucarelli P, Yousefi S, Sauter T, Sinkkonen L, **Simon HU:** ATG5 and ATG7 expression levels are reduced in cutaneous melanoma and regulated by NRF1. Front Oncol. 11 (2021), 721624.

3. Klapan K, Frangež Ž, Markov N, Yousefi S, Simon D, **Simon HU:** Evidence for lysosomal dysfunction within the epidermis in psoriasis and atopic dermatitis. J Invest Dermatol. 21, 2838-2848.

4. Wang X, Avsec D, Obreza A, Yousefi S, Mlinarič-Raščan I, **Simon HU:** A putative serine protease is required to initiate the RIPK3-MLKL-mediated necroptotic death pathway in neutrophils. Front Pharmacol. 11 (2021), 614928.

5. Greuter T, Straumann A, Fernandez-Marrero Y, Germic N, Hosseini A, Yousefi S, Simon D, Collins MH, Bussmann C, Chehade M, Dellon ES, Furuta GT, Gonsalves N, Hirano I, Moawad FJ, Biedermann L, Safroneeva E, Schoepfer AM, **Simon HU**: Characterization of eosinophilic esophagitis variants by clinical, histological and molecular analyses: a cross-sectional multi-center study. Allergy, in press.

6. Germic N, Fettrelet T, Stojkov D, Hosseini A, Horn MP, Karaulov A, Simon D, Yousefi S, **Simon HU:** The release kinetics of eosinophil peroxidase and mitochondrial DNA Is different in association with eosinophil extracellular trap formation. Cells. 10 (2021), 306.

7. Frangež Ž, Seyed Jafari SM, Hunger RE, **Simon HU**: Loss of concurrent regulation of the expression of BIF-1, BAX, and Beclin-1 in primary and metastatic melanoma. Biochemistry (Mosc). 85 (2021), 1227-1234.

8. Schoepfer AM, Henchoz S, Biedermann L, Schreiner P, Greuter T, Reinhard A, Senn J, Franke A, Burri E, Juillerat P, **Simon HU**, Straumann A, Safroneeva E, Godat S: Technical feasibility, clinical effectiveness, and safety of esophageal stricture dilation using a novel endoscopic attachment cap in adults with eosinophilic esophagitis. Gastrointest Endosc. 21 (2021), 912-919.

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11. Holvoet S, Nutten S, Dupuis L, Donnicola D, Bourdeau T, Hughes-Formella B, Simon D, **Simon HU**, Carvalho RS, Spergel JM, Koletzko S, Blanchard C: Partially hydrolysed whey-based infant formula improves skin barrier function. Nutrients. 13 (2021), 3113.

12. Bruno A, Di Sano C, **Simon HU**, Chanez P, Patti AM, Di Vincenzo S, Dino P, D'Esposito V, Formisano P, Beguinot F, Pace E: Leptin and TGF-β1 Downregulate PREP1 Expression in human adipose-derived mesenchymal stem cells and mature adipocytes. Front Cell Dev Biol. 9 (2021), 700481.

Review articles and Editorials

1. **Simon HU:** The eosinophil and its role in physiology and disease: news and views. Semin Immunopathol. 43 (2021), 291-293.

2. Germic N, Hosseini A, Yousefi S, Karaulov A, **Simon HU:** Regulation of eosinophil functions by autophagy. Semin Immunopathol. 43 (2021), 347-362.

3. Gigon L, Yousefi S, Karaulov A, **Simon HU:** Mechanisms of toxicity mediated by neutrophil and eosinophil granule proteins. Allergol Int. 70 (2021), 30-38.

4. Fettrelet T, Gigon L, Karaulov A, Yousefi S, **Simon HU**: The enigma of eosinophil degranulation. Int J Mol Sci. 22 (2021), 7091.

5. Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cadwell K, Cecconi F, Choi AMK, Choi ME, Chu CT, Codogno P, Colombo MI, Cuervo AM, Deretic V, Dikic I, Elazar Z, Eskelinen EL, Fimia GM, Gewirtz DA, Green DR, Hansen M, Jäättelä M, Johansen T, Juhász G, Karantza V, Kraft C, Kroemer G, Ktistakis NT, Kumar S, Lopez-Otin C, Macleod KF, Madeo F, Martinez J, Meléndez A, Mizushima N, Münz C, Penninger JM, Perera RM, Piacentini M, Reggiori F, Rubinsztein DC, Ryan KM, Sadoshima J, Santambrogio L, Scorrano L, **Simon HU**, Simon AK, Simonsen A, Stolz A, Tavernarakis N, Tooze SA, Yoshimori T, Yuan J, Yue Z, Zhong Q, Galluzzi L, Pietrocola F: Autophagy in major human diseases. EMBO J. 40 (2021), e108863.

6. Klionsky DJ, Abdel-Aziz AK, Abdelfatah S, Abdellatif M, (…), **Simon HU**, (…): Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition)1. Autophagy. 17 (2021), 1-382.

7. Delemarre T, Bochner BS, **Simon HU**, Bachert C: Rethinking neutrophils and eosinophils in chronic rhinosinusitis. J Allergy Clin Immunol. 148 (2021), 327-335.

