UNIVERSITÄT BERN

DEPARTMENT FOR BIOMEDICAL RESEARCH
www.dbmr.unibe.ch

Jahresbericht Annual Report 2018

Contact
Basak Ginsbourger
Administrator
Department for BioMedical Research
University of Bern
Murtenstrasse 35
3008 Bern
Switzerland

Phone: +41 31 632 3552
Fax: +41 31 632 0946
Email: basak.ginsbourger@dbmr.unibe.ch

A copy of this report can be obtained online at:
www.dbmr.unibe.ch

Cover:
Organoids
Image: PD Dr. Marianna Kruithof-de Julio

Contents


LIEBHERR
SBB CFF FFS

Foreword – Director's Report

Synergy and team science are increasingly important in biomedical research. Biomedical research has moved from single laboratory science to team science approaches. This is in part due to the high level of complexity and specialization now required to be internationally competitive. Team science is being increasingly recognized by granting organizations with awards like the SNF Sinergia and ERC Synergy, requiring groups of complementary laboratories coming together to address important gaps in science. With the opening of the new research building at Murtenstrasse 24 in autumn 2021, the DBMR leadership is taking the opportunity to reorganize our research groups geographically to boost collaboration and synergy. The new space provides opportunities for placing groups together, both in the new building and through openings in existing DBMR lab space.

To this end, we are encouraging research groups to propose thematic clusters that would help improve synergy. We estimate that a cluster will consist of 2–4 research groups, corresponding to 20–60 persons. A cluster will share lab space, for example 1–3 labs of 125 m^2 each at Mu24 or a similar amount of lab space in one of the other DBMR research buildings. Bringing groups with common research interests together as a cluster should also facilitate the application for larger, high-impact external grants (e.g., SNF SINERGIA, ERC, H2020). We also imagine that the juxtaposition of cluster laboratories will create an outstanding environment for trainees to share knowledge and technical skills. We held an informational session about the Mu24 building and the planned future development of the DBMR buildings and facilities at the Langhans Auditorium on June 18, 2019. There was good attendance and we went through some examples of potential cluster ideas.

We are asking interested groups to make formal proposals and to designate one person as the cluster contact PI, who will represent the cluster in discussions related to location, needed infrastructure, and space. We recognize that this call is only relevant to some groups. Others may have good reasons not to become part of a research cluster. The complete application deadline is September 1st, 2019. All instructions are available on the DBMR website. Cluster applicants will meet with DBMR leadership in person in September and final decisions will be made in October 2019.

I hope that the opportunities to develop new scientific configurations will inspire our membership to make ambitious plans. We are excited to see what our biomedical scientists will propose to help close gaps in clinical care and translational and basic science.

"If you want to build a ship, don't drum up people to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea."
Antoine de Saint-Exupéry

The DBMR at a Glance

The Department for BioMedical Research (DBMR) is a research department of the Faculty of Medicine at the University of Bern.

It was founded in 1994 with the mission to provide the best possible environment and infrastructure to researchers at the Inselspital, Bern University Hospital and at the Faculty of Medicine. In 2018, 48 independent research groups, covering almost all fields of biomedical research, were affiliated with the DBMR.

The DBMR aims to bridge laboratory-based biomedical and patient-oriented clinical research through the scientific support of its groups and by operating state-of-the-art Technology Core Facilities and specialized Animal Core Facilities. In addition, a strong emphasis is put on the development of translational approaches and the use of omics technologies.

Das DBMR auf einen Blick

Das Department for BioMedical Research (DBMR) ist ein Forschungsdepartement der Medizinischen Fakultät der Universität Bern.

Es wurde 1994 mit dem Auftrag gegründet, Forschenden vom Inselspital, Universitätsspital Bern und von der Medizinischen Fakultät eine optimale Infrastruktur zur Verfügung zu stellen. Im Jahr 2018 waren 48 unabhängige Forschungsgruppen dem DBMR angeschlossen, die zusammen fast alle Bereiche der biomedizinischen Forschung abdecken.

Ziel vom DBMR ist es, Brücken zu schlagen zwischen laborbasierter biomedizinischer und patientenorientierter klinischer Forschung. Erreicht wird dies durch die wissenschaftliche Unterstützung seiner Forschungsgruppen, sowie den Betrieb von, dem neusten Stand der Technik entsprechenden, Technologie und spezialisierten Tier Core Facilities. Ausserdem wird ein starkes Gewicht auf die Entwicklung von translationellen Ansätzen und der Anwendung von Omics-Technologien gelegt.

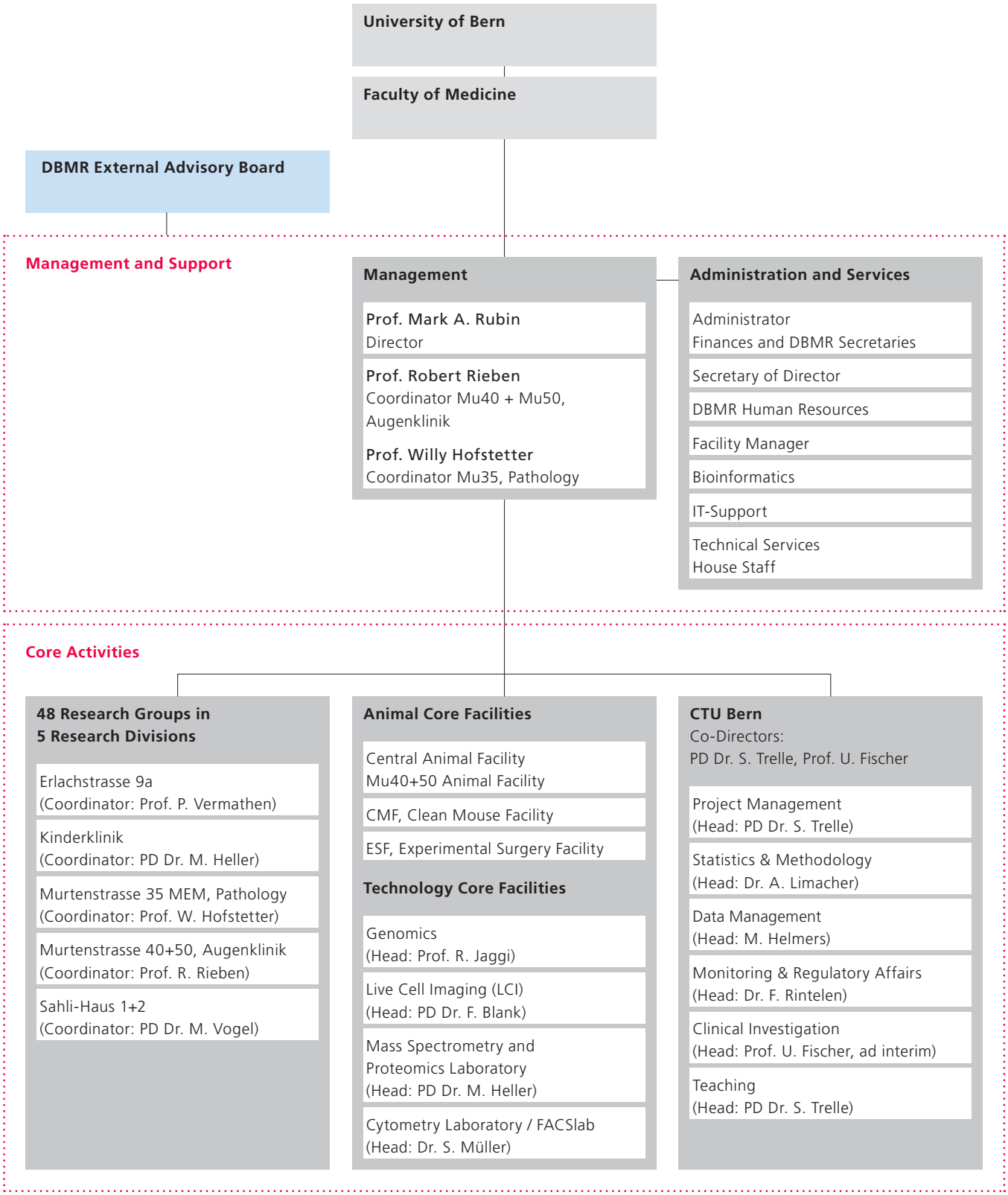
Organisation

The role of the DBMR is to provide optimal infrastructure and scientific support to its research groups, of which there were 48 at the end of 2018. The vast majority (43) of these groups are from clinics at the Inselspital, Bern University Hospital. The remainder (5) are internal DBMR groups, involved in the scientific support and coordination of equipment and infrastructure daily. The 48 groups are divided into five research divisions. Equally importantly, the DBMR is responsible for operating Technology and Animal Core Facilities. Furthermore, department groups are supported by central services responsible for administration, facility management, technical support, informatics, and bioinformatics.