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11. Renz H, Bachert C, Berek C, Hamelmann E, Levi-Schaffer F, Raap U, **Simon HU**, Ploetz S, Taube C, Valent P, Voehringer D, Werfel T, Zhang N, Ring J: Physiology and pathology of eosinophils: Recent developments: Summary of the Focus Workshop Organized by DGAKI. Scand J Immunol. 93 (2021), e13032.

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Group Prof. Stephan von Gunten

Group members: Daniëlle Verschoor, PhD student
Marjolaine Claire Hugonnet, PhD student
Darien Toledo, PhD student
Giselle Hevia Hernandez, PhD student
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Mira Christen, Lab Technician
Jovana Jankovic, 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. Rollenske T, Burkhalter S, Muerner L, **von Gunten S**, Lukasiewicz J, Wardemann H, Macpherson AJ: Parallelism of intestinal secretory IgA shapes functional microbial fitness. Nature. 10 (2021), 657-661.

2. Girousi E, Muerner L, Parisi L, Rihs S, **von Gunten S**, Katsaros C, Degen M: Lack of IRF6 Disrupts Human Epithelial Homeostasis by Altering Colony Morphology, Migration Pattern, and Differentiation Potential of Keratinocytes. Front Cell Dev Biol. 9 (2021), e718066.

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4. Wang J, **von Gunten S**, Beldi G, Grandgirard D, Leib SL, Gottstein B: Digest the Sugar, Kill the Parasite: A New Experimental Concept in Treating Alveolar Echinococcosis. Pharmacology. 106 (2021), 3-8.

Review articles and Editorials

1. Hugonnet M, Singh P, Haas Q, **von Gunten S**: The Distinct Roles of Sialyltransferases in Cancer Biology and Onco-Immunology. Front Immunol. 9 (2021) e799861.

2. Lünemann JD, **von Gunten S,** Neumann H: Targeting sialylation to treat central nervous system diseases. Trends Pharmacol Sci. 42 (2021), 998-1008.

3. Cummings RD, **von Gunten S:** Targeting the Laminated Layer of Echinococcus multilocularis as a Potential Therapeutic Strategy. Pharmacology. 106 (2021), 1-2.

Group Prof. Shida Yousefi

Group members: Meike Claus, Lab Technician* (until Aug 2021)
Dr. Joanna Boros-Majewska, Lab Technician* (since Sept 2021)
Evelyne Kozlowski, Lab Technician*
Kevin Oberson, Lab Technician*
Dr. Nina Germic, Postdoctoral fellow* (until Feb 2021)
Shuang Peng, PhD student*
Yihe Chen, PhD student*
Lea Gigon, PhD student *
Aref Hosseini, PhD student*
Timothée Fettrelet, M.Sc. student* (until Aug 2021)
Timothée Fettrelet, PhD student* (since Oct 2021)
Apinya Chanwangpong, M.Sc. pharm. student
Lavrencic, Marusa, M.Sc. pharm. student* (Feb-Aug 2021)
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*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.

The release kinetics of eosinophil peroxidase and mitochondrial DNA Is different in association with eosinophil extracellular trap formation

Germic N, Fettrelet T, Stojkov D, Hosseini A, Horn MP, Karaulov A, Simon D, Yousefi S, Simon HU

Eosinophils are a subset of granulocytes characterized by a high abundance of specific granules in their cytoplasm. To act as effector cells, eosinophils degranulate and form eosinophil extracellular traps (EETs), which contain double-stranded DNA (dsDNA) co-localized with granule proteins. The exact molecular mechanism of EET formation remains unknown. Although the term "EET release" has been used in scientific reports, it is unclear whether EETs are pre-formed in eosinophils and subsequently released. Moreover, although eosinophil degranulation has been extensively studied, a precise time-course of granule protein release has not been reported until now. In this study, we investigated the time-dependent release of eosinophil peroxidase (EPX) and mitochondrial DNA (mtDNA) following activation of both human and mouse eosinophils. Unexpectedly, maximal degranulation was already observed within 1 min with no further change upon complement factor 5 (C5a) stimulation of interleukin-5 (IL-5) or granulocyte/macrophage colony-stimulating factor (GM-CSF)-primed eosinophils. In contrast, bulk mtDNA release in the same eosinophil populations occurred much slower and reached maximal levels between 30 and 60 min. Although no single-cell analyses have been performed, these data suggest that the molecular pathways leading to degranulation and mtDNA release are at least partially different. Moreover, based on these

data, it is likely that the association between the mtDNA scaffold and granule proteins in the process of EET formation occurs in the extracellular space.
See original publication No 1

Original publications

1. Germic N, Fettrelet T, Stojkov D, Hosseini A, Horn MP, Karaulov A, Simon D, **Yousefi S**, Simon HU: The Release Kinetics of Eosinophil Peroxidase and Mitochondrial DNA Is Different in Association with Eosinophil Extracellular Trap Formation. Cells. 10 (2021), 306.

2. Frangež Ž, Gérard D, He Z, Gavriil M, Fernández-Marrero Y, Seyed Jafari SM, Hunger RE, Lucarelli P, **Yousefi S**, Sauter T, Sinkkonen L, Simon HU**:** ATG5 and ATG7 Expression Levels Are Reduced in Cutaneous Melanoma and Regulated by NRF1. Front Oncol. 11 (2021), 721624.

3. Klapan K, Frangež Ž, Markov N, **Yousefi S**, Simon D, Simon HU**:** Evidence for Lysosomal Dysfunction within the Epidermis in Psoriasis and Atopic Dermatitis. J Invest Dermatol. 21, 2838-2848.

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5. Rohner MH, Thormann K, Cazzaniga S, **Yousefi S**, Simon HU, Schlapbach C, Simon D: Dupilumab reduces inflammation and restores the skin barrier in patients with atopic dermatitis. Allergy. 76 (2021), 1268-1270.

6. Wang X, Avsec D, Obreza A, **Yousefi S**, Mlinarič-Raščan I, Simon HU: A Putative Serine Protease is Required to Initiate the RIPK3-MLKL-Mediated Necroptotic Death Pathway in Neutrophils. Front Pharmacol. 11 (2021), 614928.

7. Greuter T, Straumann A, Fernandez-Marrero Y, Germic N, Hosseini A, **Yousefi S**, Simon D, Collins MH, Bussmann C, Chehade M, Dellon ES, Furuta GT, Gonsalves N, Hirano I, Moawad FJ, Biedermann L, Safroneeva E, Schoepfer AM, Simon HU: Characterization of eosinophilic esophagitis variants by clinical, histological and molecular analyses: a cross-sectional multi-center study. Allergy, in press.

Review articles

1. Fettrelet T, Gigon L, Karaulov A, **Yousefi S**, Simon HU: The Enigma of Eosinophil Degranulation. Int J Mol Sci. 22 (2021), 7091.

2. Germic N, Hosseini A, **Yousefi S**, Karaulov A, Simon HU**:** Regulation of eosinophil functions by autophagy. Semin Immunopathol. 43 (2021), 347-362.

3. Ackermann M, Anders HJ, Bilyy R, Bowlin GL, Daniel C, De Lorenzo R, Egeblad M, Henneck T, Hidalgo A, Hoffmann M, Hohberger B, Kanthi Y, Kaplan MJ, Knight JS,

Knopf J, Kolaczkowska E, Kubes P, Leppkes M, Mahajan A, Manfredi AA, Maueröder C, Maugeri N, Mitroulis I, Muñoz LE, Narasaraju T, Naschberger E, Neeli I, Ng LG, Radic MZ, Ritis K, Rovere-Querini P, Schapher M, Schauer C, Simon HU, Singh J, Skendros P, Stark K, Stürzl M, van der Vlag J, Vandenabeele P, Vitkov L, von Köckritz-Blickwede M, Yanginlar C, **Yousefi S**, Zarbock A, Schett G, Herrmann M: Patients with COVID-19: in the dark-NETs of neutrophils. Cell Death Differ. (2021), 3125-3139.

4. Gigon L, **Yousefi S**, Karaulov A, Simon HU: Mechanisms of toxicity mediated by neutrophil and eosinophil granule proteins. Allergol Int. 70 (2021), 30-38.

Group Prof. Uwe Zangemeister-Wittke

Group members: Martin Erhardt, PhD student
Fabian Weiss, PhD student[1]

[1]Institute of Biochemistry, University of Zürich

Our research is dedicated to translational aspects of molecular oncology and tumor targeting using rationally engineered and pharmacologically improved fusion proteins and protein-drug conjugates. For tumor targeting we employ 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 proteins 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 established 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. Merten H, Brandl F, Zimmermann M, Schaefer JV, Irpinio L, Sand KMK, Nilsen J, Andersen JT, **Zangemeister-Wittke U**, Plückthun A: Half-life extension of efficiently produced DARPin serum albumin fusions as a function of FcRn affinity and recycling. Eur J Pharm Biopharm. 167 (2021), 104-113.

Group Prof. Manuel Haschke (Clinical Pharmacology)

Group members: Evangelia Liakoni, MD
Felix Hammann, MD, PhD
Rouholahnejad, Fereshteh, PhD
Vera van der Velpen, PhD
Verena Schöning, PhD
Charlotte Kern

Our research activites deal with questions reated to drug metabolism, clinical toxicology, pain treatment as well as the use of machine learning and modeling tools for the support of clinical trials. In a clinical study in healthy volunteers, the pharmacokinetics and pharmacodynamics of two different nicotine salt concentrations are carachterized and compared with standard free-base nicotine using an open vape pod system. In a subsequent SNF-financed trial in patients willing to stop cigarette smoking, the impact of the nicotine concentration on the efficacy of a nicotine salt vape pod system as smoking cessation tool is investigated. Another SNF project investigates the effect of paracetamol in patients treated with strong opioids using a double-blind drug withdrawal design. As part of the European Drug Emergency Network (EuroDEN) data on toxicity of recreational drugs and novel psychoactive substances is collected and analyzed at regular intervals. In the context of rising demand for ICU capacity during COVID-19 waves, machine-learning models were used to develop and validate a COVID-19 severity assessment score for patient triage at a tertiary care hospital. In a further set of projects, ivermectin is investigated in the framework of an endectocide-based malaria intervention field-trial in Africa.

Original publications

1. Bachmann F, Duthaler U, Meyer Zu Schwabedissen HE, Puchkov M, Huwyler J, **Haschke M**, Krähenbühl S: Metamizole is a Moderate Cytochrome P450 Inducer Via the Constitutive Androstane Receptor and a Weak Inhibitor of CYP1A2. Clin Pharmacol Ther. 109 (2021),1505-1516.