The External Advisory Board evaluates the overall strategies and operation of the DBMR.

Organigram

Department for BioMedical Research



1

M.E. Müller-Haus
Murtenstrasse 35

2

Murtenstrasse 50

3

Pathologie
Murtenstrasse 31

4

Kinderklinik
Freiburgstrasse 15

5

Sahli-Haus 1
Freiburgstrasse 14a

6

Sahli-Haus 2
Freiburgstrasse 14

7

Augenklinik
Freiburgstrasse 8

8

Murtenstrasse 40

9

Erlachstrasse 9a

10 Murtenstrasse 24
(under construction)

Key People

Management

Prof. Dr. Mark A. Rubin
Director

Prof. Dr. Robert Rieben
Coordinator Murtenstrasse 40+50, Augenklinik

Prof. Dr. Willy Hofstetter
Coordinator Murtenstr. 35 MEM, Pathology

External Advisory Board

Prof. Dr. Gisou van der Goot
EPF Lausanne (CH)

Prof. Dr. Paul Klenerman
University of Oxford (UK)

Prof. Dr. Karl Schaller
University of Geneva (CH)

Prof. Dr. Radek Skoda
University of Basel (CH)

Administration and Central Services

Administrator/Finances and DBMR Secretaries

Basak Ginsbourger, Administrator
Deborah Re, Secretary
Marla Rittiner, Secretary
Beatrix Stalder, Secretary
Uyen Vo, Secretary

Secretary of Director

Claudia Requeta
Jasmine Stiefel

DBMR Human Resources

Silvia Rösselet
Marla Rittiner

Facility Manager

Bernhard Grossniklaus

Occupational Safety, Health Protection and Environmental Safety (OHE)

François Achermann

IT-Support

Michael Ackermann
Thomas Späti
Luca Sulmoni

Bioinformatics

Dr. Irene Keller
Ilker Romann

Technical Services

Patrick Furer, Head DBMR Maintenance

Coordinators of Research Divisions

PD Dr. Manfred Heller
Kinderklinik

Prof. Dr. Willy Hofstetter
Murtenstrasse 35 MEM, Pathology

Prof. Dr. Robert Rieben
Murtenstrasse 40+50, Augenklinik

Prof. Dr. Peter Vermathen
Erlachstrasse 9a

PD Dr. Monique Vogel
Sahli-Haus 1+2

Heads of Core Facilities

PD Dr. Fabian Blank
Live Cell Imaging (LCI)

PD Dr. Manfred Heller
Mass Spectrometry and Proteomics Laboratory

Prof. Dr. Rolf Jaggi
Genomics

Dr. Stefan Müller
Cytometry Laboratory / FACSlab

Cytometry Laboratory / FACSlab

Dr. Stefan Müller
stefan.mueller@dbmr.unibe.ch

Studies in microbiology at University of Bern; PhD (1996). Postdoc (2000–2001) in intestinal mucosal immunology and Head, Flow Cytometry Laboratory (2001), School of Cellular and Molecular Medicine, University of Bristol (UK). Senior Scientist in gastroenterology (2004–2011) at DBMR. Since 2010, Head, DMBR Cytometry Laboratory / FACSlab Core Facility.

Achievements 2018

In 2018, the FACS Lab elaborated a new pricing plan with the help of the DBMR administration. This plan is in line with the new SNSF regulations. By the end of the year, it was acknowledged by the "Ausschuss Forschung" of the medical faculty. The new prices will be charged starting on January 1st, 2019. They represent a better match with the value of the FACS Lab services.

The MoFlo ASTRIOSEQ high-speed 6-way and BSL2-certified cell sorter gained wide acceptance in the scientific community. In 2018, it performed the second most sorting hours of our four high-speed sorters, though it was the least frequently requested in 2017.

All BD FACS ARIA cell sorters were upgraded with additional detectors for the violet laser. Up to six of the increasingly popular Brilliant Violet (BV)-labelled antibodies can now be used simultaneously on these sorters as well.

Performance Report 2018

Compared to 2017, FACS measurements and cell sorting increased by 6% and 18%, respectively.

FACS measurements were performed to the exact same extent by researchers from Inselspital clinics and from University of Bern institutes.

Measurements by or for external parties made up less than 1%. Regarding cell sorting, 67.5% were performed for Inselspital clinics and 30.5% for university institutes, while 2% were performed for external parties. Exactly 50% of both measurements and cell sorts were performed by or for DBMR groups.

In 2018, three 2-ECTS-points-worth FACS courses for 12 participants each were successfully carried out.

The unchanged workforce and financially critical situation caused the FACS Lab difficulties in appropriately meeting important criteria such as regular and timely QC and technical, methodological, and scientific support. However, in December, we finally advertised for an 80% technician position, which will be occupied early in 2019.

Finances 2018

As in 2017, the heavily increased bill for the yearly FlowJo software license, together with several rather expensive repairs, resulted in a negative balance. Partial reimbursements for these licenses according to a new agreement will eventually correct this negative balance.

Outlook 2019

In 2019 the long awaited MultiMag and Enhanced Depth of Field Module upgrades for our Imaging Flow Cytometer will be installed. These are crucial upgrades for innovative research experiments with innovative methods, such as Flow-Fluorescence-In-Situ-Hybridization or asymmetric cell division measurements.

The FACS Lab's web page still needs to be redone; this is now planned for 2019. Similarly, the collaborative project with other Swiss FACS core facilities towards a modular and comprehensive FACS course had to be postponed and might now be tackled in 2019. In view of the expected improvement regarding human resources, we are optimistic and excited about implementing a number of planned, but thus far postponed projects, in addition to our website and the FACS course.

Staff Members

Dr. Stefan Müller, Head
Bernadette Nyfeler, Laboratory Technician and Operational Lead
Dr. Thomas Schaffer, Scientific and Educational Support, Technical Assistance
Dr. Claudio Vallan, Scientific and Educational Support

www.facslab.unibe.ch
www.dbmr.unibe.ch/services/core_facilities/cytometry_laboratory___facslab/index_eng.html

Live Cell Imaging (LCI)

PD Dr. Fabian Blank
fabian.blank@dbmr.unibe.ch

MSc in Cell Biology (2003) and PhD in Structural Biology (2006) at the University of Bern. Postdocs at the Institute of Anatomy, University of Bern (2007–2008) and the Telethon Institute for Child Health Research, Perth (AU) (2008–2009). Since 2009, Senior Scientist, Pulmonary Medicine (Adults), DBMR; since 2010, Commission Member, Microscopy Imaging Centre. Since 2012, Head, Live Cell Imaging (LCI) Core Facility, DBMR. Venia docendi (2016).

Achievements 2018

In 2018, the IncuCyte S3 Live-Cell Analysis System was introduced in the LCI Core Facility. This system allows fully automated long-term live visualization in phase contrast and fluorescence for cell cultures grown in multi-well plates, cell culture flasks, and petri dishes with simultaneous quantitative analysis of cell growth, differentiation, and migration. The microscope is located at Murtenstrasse 35 in room G802. Please contact Selina Steiner for more information regarding specific services and pricing.

Since its launch in 2012, the LCI Core Facility has been supported by the Microscopy Imaging Centre (MIC), an interfaculty platform that coordinates, prioritizes and supports funding applications in high-end microscopy, as well as organizing access to microscopy equipment for all members of the University of Bern.

Performance Report 2018

The total booked hours for using LCI equipment were 4,620 in 2018. These do not include systems that have to be booked on a daily basis, such as the IncuCyte S3 System or the Nikon Biostation CT. In 2018, the LCI staff spent a total of 159 hours for introduction trainings on LCI microscopes (170 hours in 2017). Working hours spent on collaboration with other research groups from the DBMR have increased to 672 (424 hours in 2017). Hours spent on technical assistance decreased to 181 (2017: 195). As in the years before, the facility contributed to the advanced microscopy lectures and practical modules organized by the MIC. A total of 11 students were trained in practical modules at the LCI in 2018.

Finances 2018

Revenues have increased only slightly compared to 2017. As in previous years, the facility has received a working credit of CHF 4,000 from the DBMR for general maintenance and repairs. Also, as in previous years, the LCI Core Facility has covered the yearly IMARIS software license fee for three floating licenses. The software is available for free for users of the facility and installed on the workstations that are available for booking.

Outlook 2019

Due to a significant increase in demand and importance, digital image processing and visualization and digital data handling in general will be in the focus of the coming year. The LCI Core Facility will provide personal training and specific courses for the use of dedicated software for interested users. Furthermore, funding for a new single-point confocal system as backup/replacement of the Zeiss LSM710 will be organized in the coming year.