2. Banholzer, S., L. Dunkelmann, **M. Haschke**, A. Derungs, A. Exadaktylos, S. Krahenbuhl and E. Liakoni: "Retrospective analysis of adverse drug reactions leading to short-term emergency hospital readmission." Swiss Med Wkly 151(2021), w20400.

3. Blaser, L. S., U. Duthaler, J. Bouitbir, A. B. Leuppi-Taegtmeyer, E. Liakoni, R. Dolf, M. Mayr, J. Drewe, S. Krahenbuhl and **M. Haschke**: "Comparative Effects of Metamizole (Dipyrone) and Naproxen on Renal Function and Prostacyclin Synthesis in Salt-Depleted Healthy Subjects - A Randomized Controlled Parallel Group Study." Front Pharmacol 12 (2021), 620635.

4. Glinz, D., C. Blasi, A. Villiger, A. Meienberg, T. Socrates, O. Pfister, M. Mayr, **M. Haschke**, A. S. Vischer and T. Burkard: "Hemodynamic profiles in treatment-naive arte-

rial hypertension and their clinical implication for treatment choice: an exploratory post hoc analysis." J Hypertens 39 (2021), 1246-1253.

5. Preisig, D., F. Varum, R. Bravo, C. Hartig, J. Spleiss, S. Abbes, F. Caobelli, D. Wild, M. Puchkov, J. Huwyler and **M. Haschke**: "Colonic delivery of metronidazole-loaded capsules for local treatment of bacterial infections: A clinical pharmacoscintigraphy study." Eur J Pharm Biopharm 165 (2021), 22-30.

6. Scholz, I., E. Liakoni, F. Hammann, K. E. Grafinger, U. Duthaler, M. Nagler, S. Krahenbuhl and **M. Haschke**: "Effects of Hypericum perforatum (St John's wort) on the pharmacokinetics and pharmacodynamics of rivaroxaban in humans." Br J Clin Pharmacol 87 (2021), 1466-1474.

7. Vischer, A. S., G. M. Kuster, R. Twerenbold, O. Pfister, Q. Zhou, A. Villiger, M. Poglitsch, S. Krahenbuhl, M. Mayr, S. Osswald, **M. Haschke** and T. Burkard: "Influence of Antihypertensive Treatment on RAAS Peptides in Newly Diagnosed Hypertensive Patients." Cells 10 (2021), 534-546.

8. Wertli, M. M., J. S. Flury, S. Streit, A. Limacher, V. Schuler, A. N. Ferrante, C. Rimensberger and **M. Haschke**: "Efficacy of metamizole versus ibuprofen and a short educational intervention versus standard care in acute and subacute low back pain: a study protocol of a randomised, multicentre, factorial trial (EMISI trial)." BMJ Open 11 (2021), e048531.

9. Zerah, L., S. Henrard, I. Wilting, D. O'Mahony, N. Rodondi, O. Dalleur, K. Dalton, W. Knol, **M. Haschke** and A. Spinewine: "Prevalence of drug-drug interactions in older people before and after hospital admission: analysis from the OPERAM trial." BMC Geriatr 21(2021), 571.

Review articles

1. Liakoni E, Benowitz NL. Treatment of tobacco dependence: pharmacotherapy. In: ERS monograph, Supporting Tobacco Cessation, Educational Publications, (2021), 97-117.

2. Benowitz NL, St Helen G, Liakoni E. Clinical Pharmacology of Electronic Nicotine Delivery Systems (ENDS): Implications for Benefits and Risks in the Promotion of the Combusted Tobacco Endgame. J Clin Pharmacol. (2021), 18-36.

3. Benowitz NL, Liakoni E. Tobacco Use Disorder and Cardiovascular Health. Addiction. (2021), doi: 10.1111/add.15703. Epub ahead of print.

Case reports

1. Stutz US, Braun A, Zubler F, Vock C, Liakoni E. Rezidivierender Priapismus – unerwünschte Wirkung einer Therapie mit Neuroleptika. Schweiz Med Forum (2021), in press.

Additional Publications by PKI Members

Original publications

Spirk D, Sebastian T, Beer JH, Mazzolai L, Aujesky D, Hayoz D, Engelberger RP, Korte W, Kucher N, Barco S: Role of age, sex, and specific provoking factors on the distal versus proximal presentation of first symptomatic deep vein thrombosis: analysis of the SWIss Venous ThromboEmbolism Registry (SWIVTER). Intern Emerg Med. (2021), doi.org/10.1007/s11739-021-02878-7.

Zanchin C, Koskinas KC, Ueki Y, Losdat S, Häner JD, Bär S, Otsuka T, Inderkum A, Jensen MRJ, Lonborg J, Fahrni G, Ondracek AS, Daemen J, van Geuns RJ, Iglesias JF, Matter CM, **Spirk D**, Juni P, Mach F, Heg D, Engstrom T, Lang I, Windecker S, Räber L: Effects of the PCSK9 antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction: a serial, multivessel, intravascular ultrasound, near-infrared spectroscopy and optical coherence tomography imaging study-Rationale and design of the PACMAN-AMI trial. Am Heart J. 238 (2021), 33-44.

Barco S, Valerio L, Gallo A, Turatti G, Mahmoudpour SH, Ageno W, Castellucci LA, Cesarman-Maus G, Ddungu H, De Paula EV, Dumantepe M, Goldhaber SZ, Guillermo Esposito MC, Klok FA, Kucher N, McLintock C, Ní Áinle F, Simioni P, **Spirk D**, Spyropoulos AC, Urano T, Zhai ZG, Hunt BJ, Konstantinides SV: Global reporting of pulmonary embolism-related deaths in the World Health Organization mortality database: Vital registration data from 123 countries. Res Pract Thromb Haemost. 5 (2021), e12520.

Zanchin C, Ueki Y, Losdat S, Fahrni G, Daemen J, Ondracek AS, Häner JD, Stortecky S, Otsuka T, Siontis GCM, Rigamonti F, Radu M, **Spirk D**, Kaiser C, Engstrom T, Lang I, Koskinas KC, Räber L: In vivo relationship between near-infrared spectroscopy-detected lipid-rich plaques and morphological plaque characteristics by optical coherence tomography and intravascular ultrasound: a multimodality intravascular imaging study. Eur Heart J Cardiovasc Imaging. 22 (2021), 824-834.

Spirk D, Sebastian T, Barco S, Banyai M, Beer JH, Mazzolai L, Baldi T, Aujesky D, Hayoz D, Engelberger RP, Kaeslin T, Korte W, Escher R, Husmann M, Blondon M, Kucher N: Clinical Outcomes of Incidental Venous Thromboembolism in Cancer and Noncancer Patients: The SWIss Venous ThromboEmbolism Registry (SWIVTER). Thromb Haemost. 121 (2021), 641-649.

Sebastian T, Gnanapiragasam S, **Spirk D**, Engelberger RP, Moeri L, Lodigiani C, Kreuzpointner R, Barco S, Kucher N: Self-Expandable Nitinol Stents for the Treatment of Nonmalignant Deep Venous Obstruction. Circ Cardiovasc Interv. 12 (2020), e009673.

Review articles

Dalakas MC, **Spaeth PJ:** The importance of FcRn in neuro-immunotherapies: From IgG catabolism, FCGRT gene polymorphisms, IVIg dosing and efficiency to specific FcRn inhibitors. Ther Adv Neurol Disord. 14 (2021), 1756286421997381.

Wenger N, Sebastian T, Engelberger RP, Kucher N, **Spirk D:** Pulmonary embolism and deep vein thrombosis: Similar but different. Thromb Res. 206 (2021), 88-98.

Wuillemin WA, **Spirk D**, Jeanneret-Gris C, Meier B: Schweizer Expertenkommentare zu den ASH- und ESC-Guidelines für thromboembolische Erkrankungen. Schweiz Med Forum. 33-34 (2021), 563-565.

Nagler N, Asmis L, Gerber B, Ruosch S, **Spirk D**, Surbek D, Studt JD, Tsakiris DA, Wuillemin WA: Venöse Thromboembolie in Gynäkologie und Geburtshilfe. Schweiz Med Forum. 29-30 (2021), 503-508.

4.2. Congress Invitations

Prof. Hans-Uwe Simon
15th International Congress of Immunology and Allergy (ICIA-2021), Ahvaz (Iran); Jan. 27-29, 2021 (virtual):
Molecular mechanism of neutrophil extracellular traps.

61st Congress of the German Society of Pneumology (DGP 2021); June 2-5, 2021 (virtual):
Die Rolle des Eosinophilen als Biomarker für schweres Asthma.

61st Congress of the German Society of Pneumology (DGP 2021); June 2-5, 2021 (virtual):
Die Rolle von IL-5 bei eosinophilen Erkrankungen.

Year 2021 Working Conference on Eosinophil Disorders and Related Syndromes,
Vienna (A); Sept. 24-26, 2021:
Mechanisms underlying HES-related organ damage.

APAAACI 2021 International Conference, Taiwan; Oct. 15-17, 2021 (virtual):
Eosinophil extracellular DNA traps in skin diseases.

51st Annual Meeting of the Japanese Society for Cutaneous Immunology and Allergy (JSCIA), Tokyo (Japan); Nov. 26-28, 2021:
Recent advances in eosinophil biology.

Prof. Thomas Kaufmann
Virtually Dead, episode IV: Cancer and Cell Death, Nov. 12, 2021 (virtual meeting):
Regulation of BOK and its role in uridine metabolism.

Amity University Five Days Faculty Enrichment Programme (FEP) on “Cutting Edge Science in Cellular and Molecular Biomedicine”, July 30th, 2021 (virtual):
The multifaceted roles of the BCL-2 family member BOK.

PD Dr. Peter Späth
Virtual congress: eKININ, Annecy, France, June 8, 2021:
Concluding Remarks

4.3. Seminar Invitations

Prof. Hans-Uwe Simon
South Ural State Medical University, Chelyabinsk (Ru); June 6, 2021;
Guest of Prof. Ilya Dolgushin:
Neutrophil extracellular traps – molecular mechanisms and clinical relevance (webinar).

AstraZeneca AG, Bern (CH); June 9, 2021; guest of Dr. Claudio Schuoler:
The role of eosinophils in health and disease.