Staff Members

PD Dr. Fabian Blank, Head
Carlos Wotzkow, Laboratory Technician
Selina Steiner, Laboratory Technician

www.lci.dkf.unibe.ch

Genomics (Core Facility) / Molecular Biology (Research Group)

Prof. Dr. Rolf Jaggi
rolf.jaggi@dbmr.unibe.ch

Studies and PhD (1982) at the University of Bern. Postdoc (1984–1988) at the Ludwig Institute for Cancer Research, Bern. Head of research group (1988–1996) at the Institute of Clinical and Experimental Cancer Research, Bern. Residence in the group of Prof. F. Martin, University College, Dublin (IE). Habilitation (1990); Professor (1996) at the University of Bern. Group Leader in DCR and then DBMR and Head of Genomics Core Facility 2011–2018. Retirement 2018.

Achievements 2018

Molecular Biology

We completed the collaboration with the University Hospital in Bern, the Department of Medical Oncology, Cantonal Hospital of Lucerne, and Masaryk University, Brno, Czech Republic, and submitted a manuscript to BMC Cancer Research, which is under revision for publication. The study is based on 132 human breast cancer specimens, 87 primary tumors, 20 of local recurrences (16 matched to primary tumors), and 25 of brain metastases (19 matched to primary tumors). Gene expression was measured, and molecular scores were determined for RISK, RS (recurrence score), EP (EndoPredict), and Risk of Recurrence (ROR) of PAM50, and PAM50. Clearly, the four molecular scores were strikingly similar, and none of them performed superior to the others. Primary tumors that would progress and lead to brain metastases had significantly higher scores than control tumors that remained recurrence-free. This was expected from various data from the literature. We also compared primary tumors that progressed by forming local recurrences with control tumors that remained recurrence-free. Interestingly, none of the four molecular scores discriminated between these two groups. In other words, primary tumors that progressed with local recurrences could not be discriminated from recurrence-free control tumors on the basis of the molecular scores. This seems to be in contradiction to some data in the literature that claims that occurrences of primary tumors with local recurrences are higher than primary tumors that do not recur. In fact, the discrepancy may be the result of a different classification for local recurrence: we used a rather narrow definition for local recurrence, while other reports also used "local" for recurrences in the chest wall. Our results reveal that there is still a lack of molecular parameters (scores) that allow for discrimination between primary breast cancer progressing as local recurrences and primary breast cancer that does not appear after regular treatment.

In the second project we used Crispr/Cas9 to develop several pools of cells that expressed reduced progesterone receptors (PR). The cell pools were termed PR-low. They were compared to original cells that were mock-transfected with an unrelated Crispr construct directed against a luciferase gene.

RNA-seq analyses were performed on three independent PR-low pools and control cells. The expression data from several thousand genes were carefully analyzed, and differentially expressed genes and pathways were identified. The data from this cell culture model were compared to publicly available gene expression data from PR-positive and PR-negative human breast cancer specimens. The level of PR is clinically relevant, as seen in PR-positive breast cancers, which have a better prognosis than PR-negative tumors. Our results will hopefully add some novel information thereby contributing to a better understanding of this complex disease. The results are being prepared for a manuscript.

www.gcf.dkf.unibe.ch
www.molbiol.dkf.unibe.ch

Performance Report 2018 / Outlook 2019

Genomics Platform

The Genomics Core Facility has offered support to individuals and groups from the Faculty of Medicine using next-generation sequencing and other technologies based on RNA and DNA. The Genomics Core Facility will be discontinued in 2019, but some technologies and the equipment will still be available to groups who want to use it.

Staff Members

Prof. Dr. Rolf Jaggi, Group Leader and Head of Genomics Core Facility group leader until the end of 2018
PD Dr. Heinz Keller, Neurologist (Inselspital)
Dr. Irene Keller, Bioinformatician (Core Facility)
Nathalie Schuster, Laboratory Technician (Research Group & Core Facility) until April 2018
Mariana Bustamante, PhD Student until July 2018, Research assistant from Aug to Oct 2018

Collaborators

Aebi S, Lucerne Cantonal Hospital (CH)
Popovici V, Masaryk University (CZ)

Publications

Krestel H, Meier JC. RNA Editing and Retrotransposons in Neurology. Front Mol Neurosci. 2018; 11:163. doi: 10.3389.

Bustamente Eduardo M, Popovici V, Imboden S, Aebi S, Ballabio N, Altermatt HJ, Günthert A and Jaggi R. Characterization of molecular scores and gene expression signatures in primary breast cancer, local recurrences and brain metastases. BMC Cancer Res (under revision).

Bustamente Eduardo M, Keller I, Schuster N, Aebi S and Jaggi, R. Analysis of the role of the progesterone receptor in breast cancer cells. (in preparation).

Mass Spectrometry and Proteomics Laboratory (Core Facility)

Protein and Cell Biology (Research Group)

PD Dr. Manfred Heller
manfred.heller@dbmr.unibe.ch

PhD in Biochemistry (1994) at University of Bern. Postdocs at University of Auckland (NZ) and Washington, Seattle (US). Return to Switzerland in 1999 to University of Geneva for one year as Senior Assistant, followed by three years as Senior Scientist at GeneProt Inc., Geneva and DiagnoSwiss, Monthey. Since 2003, Head of Proteomics and Mass Spectrometry Laboratory, a DBMR Core Facility since 2008. Twenty-one years of experience in mass spectrometry, proteomics, and bioinformatics.

Achievements 2018

Mass Spectrometry and Proteomics
As in recent years, the demand for our service was constantly high and we could assist in a variety of proteomics projects encompassing many different sample types collected from a variety of species. Our efforts to raise awareness about sample purity among our customers have obviously been successful, as much fewer column or ion source spoilings have occurred. We have made progress in acquiring mass spectrometry data with a data-independent approach and used it to participate in a round-robin challenge organized by ABRFAs every year, we would like to thank all customers for their trust in our service and their patience while waiting for results. A special thanks to all who responded to our questionnaire. The feedback received is generally very positive (see bar graph figure).

Finally, we had the pleasure of supervising a bioinformatics student during a four-week practical in summer and for her ongoing master's thesis. Her excellent work will help us to solve some long-standing bio-informatics bottlenecks.

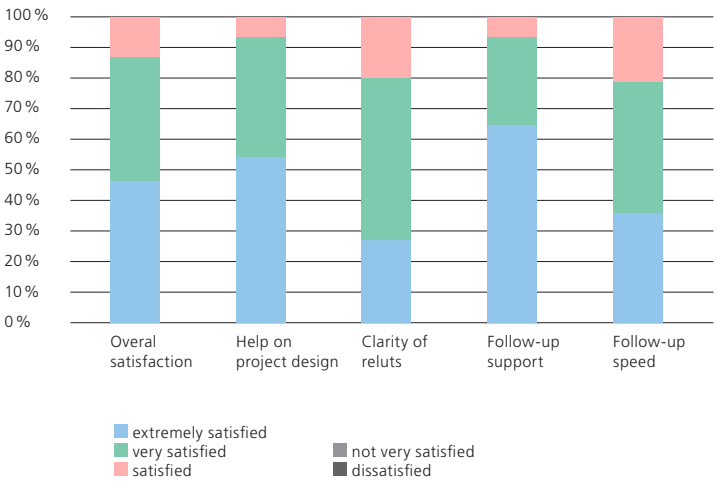
Protein and Cell Biology
We could successfully finalize the CTI project about grapevine red blotch virus quantification in grapevine tissues in form of a publication in Frontiers in Plant Science.

Furthermore, we continued our work to improve the purity of extracellular vesicles (EV) after isolation from human blood. We also finalized the data analyses on the influence the transport of blood has on the protein composition of EVs and are about to prepare a manuscript for publication.

Plans for 2019

We aim to 1) publish our work on EVs and the bioinformatic developments, 2) analyze the protein composition of circulating EV from about 20 MDS patients, and 3) develop a super-fast protein digestion protocol based on immobilized proteases in collaboration with INOFEA AG.

Questionnaire summary



www.pmscf.dkf.unibe.ch

Performance Report 2018

Mass Spectrometry and Proteomics
We processed around 1,450 samples during the year (-950 compared to 2017) submitted by laboratories from the Faculty of Medicine (27%), Faculty of Science (31%), the Vetsuisse Faculty (14%), external institutions (3%), and from developments for our customers and in favor of the core facility (15%). This related to about 3,325 LC-MS/MS runs, an average of 2.3 runs per sample compared to a factor of 1.5 in 2017. This increased factor indicates a proportional increase of samples for quantitative proteomics projects. Furthermore, we ran 573 QC standards and 3,002 blanks for quality assurance.