Department of Clinical Immunology and Allergology, Sechenov University, Moscow (Ru); June 12, 2021; guest of Prof. Alexander Karaulov:
The role of eosinophils in health and disease (webinar).

Department of Clinical Immunology and Allergology, Sechenov University, Moscow (Ru); June 12, 2021; guest of Prof. Alexander Karaulov:
Eosinophil effector functions and their regulation by autophagy (webinar).

Department of Clinical Immunology and Allergology, Sechenov University, Moscow (Ru); June 12, 2021; guest of Prof. Alexander Karaulov:
Pathogenesis and treatment of eosinophilic esophagitis (EoE) (webinar).

Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan (Ru); July 14,2021; guest of Prof. Albert Rizvanov:
The role of eosinophils in health and disease.

Brandenburg Medical School, Campus Neuruppin, Neuruppin (D);
Seminar series: Research is calling; Sept. 7, 2021; Gast von Prof. Charlotte Buhre:
Eosinophile und eosinophile Erkrankungen (Webinar).

Webinar GSK; Oct. 19, 2021; guest of Dr. Irene Wölfel:
Herkunft und Aufgaben der Eosinophilen.

Prof. Georgia Konstantinidou
Department of Biomedical Sciences, University of Lausanne, Lausanne (CH), March 17, 2021 (zoom meeting); guest of Prof. Bernhard Thorens:
Understanding KRAS-driven tumor biology.

Swiss Institute for Experimental Cancer Research (ISREC), EPFL, Lausanne (CH), July 6, 2021; guest of Prof. Freddy Radtke:
Insights into the lipid metabolic regulation of KRAS-driven tumors.

PD Dr. Peter Späth
Virtual educational meeting for ukraininan MDs organized by LLC ‘Biopharma’, Kyiv (UKR), February 23-24, 2021
Clinical use of plasma proteins.

4.4. Organization of Meetings and Courses

Prof. Hans-Uwe Simon
Symposium of the Swiss Society of Pharmacology and Toxicology (SSPT): Progress in Pharmacology - Therapy of eye diseases,
Bern (CH), Jan. 20, 2021.

20th III-Bern International Summer School,
Emmetten (CH), July 4-6, 2021.

Year 2021 Working Conference on Eosinophil Disorders and Related Syndromes (together with P. Valent, E. Hadzijusufovic and W.R. Sperr),
Vienna (A), Sept. 25-26, 2021.

International Workshop: mTOR complex I regulation by mitochondrial metabolism: implications for inflammation and cancer.
Bern (CH), Dec. 3-4, 2021.

Prof. Thomas Kaufmann
Co-organizer of 11th Swiss Apoptosis and Autophagy Meeting (SAAM),
Bern (CH) and online (hybrid), Sep 9-10, 2021.

Prof. Georgia Konstantinidou
Swiss Society for Pharmacology and Toxicology (SSPT) Spring Meeting 2021, Gene and Cell Therapy
Bern (CH) and online, April 15, 2021.

Prof. Stephan von Gunten
Swiss Society for Pharmacology and Toxicology (SSPT) Spring Meeting 2021, Gene and Cell Therapy
Bern (CH) and online, April 15, 2021.

4.5. Invited Chairperson at Congresses

Prof. Hans-Uwe Simon
Symposium of the Swiss Society of Pharmacology and Toxicology: Progress in Pharmacology – Therapy of Eye Diseases, Morning session;
Bern (CH), Jan. 20, 2021.

Year 2021 Working Conference on Eosinophil Disorders and Related Syndromes; Session VI: Clinical Immunology & Disease Heterogeneity;
Vienna (A), Sept. 24-26, 2021.

4.6. Referee Work for Peer-Reviewed Journals

Dr. Zhaoyue He
Cell Death Differ. Cell Death Dis.

Dr. Ziva Frangez

Cell Death Dis.
Int. Arch. Allergy Immunol.

Prof. Andrea Huwiler

Biochem. Pharmacol.
Biochim. Biophys. Acta
Br. J. Pharmacol.
Cellular Signaling
Cell. Physiol. Biochem
Clin. Chem. Lab. Med.
Eur. J. Pharmacol.
Frontiers in Pharmacology
Int. J. Mol. Sci.
J. Cell. Biochem.
J. Exp. Pharmacol. Ther.
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
Immunology and Cell Biology
Int. Arch. Allergy Immunology
Trends Cell Bioology
Int. Rev. Cell Mol. Biol.
Sci. Rep.
J. Hepatology
J. Molecular Cell Biology
J. Neuroscience
Methods
Molecular Cancer Therapeutics
Mol. Cell. Oncology
Oncogene
PLoS One
Hepatology

Prof. Georgia Konstantinidou

Cell Death Dis.
Oncotarget
Frontiers in Oncology
J Exp Clin Res
eLIFE
Cancer research
Cancers

Prof. Hans-Uwe Simon

Allergy
Apoptosis
Autophagy
Blood
FEBS J.
Eur. J. Acad. Dermatol. Venerol.
Eur. J. Immunol.
Cell Death Differ.
Cell Death Dis.
EMBO Rep.
J. Allergy Clin. Immunol.
J. Exp. Med.
J. Immunol.
Oncogene
Nat. Commun.
PLOS Biology
Sci. Adv.
Cell Rep.

PD Dr. Peter Späth

Neuroim**.** & Neuroinflam**.**
Neurotherapeutics

Dr. Bisera Stepanovska Tanturovska

Biochem. Pharmacol.
Eur. J. Cell Biol

Prof. Stephan von Gunten

ACS Chemical Biology
ACS Omega
Allergy
Am. J. Respir. Cell Mol. Biol.
Ann. Sports Med. Res.
Arch Immunol Ther Exp
Arch Toxicol
Arthritis Res. Ther.
Blood
BMC Biotech.
Cell Death Differ.
Cell Death Dis.
Cell Mol Immunol
Comput Biol Chem
Curr. Med. Chem.
Cytotherapy
FASEB
Frontiers Oncology
Frontiers Pediatrics
Gene Therapy
Glycoconj J
Glycobiol.
Immunol. Cell Biol.
Immunol. Lett.
Int Arch Allergy Immunol
Int. Immunopharm.
JACI pract
J. Allergy Clin. Immunol.
J. Clin. Invest.
J Invest. Dermatol
J. Immunol.
J. Immunotox.
Med. Inflamm.
Nat Chem Biol
Respiration
Oncotarget
Pathobiology
Pediatrics
PLoS Pathogens
PLoS One
PNAS
Respir. Res
Scientific Reports
Tuberculosis
Tumor biology

Prof. Shida Yousefi

Cell Biol. Int.
Cell Biochem. Biophys.
Cell Death Differ.
Cell Death Dis.
Eur. J. Immunol.
Exp. Lung Res.
Int. J. Mol. Sci.
J. Vasc. Intervent. Radiol.
J. Cell. Biochem.
Respir. Res.
Sci. Rep.
Int. J. Biochem. Cell Biol.
Thorax
Immunology

Prof. Manuel Haschke

Analytical Chemistry
British Jour. of Clin. Pharmacology
Basic & Clin. Pharmacology & Toxicology
J. Eur. Acad. Dermatol. Venerol.
Swiss Medical Forum
Clin. Infect. Dis.

PD Evangelia Liakoni

Brain Sciences
Case reports in Emergency Medicine
Clin. Toxicology
Drug and Alcohol Dependence
Life
Pharmaceutics
Pharmacology
Swiss Medical Forum
Toxicon

PD Felix Hammann

Scientific Reports
Frontiers in Pharmacology
Clinical Pharmacokinetics
Expert Opinion in Drug Discovery
Pharmacology
Swiss Medical Forum
J. of Medicinal Chemistry
Exp. Opinion on Drug Metab. and Toxic.

4.7. Referee Work for Grant Bodies

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

Prof. Thomas Kaufmann
Agence Nationale de la Recherche (ANR)
Austrian Science Fund (FWF)
German Research Foundation (DFG)
L'Oréal Österreich
National Science Centre Poland
Swiss Cancer League
Swiss National Science Foundation (SNF)

Prof. Hans-Uwe Simon
Swiss National Science Foundation (SNF)
Novartis Foundation
Swiss Cancer League
European Research Council (ERC)

Prof. Georgia Konstantinidou
European Research Council (ERC)
Bernese Cancer league

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

4.8. Awards

Prof. Hans-Uwe Simon
Doctor Honoris Causa of South Ural State Medical University
Chelyabinsk (Russia), June 2021

Dr. Bisera Stepanovska Tanturovska
Sphingolipid Club short talk award
Lysophospholipid and related Mediators FASEB Conference, July 2021

Dr. Kim Klapan
Prize for an excellent poster presentation
SSPT Spring Meeting, Bern (CH), April 2021

5. Administrative, Advisory, and Honorary Posts

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

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

Member of the Evaluation Committee, Postdoc mobility grants, Swiss National Science Foundation

President of the Commission Pharmacology/Physiology of the German Society of Nephrology (DGfN)

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

Member of the Editorial Board of the International Journal of Molecular Sciences

Collection Editor of the Topical Collection of "Sphingolipids in health and disease" in Int. J. Mol. Sci.; Section: Mol. Pharmacol.

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 Ethical Board, Cell Death and Differentiation, Cell Death and Disease, Cell Death and Discovery

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

Member of the Editorial Board, Frontiers in Cell and Developmental Biology - Cell Death and Survival

Member of the Editorial Board, International Archives of Allergy and Immunology

Member of the Editorial Board, Pharmacology

Coordinator for FACS, Fluorescence Microscope

Coordinator FPLC (Äkta)

Safety Officer PKI (GeSiBe)

Kevin Oberson
Biological Safety officer PKI (BSO)

Daniel Bachmann
Chemical Safety officer PKI (CSO)

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.