Finances 2018

Mass Spectrometry and Proteomics
Our financial situation profited from the fact that we often do maintenance work ourselves. However, we had to spend 110 kCHF on a software upgrade and the purchase of a nano-UPLC needed to fully integrate the RTC PAL with tandem mass spectrometry.

The facility received a working credit of CHF 10,000 from the DBMR for general maintenance and repairs.

Staff Members

PD Dr. Manfred Heller, Group Leader (Research Group) and Head (Core Facility)
François Achermann, Laboratory Technician (40% Core Facility & Research Group), DBMR Head of Occupational Safety, Health Protection and Environmental Safety (OHE)
Sophie Braga, Laboratory Assistant (Core Facility & Research Group)
Natasha Buchs, Laboratory Technician (Core Facility & Research Group)
Maïwenn Jornod, Master's student in bioinformatics (Core Facility & Research Group)
Ilker Yegit, IT Specialist (20% Core Facility)
Dr. Anne-Christine Uldry, Computational Scientist (80% Core Facility)

Collaborators

Böhm G, CTC Analytics AG (CH)
Bonadies N, University Hospital of Bern (CH)
Burgener M, Geistlich AG (CH)
Tiem A., Grether Y., INOFEA AG, Basel (CH)

Teaching activities

- MSc Biomedical Sciences: Tumour Biology – proteomics lecture
- MSc Biology: From Genomes to Metabolomes – proteomics lecture
- MSc in Bioinformatics: Mass Spectrometry to Systems Biology course

Publications

Basaco T, Pektor S, Bermudez JM, Meneses N, Heller M, Galván JA, Boligán KF, Schürch S, von Gunten S, Türler A, Miederer M. Evaluation of radiolabeled Girentuximab in vitro and in vivo. Pharmaceuticals. (2018) 132, doi: 10.3390/ph11040132.

Nasher F, Aguilar F, Aebi S, Hermans P, Heller M, Hathaway LJ. Peptide ligands of AmiA, AliA and AliB proteins determine pneumococcal phenotype. Frontiers in Microbiol. (2018) 9:3013.

Buchs N, Braga-Lagache S, Uldry A-C, Brodard J, Debonneville C, Reynard J-S, Heller M. Absolute Quantification of Grapevine Red Blotch Virus in Grapevine Leaf and Petiole Tissues by Proteomics. Frontiers in Plant Science. (2018) 9:1735, doi: 10.3389/fpls.2018.01735.

Pieróg J, Fytianos K, Tamò L, Simillion C, Taddeo A, Kocher G, Gugger M, Grodzki T, Heller M, Geiser T, Blank F, Gazdhar A, Schmid RA. Stem cell secretome attenuate acute rejection in rat lung allotransplantation. Interactive CardioVascular and Thoracic Surgery. (2018) 1-7, doi:10.1093/icvts/ivy306.

Jack T, Leuenberger M, Ruepp MD, Vernekar SKV, Thompson AJ, Braga-Lagache S, Heller M, Lochner M. Mapping the Orthosteric Binding Site of the Human 5-HT(3) Receptor Using Photo-crosslinking Antagonists. ACS Chem Neurosci. (2018), doi: 10.1021/acschemneuro.8b00327.

Taboada H, Meneses N, Dunn MF, Vargas-Lagunas C, Buchs N, Castro-Mondragon JA, Heller M, Encarnación S. Proteins in the periplasmic space and outer membrane vesicles of Rhizobium etli CE3 grown in minimal medium are largely distinct and change with growth phase. Microbiology. (2018), doi: 10.1099/mic.0.000720.

Nasher F, Förster S, Yildirim EC, Grandgirard D, Leib SL, Heller M, Hathaway LJ. Foreign peptide triggers boost in pneumococcal metabolism and growth. BMC Microbiol. (2018) 18:23.

Nasher F, Heller M, Hathaway LJ. Streptococcus pneumoniae Proteins AmiA, AliA, and AliB Bind Peptides Found in Ribosomal Proteins of Other Bacterial Species. Frontiers in Microbiol. 8:2688. (2018), doi:10.3389/fmicb.2017.02688.

Link to publication list:
www.pmscf.dbmr.unibe.ch/research/publications/

Bone Biology & Orthopaedic Research

Prof. Dr. Willy Hofstetter
hofstetter@dbmr.unibe.ch

MSc in Biochemistry at ETH Zurich; PhD in Biochemistry (supervisor Prof. N. Herschkowitz) at Children's Hospital, Inselspital. Postdoc at the University of Georgia (US). Then joined the Institute of Pathophysiology, University of Bern. Since 1997, Head, Bone Biology & Orthopaedic Research Group, DBMR.

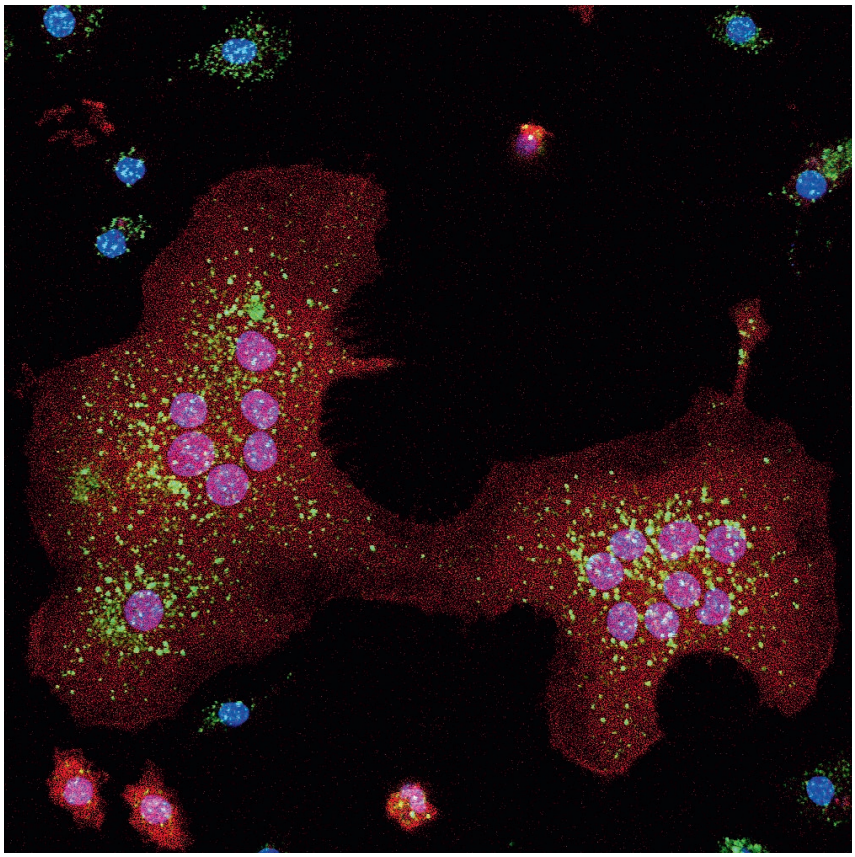
Research Highlights 2018 / Outlook 2019

Bone Biology & Orthopaedic Research Group

Highlights of our research on bone cell biology are described below:

- Iron is a major trace element with diverse functions and plays a part, among others, in oxidative phosphorylation and cellular energy metabolism. The finding that iron transporters are highly regulated during the development of osteoclasts in vitro initiated studies on the expression of iron transporters in conditions interfering with energy metabolism, including iron deficiency and low oxygen pressure. In normoxic conditions, iron deprivation and active mineral dissolution caused an increase in the expression of the iron uptake system. This was not the case under low oxygen pressure, where bone resorption was blocked and transcripts encoding iron transporters were not upregulated. Similarly, exposure to calcitonin, a potent inhibitor of osteoclast activity, prevented the elevation of iron transporter mRNA levels. In further studies, the roles of iron and oxygen in osteoclast activity, energy metabolism, and oxidative stress will be investigated (NCCR TransCure, PhD project R. Cabra).
- The studies on the healing of defects in osteoporotic bones under treatment with an anti-resorptive bisphosphonate (alendronate ALN) could be successfully concluded (PhD project Michel Hauser). The conclusions from these studies were that ALN indeed caused a delay in the healing of bone defects due to a block of the remodeling of the primary woven bone. Similarly, a CaP ceramic, used as filler for a large defect, was not turned over in the presence of ALN. The accruement of new bone, however, was not affected by the medication. In a next step, a transcriptome analysis will be performed to study the healing process of critical size defect filled with ßTCP in a mouse model (Alfred and Anneliese Sutter-Stöttner Foundation).
- Bone Morphogenetic Proteins (BMP) are used clinically to induce osteogenesis. Their activity in vivo, however, is impaired by endogenously synthesized antagonists, rendering them rather inefficient. Recent evidence suggests that the spectrum of biological effects of BMP antagonists is not limited to antagonizing BMP, but that they exert autonomous effects on bone cell lineage cells as well. Indeed, we found GM-CSF, an inflammatory cytokine and potent inhibitor of osteoclastogenesis, to be released by osteoblast-lineage cells in response to a challenge with BMP antagonists. The molecular base of the antagonists' actions on bone cells will be the focus of follow-up studies (in collaboration with PD Frank Klenke, the RMS Foundation and Clinic of Orthopaedic Surgery, and PhD project by Fatemeh Safari).
- Gadolinium is widely used as a contrast agent in radiologic diagnostics. Recently, it has become evident that Gd is stored in a multitude of tissues, including CNS and bone, but nothing is known about the potential cellular effects of long-term exposure. It will be the aim of this project to elucidate some aspects of the effects exerted by Gd on bone cell lineages (in collaboration with Dr. Rainer Egli, the Robert Mathys Foundation and support through a CTU Grant of the Inselspital).

www.bonebiology.dbmr.unibe.ch



Group Members

Prof. Dr. Willy Hofstetter, Group Leader
Silvia Dolder, Laboratory Technician
Mark Siegrist, Laboratory Technician
Romina Cabra, PhD Student
Michel Hauser, PhD Student
Fatemeh Safari, PhD Student

Clinicians with projects in the group
Dr. Rainer Egli, Project Leader
PD Dr. Frank Klenke, Project Leader

Collaborators

Bohner M, RMS Foundation (CH)
Bonny O, Universite de Lausanne, Lausanne (CH)
Engelhardt B, TKI, Bern (CH)
Fuster D, Inselspital (CH)
Iizuka T, Inselspital (CH)
Saulacic N, Inselspital (CH)
Seitz M, Inselspital (CH)
Siebenrock KA, Inselspital (CH)

Teaching Activities

- MSc Biomedical Engineering: Osteology course (Hofstetter)
- 3rd-year dentistry students: Pathophysiology
- Skeleton (Hofstetter)
- 1st-year medical students: Molecular biology practical courses (Hofstetter)
- 2nd-year medical students: Kidney block – Calcium and phosphate metabolism (Hofstetter)

Publications

Hauser M, Siegrist M, Denzer A, Saulacic N, Grosjean J, Bohner M, Hofstetter W (2018) Bisphosphonates reduce biomaterial turnover in healing of critical-size rat femoral defects. J Orthop Surg 26:1-10.

Moor M, Ramakrishnan SL, Legrand F, Dolder S, Siegrist M, Durussel F, Centeno G, Firsov D, Hynes NE, Hofstetter W, Bonny O (2018) Redox-dependent bone alkaline phosphatase dysfunction drives part of the complex bone phenotype in mice deficient for Memo1. JBMR Plus 2:195-205.

Hauser M, Siegrist M, Keller I, Hofstetter W (2018) Healing of fractures in osteoporotic bones in mice treated with bisphosphonates–a transriptome analysis. Bone 112:107-119.

Uster S, Coelho FM, Aeberli D, Stein JV, Hofstetter W, Engelhardt B, Seitz M (2018) TNFα blockade mediates bone protection in antigen-induced arthritis by reducing osteoclast precursor supply Bne 107:56-65.

Link to publication list:
www.bonebiology.dbmr.unibe.ch/research/publications/

Cardiovascular Research

Prof. Dr. Robert Rieben
robert.rieben@dbmr.unibe.ch

Studies in biology at the University of Bern; PhD in Immunology (1992). SNSF postdoc on xenotransplantation (1995–1997) in Leiden (NL). Return to Bern in 1997 to establish a research group. Habilitation (2002); Associate Professor (2007). Sabbatical in Melbourne (AU) in autumn/winter 2015/2016. Since 2005, Group Leader, Cardiovascular Research, DBMR.

Research Highlights 2018 / Outlook 2019

The clear 2018 research highlight of our group was the Nature publication of long-term survival of genetically modified pig hearts orthotopically transplanted into baboons. Based on two decades of continuous basic research into rejection mechanisms of xenografts our partners in Munich managed to achieve continuous success in life-supporting cardiac xenotransplantation in a very challenging pre-clinical model. This break-through was possible thanks to the use of genetically donor pigs which carry two human genes, the coagulation regulator thrombomodulin and the complement regulatory protein CD46. In addition, the major xenoantigen Gal-alpha 1,3-Gal has been knocked out in these pigs. Our group contributed to this work by analyzing tissue samples for activation of the innate immune system by immunofluorescence and quantitation of xenoreactive antibodies in the plasma of the baboons using FACS analysis. Also, our research into the effect of genetic modification of porcine endothelial cells on antibody- and complement mediated innate immune attack was important as a basis for this pre-clinical success.

Currently, in 2019, the research collaboration with the German xenotransplantation consortium TR127 continues. Our group will focus on the use of 3D endothelial cell culture using microfluidic systems in which the cells are exposed to near-physiological flow and shear stress conditions. This model was published in 2018 in Nature Scientific Reports and currently allows us to study the function of endothelial cells in vitro in a much better way than this was possible before with standard flat-bed cell culture. The effect of this model on 3R – reduce, refine, replace animal experiments – is evident in that we could completely stop our small animal models on ischemia/reperfusion injury for the time being. Our aim for 2019 and further is to test the effect of new sets of genetic modifications of porcine endothelial cells on activation of the cells mediated by complement and/or coagulation. Ideally, we should be able to test the effect of the genetic modifications, which can include a dozen or even more genes, before the respective pigs are cloned.

In the context of the currently running SNF project "Endothelial cell protection in ischemia / reperfusion injury: Investigation into the roles of the glycocalyx and the plasma cascade systems" we will also use the 3D microfluidic system for endothelial cell culture. The focus of this project lies on understanding the role of the endothelial cell glycocalyx as a scavenger of plasma proteins like antithrombin III, superoxide dismutase, C1-inhibitor and many others, which are important for the anticoagulant, anti-inflammatory and pro-fibrinolytic function of a healthy endothelium. Using labeled proteins and confocal laser scanning microscopy a 'protein-binding fingerprint' of endothelial cells shall be established and cells from different anatomical locations and/or exposed to different flow- and shear stress conditions compared.

www.cvrc.unibe.ch/research/ischemia___reperfusion/
www.dbmr.unibe.ch/research/research_groups/cardiovascular_research/index_eng.html

Group Members

Prof. Dr. Robert Rieben, Group Leader
Alain Despont, Laboratory Technician
Jane Shaw-Boden, Laboratory Technician
Uyen Vo, Secretary and Web Administrator
Marla Rittiner, Secretary
Dzhuliya Dzhonova, PhD Student until May 2018
Riccardo Sfriso, PhD Student until Nov 2018 and Postdoc since Dec 2018

Collaborators

Ayares D, Revivicor Inc (US)
Bovin N, Korchagina E, Russian Academy of Sciences, Moscow (RU)
Constantinescu MA, Olariu R, Inselspital (CH)
Cowan P, Bongoni A, St. Vincent's Hospital, Melbourne (AU)
Garweg J, Zandi S, Berner Augenklinik am Lindenhofspital, Bern (CH)
Guenat O, University of Bern (CH)
Heinis Ch, EPFL, Lausanne (CH)
Hofstetter W, University of Bern (CH)
Jenni HJ, Inselspital (CH)
Langelé B, Duisit J, Université Catholique de Louvain, Brussels (BE)
Mollnes T, Pischke S, Oslo University Hospital (NO)
Niemann H, Friedrich Loeffler Institut, Neustadt (DE)
Reichart B, Abicht J, Ludwig Maximilian University of Munich (DE)
Schnieke A, Fischer K, Technical University of Munich (DE)
Seebach J, Geneva University Hospital (CH)
Spirig R, CSL Behring AG (CH)
Vemula P, inStem (IN)
Vögelin E, Taddeo A, Inselspital (CH)
von Gunten S, Frias Boligan K, University of Bern (CH)
Waskow C, Technical University of Dresden (DE)
Wolf E, Klymiuk N, Bähr A, Ludwig Maximilian University of Munich (DE)

Teaching Activities

- MSc in Biomedical Sciences: Elective modules, 2 Master students (6 months internship each)
- Bachelor in Medicine: Elective course 33004 – Ihr Partner im Labor: Forschung auf den Gebieten Organtransplantation, Chirurgie und Herzinfarkt
- BSc in Life Sciences: Practical Course in Immunology, research internships
- MSc in Life Sciences: Lecture "Interactions of the Plasma Cascade Systems in Inflammation" (MOBIFLAM), 1 Master student (18 months internship)
- PhD students in Graduate School for Cellular and Biomedical Sciences: Immunology tutorial
- High school students: Patenschaften für Maturaarbeiten (6 students with 2-week lab stay each)

Publications

Garweg JG, Zandi S, Pfister I, Rieben R, Skowronska M, Tappeiner C. Cytokine profiles of phakic and pseudophakic eyes with primary retinal detachment. Acta Ophthalmol. 2018 Dec 18. DOI: 10.1111/aos.13998.