Secretary of the Swiss Society of Experimental Pharmacology (SSEP)

Associate Editor, Frontiers in Molecular and Cellular Oncology

Associate Editor, Biomedicines

Prof. Hans-Uwe Simon
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

Member of the board, EoE Foundation Switzerland

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)

Visiting-Professor, Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan (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

Core team member for preparing a “Measles Intravenous Immunoglobulin G Guideline” The team work resulted in the following publications becoming effective 1 January 2022:
Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) - EMA/CHMP/BPWP/94038/2007 Rev.5
Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) - EMA/CHMP/BPWP/94033/2007 rev. 4

Member of taskforce for the 2021 revision and update of the WAO/EAACI HAE guideline – delegated for the recommendations on „Nomenclature and diagnosis of HAE”

Member of the Scientific Board, 12th C1 Inhibitor Deficiency and Angioedema Workshop, Budapest, Hungary, June 3-6, 2021 (virtual conference)

Head Jury awarding the “Grant for Young Investigators”, 12th C1 Inhibitor Deficiency Workshop, Budapest, Hungary, June 3-6, 2021 (virtual conference)

Member of the Board, eKININ, Annecy, France, June 8, 2021 (virtual conference)

Prof. Stephan von Gunten
Editor-in-Chief, PHARMACOLOGY, International Journal of Experimental and Clinical Pharmacology, Karger Publishers, Basel, Switzerland

Past-president and Board Member 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

Coordinator library at the PKI

Prof. Shida Yousefi
Coordinator for Radioactive Work,

Coordinator of confocal Microscopy

Coordinator of imaging analysis

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

PD Evangelia Liakoni
Executive Committee member of the Swiss Society of Clinical Pharmacology and Toxicology (SSCPT)

Scientific and Meetings Committee member European Association of Poisons Centres and Clinical Toxicologists (EAPCCT)

Swiss Society of Clinical Pharmacology and Toxicology (SSCPT) Delegierte FMH-Gutachterstelle

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

PD Felix Hammann
Grand Ormond Street Hospital for Children, London

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, and LSM 800, 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, FACSVerse 8 color Flow Cytometer instruments and FACSLyric able to detect up to 12 col-ors. A service is provided for analyzing potential pathogenic mechanisms of eosinophilic disorders and other inflammatory diseases. Monitoring of patients under immunomodulatory therapy is also included. The costs are currently covered by research grants of the coordinator (Prof. H.-U. Simon, FAMH Clinical Immunology), who can also be consulted for scientific support. Usage of the flow cytometer by non-members of the institute within collaborative projects is also possible.

7. Public Work

7.1. Bürgi prize

Our institute donates the Bürgi Prize, which rewards the best original publication addressing a problem in the fields of Experimental or Clinical Pharmacology every other year. The applicant should be first author of the publication and not older than 35 years.

The prize winner in 2021 was

Dr. Dasha Nelidova, University of Basel, for her work:

“Restoring light sensitivity using tunable near-infrared sensors”.

Dr. Nelidova presented a public lecture on July 13, 2021, in the seminar room of our institute.

8. Sponsors

8.1. Research Grants

Dr. Faik Imeri
Swiss National Science Foundation (grant No. 310030_175561)

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

Prof. Thomas Kaufmann
Swiss National Science Foundation (grant No 31003A_173006)
Swiss National Science Foundation (grant No 310030_201199)
Innosuisse-Swiss Innovation Agency; co-applicant, # 52202.1 IP-LS

Prof. Georgia Konstantinidou
Swiss National Science Foundation, SNF-Professorship until July 2020 (grant No. PP00P3_163929) and 2-year prolongation from August 2020 (grant No. PP00P3_194810)
Novartis Foundation for Biological-Medical Research, Novartis, Basel (CH)
Innosuisse-Swiss Innovation Agency #40922.1 IP-LS
Swiss Cancer League (KFS-5115-08-2020)

Prof. Hans-Uwe Simon
Swiss National Science Foundation (grant No. 310030_184816)
GSK Switzerland Pharma, Münchenbuchsee, Switzerland
EoE Foundation, Olten, Switzerland
Russian Government Program “Recruitment of the Leading Scientists into the Russian Institutions of Higher Education”

Prof. Stephan von Gunten
Swiss National Science Foundation (Grant No. 310030_184757/1)
Swiss Cancer League (KFS-4958-02-2020)
Bern Center for Precision Medicine (BCPM) Grant

Prof. Shida Yousefi
Swiss National Science Foundation (grant No. 31003A_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 (32003B_189132 / 32003B_179346)

PD Dr. Evangelia Liakoni
Swiss National Science Foundation (32003B_189132), main applicant
Swiss National Science Foundation (32003B_201072/1) main applicant
CTU-Forschungsgrant (2019-06), main applicant
Batzebär Fondskommission, Kinderkliniken Bern (co-applicant)

PD Dr. Felix Hammann
Broad One Health Endectocide-based Malaria Intervention in Africa (BOHEMIA, unitaid.org)

8.2. Meetings

Swiss Society of Pharmacology and Toxicology (SSPT): Progress in Pharmacology – Progress in Pharmacology, Therapy of eye diseases; Bern (CH), Jan. 20, 2021
Bayer (Schweiz) AG, Zürich
Novartis Pharma Schweiz AG, Rotkreuz
Théa PHARMA S.A. (Schweiz), Schaffhausen
Pharma Medica (together with Mediconsult), Roggwil
Mediconsult AG, Roggwil
Haag-Streit AG, Köniz

20th III-Bern International Summer School
Seminarhotel Seeblick, CH 6376 - Emmetten, July 4 – 6, 2021
Carl Zeiss AG, Feldbach
Medizinische Fakultät, Universität Bern
Mycrosynth AG, Balgach
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)
GSK, Münchenbuchsee

8.4. Travel Support

No travel support in 2021.

8.5. Other Support

Bürgi Fonds Seminar series of the institute and Bürgi prize.