Zhang S, Shaw-Boden J, Banz Y, Bongoni AK, Taddeo A, Spirig R, Nolte MW, Cowan PJ, Rieben R. Effects of C1 inhibitor on endothelial cell activation in a rat hind limb ischemia-reperfusion injury model. J Vasc Surg. 2018 Dec;68(6S):209S-221S.e2. DOI: 10.1016/j.jvs.2017.10.072.

Längin M, Mayr T, Reichart B, Michel S, Buchholz S, Guethoff S, Dashkevich A, Baehr A, Egerer S, Bauer A, Mihalj M, Panelli A, Issl L, Ying J, Fresch AK, Buttgereit I, Mokelke M, Radan J, Werner F, Lutzmann I, Steen S, Sjöberg T, Paskevicius A, Qiuming L, Sfriso R, Rieben R, Dahlhoff M, Kessler B, Kemter E, Klett K, Hinkel R, Kupatt C, Falkenau A, Reu S, Ellgass R, Herzog R, Binder U, Wich G, Skerra A, Ayares D, Kind A, Schönmann U, Kaup FJ, Hagl C, Wolf E, Klymiuk N, Brenner P, Abicht JM. Consistent success in life-supporting porcine cardiac xenotransplantation. Nature. 2018 Dec;564(7736):430-433. DOI: 10.1038/s41586-018-0765-z.

Taddeo A, Tsai C, Vögelin E, Rieben R. Novel targeted drug delivery systems to minimize systemic immunosuppression in vascularized composite allotransplantation. Curr Opin Organ Transplant. 2018 Oct;23(5):568-576. DOI: 10.1097/MOT.0000000000000564.

Dzhonova D, Olariu R, Leckenby J, Dhayani A, Vemula PK, Prost JC, Banz Y, Taddeo A, Dzhonova D, Olariu R, Leckenby J, Dhayani A, Vemula PK, Prost JC, Banz Y, Taddeo A, Rieben R. Local release of tacrolimus from hydrogel-based drug delivery system is controlled by inflammatory enzymes in vivo and can be monitored non-invasively using in vivo imaging. PLoS One. 2018 Aug 30;13(8):e0203409. DOI: 10.1371/journal.pone.0203409.

Dzhonova D, Olariu R, Leckenby J, Banz Y, Prost JC, Dhayani A, Vemula PK, Voegelin E, Taddeo A, Rieben R. Local injections of tacrolimus-loaded hydrogel reduce systemic immunosuppression-related toxicity in vascularized composite allotransplantation. Transplantation 2018, Oct;102(10):1684-1694. DOI: 10.1097/TP.0000000000002283.

Sfriso R, Zhang S, Bichsel CA, Steck O, Despont A, Guenat OT, Rieben R. 3D artificial round section microvessels to investigate endothelial cells under physiological flow conditions. Sci Rep 2018, 8(1):5898. DOI 10.1038/s41598-018-24273-7.

Duisit J, Amiel H, Wüthrich T, Taddeo A, Dedriche A, Destoop V, Pardoen T, Bouzin C, Joris V, Magee D, Vögelin E, Harriman D, Dessy C, Orlando G, Behets C, Rieben R, Gianello P, Lengelé B. Perfusion-decellularization of human ear grafts enables ECM-based scaffolds for auricular vascularized composite tissue engineering, Acta Biomaterialia 2018, in press. doi: 10.1016/j.actbio.2018.04.009.

Abdelhafez MM, Shaw J, Wilbs J, Despont A, Rieben R. Improvement of a Closed Chest Porcine Myocardial Infarction Model by Standardization of Tissue and Blood Sampling Procedures. J Vis Exp 2018, (133), e56856. DOI 10.3791/56856.

Abicht JM, Sfriso R, Reichart B, Längin M, Gahle K, Puga Yung GL, Seebach JD, Rieben R, Ayares D, Wold E, Klymiuk N, Baehr A, Kind A, Mayr T, Bauer A. Multiple genetically modified GTKO/hCD46/HLA-E/hβ2-mg porcine hearts are protected from complement activation and natural killer cell infiltration during ex vivo perfusion with human blood. Xenotransplantation. 2018, e12390. DOI 10.1111/xen.12390.

Link to publication list:
www.cvrc.unibe.ch/research/ischemia___reperfusion/publications/

Precision Oncology

Prof. Dr. Mark A. Rubin
mark.rubin@dbmr.unibe.ch

Prof. Rubin is Director of the Department for Biomedical Research and heads the Bern Center for Precision Medicine. He is a leader in prostate cancer biology and cancer Precision Medicine. His landmark studies have defined many molecular features of prostate cancer and their involvement in disease progression. Many of his discoveries have been translated into applied clinical tests.

Research Highlights 2018 / Outlook 2019

Precision Oncology focusses on Precision Medicine approaches to understand mechanisms of prostate cancer progression and therapy resistance. In 2018, the group has successfully acquired more funds and initiated new projects. In 2019, the group will be developing additional research projects investigating the impact of epigenetic and epitranscriptomic events on gene regulation, particularly in the context of advanced prostate cancer.

1) **Swiss Oncology and Cancer Immunology Breakthrough Platform (SOCIBP).** This project co-lead by Holger Moch (UHZ), George Coukos (CHUV/UNIL), and Gunnar Rätsch (ETHZ) is funded by the Swiss government via SPHN/PHRT. It will provide important new tools for the Swiss and international research community for Precision Oncology and got well underway since May 2018.

2) **Understanding non-canonical phosphatidylinositol kinases in the maintenance of prostate metabolism.** In this SNSF and MSCA-funded project, we are exploring the function of a family of poorly understood lipid kinases, the type II phosphatidylinositol-5- phosphate 4-kinases (PI5P4Ks). We posit that PI5P4Ks control cellular metabolism, which could be pivotal in the regulation of prostate tissue androgen receptor signaling. In 2018 we have produced the first prostate-specific murine models to study PI5P4K.

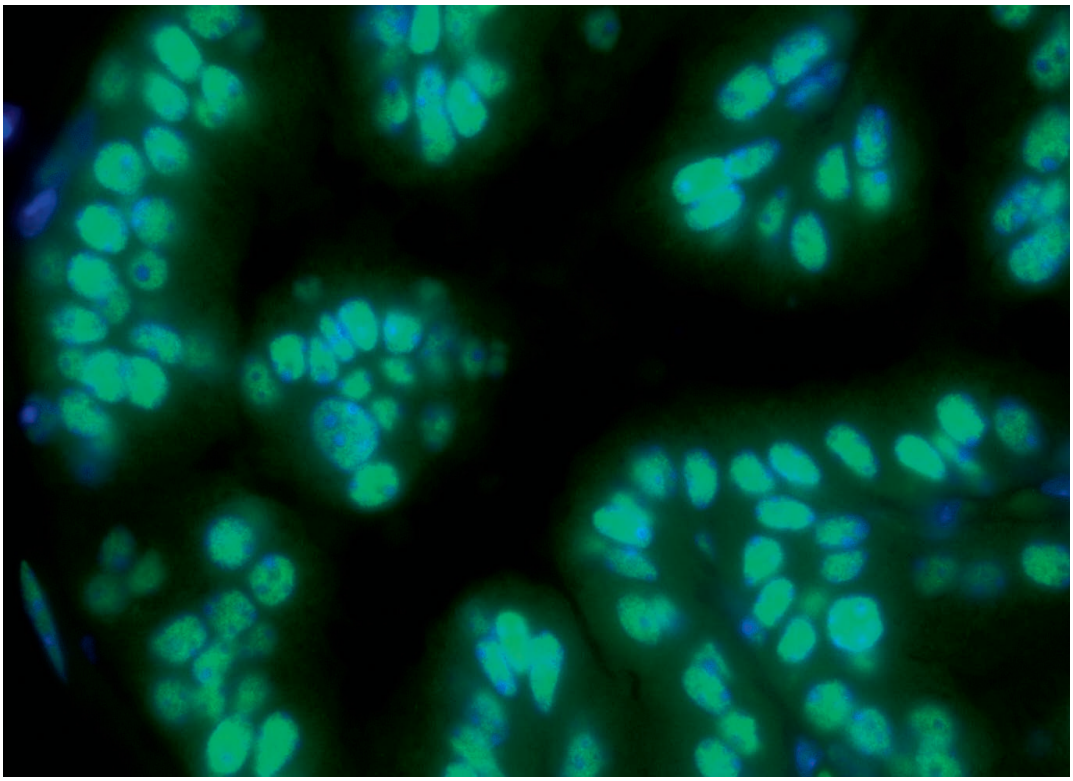
3) **Towards a precision therapy for SPOP mutant prostate cancer.** This project funded by the Swiss Krebsliga in collaboration with Ruedi Aebersold (ETHZ) focuses on the downstream effectors of speckle-type POZ protein (SPOP) by targeted proteomics, to help develop clinical biomarkers. Our overarching hypothesis is that SPOP mutant prostate cancer will respond distinctly to targeted therapy. Further areas of SPOP biology were supported by an NCI grant.

4) **Towards understanding and modulating neuroendocrine transdifferentiation in prostate cancer.** This project seeks to understand the lineage plasticity of neuroendocrine prostate cancer (NEPC), which will help create therapeutic approaches that can delay or inhibit this terminal form of prostate cancer and lead to earlier co-targeted therapies prior to disease progression.

5) **Role of m^6A methylation in post-transcriptional regulation and prostate cancer disease progression.** m^6A methylation of mRNAs alters transcript stability, translation efficiency, and patterns of alternative splicing. m^6A has recently been shown to regulate both expression and translation of oncogenes and tumor suppressors. This PCF-funded project aims to explore the role of m^6A modification of mRNAs in the context of prostate cancer, and its functional consequences for disease progression.

6) **Immune-radiation therapy for metastatic castration-resistant prostate cancer.** The aim of this PCF-funded project co-lead by George Coukos (CHUV) is to expand on current approaches to immuno-oncology and elucidate potential immunotherapeutic targets for metastatic prostate cancer.

www.rubinlab.unibe.ch



Group Members

Prof. Dr. Mark A. Rubin, Group Leader
Dr. Anke Augspach, Postdoctoral Fellow
Dr. Laura Brandt, Postdoctoral Fellow
Dr. Kellie Anne Cotter, Postdoctoral Fellow
Dr. Joanna Triscott, Postdoctoral Fellow
Dr. Stephan Christen, Lab Manager
Matthias Reist, Technician (since June)
Muriel Jaquet, Technician (since August)

Collaborators

Emerling B, Sanford Burnham Prebys Medical Discovery Institute (USA)
Aebersold R, ETH Zurich (CH)
Moch H, University of Zurich (CH)
Coukos G, University of Lausanne (CH)
Rätsch G, ETH Zurich (CH)

Selected Publications

Triscott J, Rubin MA. Prostate Power Play: Does Pik3ca Accelerate Pten-Deficient Cancer Progression? Cancer Discov. 2018 Jun; 8(6):682-685. PMID: 29858226

Puca L, Bareja R, Prandi D, Shaw R, Benelli M, Karthaus WR, Hess J, Sigouros M, Donoghue A, Kossai M, Gao D, Cyrta J, Sailer V, Vosoughi A, Pauli C, Churakova Y, Cheung C, Deonarine LD, McNary TJ, Rosati R, Tagawa ST, Nanus DM, Mosquera JM, Sawyers CL, Chen Y, Inghirami G, Rao RA, Grandori C, Elemento O, Sboner A, Demichelis F, Rubin MA, Beltran H. Patient derived organoids to model rare prostate cancer phenotypes. Nat Commun. 2018 Jun 19; 9(1):2404. PMID: 29921838

Hopkins BD, Pauli C, Du X, Wang DG, Li X, Wu D, Amadiume SC, Goncalves MD, Hodakoski C, Lundquist MR, Bareja R, Ma Y, Harris EM, Sboner A, Beltran H, Rubin MA, Mukherjee S and Cantley LC. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature. 2018 Aug; 560(7719):499-503. PMID: 30051890. Erratum in: Nature. 2018 Aug 29. Du Xing [corrected to Xing Du]

Demichelis F, Rubin MA. The Genomics of Prostate Cancer: A Historic Perspective. Cold Spring Harb Perspect Med. 2018 Apr 30. pii: a034942. PMID: 29712681 [Epub ahead of print]

Cotter K, Rubin MA. Sequence of events in prostate cancer. Nature 2018 Aug 24: 560(7720):557-559. PMID: 30143757. Comment

DBMR Research Groups

Forty-two research groups from departments of the Inselspital and other clinics were affiliated with the DBMR at the end of 2018. Below is a list of the groups. Five of the groups are featured on the following pages.

Anesthesiology
Prof. Dr. Frank Stüber, Dr. Christoph Lippuner, PD Dr. Martin Luginbühl, PD Dr. Andreas Vogt

Angiology
Prof. Dr. Iris Baumgartner

Audiology
Prof. Dr. Marco Caversaccio, Prof. Dr. Martin Kompis

Cardiology
Prof. Dr. Stephan Windecker, Prof. Dr. Paul Mohacsi, Prof. Dr. Christian Seiler, Prof. Dr. Stefano Rimoldi, Prof. Dr. Thomas Suter, Prof. Dr. Hildegard Tanner

Cardiovascular Surgery
Prof. Dr. Thierry Carrel, PD Dr. Sarah Longnus, PD Dr. Henriette Most

Clinical Radiopharmacy
Prof. Dr. Thomas M. Krause, Prof. Dr. Martin A. Walter

Cranio-Maxillofacial Surgery
Prof. Dr. Tateyuki Iizuka, Dr. Matthias Mottini, Dr. Benoît Schaller

Dermatology
Prof. Dr. Luca Borradori, Dr. Arnaud Galichet, Prof. Dr. Robert Hunger, Prof. Dr. Eliane J. Müller, Prof. Dr. Christoph Schlapbach, Prof. Dr. Dagmar Simon, Prof. Dr. Nikhil Yawalkar

Endocrinology / Diabetology (Adults)
Prof. Dr. Christoph Stettler

Endocrinology / Diabetology / Metabolism (Pediatrics)
Prof. Dr. Christa F. Flück, PD Dr. Jean-Marc Nuoffer, PD Dr. Amit V. Pandey

Endocrinology of the Breast
Prof. Dr. Petra Stute

Endometriosis and Gynecological Oncology
Prof. Dr. Michel D. Müller, Prof. Dr. Nick A. Bersinger, Dr. Thomas Andrieu

Endometrium & Ovary
Prof. Dr. Michael von Wolff

Experimental Hemostasis
Prof. Dr. Hans-Peter Kohler, PD Dr. Verena Schröder

Experimental Radiology
Prof. Dr. Johannes Heverhagen, Prof. Dr. Hendrik von Tengg-Kobligk

Gastroenterology/Mucosal Immunology
Prof. Dr. Andrew Macpherson, Dr. Stephanie Ganal-Vonarburg, Dr. Mercedes Gomez de Agüero

Hand Surgery
Prof. Dr. Esther Vögelin, Dr. Adriano Taddeo

Hematology (Adults)
Prof. Dr. Anne Angelillo-Scherrer, Prof. Dr. Gabriela Baerlocher, PD Dr. Elisabeth Oppliger Leibundgut, Prof. Dr. Johanna Kremer, Prof. Dr. Ramanjaneyulu Allam

Hematology/Oncology (Pediatrics)
Prof. Dr. Jochen Rössler

Hepatology
Prof. Dr. Jean-François Dufour, Prof. Dr. Annalisa Berzigotti, Prof. Dr. Andrea De Gottardi, Prof. Dr. Nasser Semmo, Dr. Guido Stirnimann

Human Genetics
Prof. Dr. Sabina Gallati, PD Dr. André Schaller

Intensive Care Medicine
Prof. Dr. Jukka Takala, Prof. Dr. Stephan Jakob

Magnetic Resonance Spectroscopy and Methodology, AMSM
Prof. Dr. Roland Kreis, Prof. Dr. Peter Vermathen

Nephrology and Hypertension
Prof. Dr. Bruno Vogt, PD Dr. Geneviève Escher, Prof. Dr. Daniel Fuster, Prof. Dr. Uyen Huynh-Do, Prof. Dr. Stephan Krähenbühl, Prof. Dr. Markus Mohaupt, PD Dr. Andreas Pasch, Prof. Dr. Dominik Uehlinger

Neurology
Prof. Dr. Claudio Basseti, Prof. Dr. Antoine Adamantidis, Prof. Dr. Kaspar Schindler, Prof. Dr. Arnold Marcel, Prof. Dr. Urs Fischer, PD Dr. Simon Jung, PD Dr. Michael Schüpbach, Prof. Dr. Matthias Sturzenegger, Prof. Dr. René Müri, Prof. Dr. Kai Rösler, Prof. Dr. Werner Z'Graggen, Prof. Dr. Kalla Roger, Prof. Dr. Andrew Chan, Prof. Dr. Roland von Känel, Prof. Dr. Saxena Smita

Neurosurgery
Prof. Dr. Hans-Rudolf Widmer

Oncology/Hematology (Adults)
Prof. Dr. Thomas Pabst, PD Dr. Katja Seipel

Ophthalmology
Prof Dr. Sebastian Wolf, Prof. Dr. Volker Enzmann, Prof. Dr. Martin Zinkernagel, PD Dr. Pascal Escher,

Orthopedic Surgery
Prof. Dr. Klaus-Arno Siebenrock, Prof. Dr. Marius Keel, Prof. Dr. Ernst B. Hunziker

Osteoporosis
Prof. Dr. Kurt Lippuner, Dr. Nahoko Shintani

Pediatric Surgery
Prof. Dr. Steffen Berger, PD Dr. Elizaveta Fasler-Kan

Plastic Surgery
Prof. Dr. Mihai Constantinescu

Prenatal Medicine
Prof. Dr. Daniel Surbek, PD Dr. Andreina Schoeberlein, PD Dr. Marc Baumann, PD Dr. Martin Müller

Pulmonary Medicine (Adults)
Prof. Dr. Thomas Geiser, Prof. Dr. Christophe von Garnier, Dr. Manuela Funke-Chambour

Pulmonary Medicine (Paediatrics)
Prof. Dr. Thomas Geiser, Prof. Dr. Philipp Latzin, Dr. Loretta Müller-Urech

Radiation Oncology
Prof. Dr. Daniel Aebersold, PD Dr. Yitzhak Zimmer, Dr. Michaela Medova, PD Dr. Kathrin Zaugg

Rheumatology
Prof. Dr. Peter M. Villiger, Prof. Dr. Martin Bachmann, Dr. Alexander Eggel, PD Dr. Frauke Förger, Dr. Stefan Kuchen, Prof. Dr. Burkhard Möller, Prof. Dr. Michael Seitz, Prof. Dr. Beat Trueb, Dr. Daniel Yerly

RNA & Cancer (NCCR RNA & Disease)
Prof. Dr. Rory Johnson

Thoracic Surgery
Prof. Dr. Ralph A. Schmid, Dr. Sean R.R. Hall, Dr. Thomas Marti, PD Dr. Ren-Wang Peng

Tumor-Immunology
Prof. Dr. Adrian Ochsenbein, PD Dr. Carsten Riether

Urology
Prof. Dr. George Thalmann, PD Dr. Marianna Kruithof-de Julio, Prof. Dr. Katia Monastyrskaya, Prof. Dr. Fiona C. Burkhard

Visceral and Transplantation Surgery
Prof. Dr. Daniel Candinas, PD Dr. Deborah Keogh-Stroka, PD Dr. Vanessa Banz Wüthrich, Prof. Dr. Guido Beldi, PD Dr. Lukas Brügger

Hematology (Adults)

SNF Prof. Dr. Ramanajneyulu Allam
allam.ramanjaneyulu@dbmr.unibe.ch

PhD (2010) at University of Munich (DE). Postdoc at University of Lausanne (2010–2014) and University of Bern (2014–2015). Since 2015, SNF Professor, Department of Hematology, Inselspital and Group Leader, Inflammation and Hematopoiesis, DBMR. Inflammation and Hematopoiesis.

Prof. Dr. Anne Angelillo-Scherrer
anne.angelillo-scherrer@insel.ch

MD at University of Geneva; FMH certification in Internal Medicine and Hematology (1999); Research fellowships in the field of fibrinolysis at the University of Lausanne and at the University of Geneva (1989–1991), at the Center for Transgene Technology and Gene Therapy, Flanders Interuniversity Institute for Biotechnology, Catholic University of Leuven (Belgium) (1998–2000); Attending Physician/Group Leader (2000–2005) at Division of Angiology and Hemostasis, University Hospitals Geneva. SNF Professor (2005–2011); Associate Professor (2011–2013); Director, Hemophilia Center and Hemostasis Laboratory (2005–2013), Lausanne University Hospital. Since 2013, Full Professor of Hematology and Chair, Department of Hematology, Inselspital; member of the National Research Council of the Swiss National Scientific Foundation and of the Swiss Academy for Medical Sciences since 2018. Mouse models of hematophysiology and hematopathology and their translation to human hematological disorders.

Research Highlights 2018 / Outlook 2019

Hematology research include the investigation of blood production, blood function and blood-related diseases. The mission of our department is to develop a competitive research program in basic, translational, and clinical research.

Inflammation and Hematopoiesis

This group focusses on investigating the relationship between hematopoiesis and inflammation. A paper published in 2018 showed that Ribonuclease Inhibitor (RNH1) is a new regulator in hematopoiesis and identified RNH1 as a ribosomal associated protein that regulates erythropoiesis by controlling the translation of erythroid transcription factor GATA1.

Mouse models of hematophysiology and hematopathology and their translation to human hematological disorders

This group found that targeting the anticoagulant protein S (PS) gene in hemophilic mice by silencing RNA protects them against bleeding. In hemophilia patients, blocking plasma PS restores coagulation. Thus, PS silencing RNA constitutes a new therapy concept for hemophilia. Further studies on PS and prohemostatic Gas6 as therapy targets are ongoing.

Targeted diagnostics in hematological malignancies

For AML patients in the Argenx study we established flow cytometric minimal residual disease (MRD) assessment and a novel molecular MRD approach integrating NGS. We improved flow cytometric MRD diagnostics for myeloma patients after autologous transplantation. Currently, this group is establishing the diagnostic workflow accompanying CAR-T therapy.

Hematopoiesis and molecular genetics

Telomere biology plays a major role in cellular replication and cancerogenesis. We studied mutations and family segregation in telomeropathies and their functional consequences. We investigate pathologic upregulation of telomerase in cancer, biomarkers and targeted treatments also based on a novel monocytic culture assay. Mechanisms to improve cellular therapies are explored (Candy Heberlein Prize 2018 to G. Baerlocher).

Personalized treatment for patients with myeloid malignancies

This group is performing translational and clinical research in patients with myeloid neoplasms. They are applying phosphoproteomics for inference of kinase activities as functional biomarkers to targeted treatment. The group leader is the coordinator of the Swiss MDS Study Group, the Swiss MDS Registry/Biobank as well as the "I-CARE for MDS" health-care project.

Hemostasis

This group focusses on ADAMTS13 and thrombotic thrombocytopenic purpura (TTP), a rare life-threatening disease due to a severe ADAMTS13 deficiency. The consequences of severe congenital ADAMTS13 deficiency are being studied in an international cohort study, the Hereditary TTP Registry. The second large topic in the study is the characterization of the pathogenic, ADAMTS13-specific autoimmune response in acquired TTP.

Epidemiology, laboratory medicine, vascular medicine, and bleeding disorders

Supported by the Swiss National Science Foundation, this group conducts studies investigating the performance of diagnostic tools, predictive measures, and monitoring instruments. The group

Prof. Dr. Vera Ulrike Bacher, MHBA
veraulrike.bacher@insel.ch

MD at the University of Tübingen (1997), specialization for Internal Medicine (2002) and Hematology/Medical Oncology (2005; Munich, Germany), Venia Docendi (2008) and Ausserplanmässige Professur (2012) at Hamburg University, Germany. Current position: Head Physician, Department of Hematology, Inselspital Bern, and Deputy Head of the Center of Laboratory Medicine (ZLM). Medical Leadership of Hematology Molecular Diagnostics. Associate Professorship, University of Bern (2016). FAMH Hematology (2017). MHBA, University Erlangen-Nürnberg (2015). Targeted diagnostics in hematological malignancies.

Prof. Dr. Gabriela M. Baerlocher
gabriela.baerlocher@insel.ch

MD (1990) at University of Bern; FMH and FAMH certification (1999, 2002). Postdoc at University of Southern California, Los Angeles (US) (1991–1992) and Terry Fox Institute, Vancouver (CA) (1999–2002). Venia docendi (2006). Since 2005, Head, Clinical Stem Cell Laboratory. Associate Professor (since 2010), Department of Hematology, Insel AG and Board member of the Swiss Group of Clinical Cancer Research. Hematopoiesis and molecular genetics.

PD Dr. Nicolas Bonadies
Nicolas.Bonadies@insel.ch

MD at University of Bern (2002); Postdoctoral fellowship at Cambridge University (UK) (2007–2009). FMH certification in Internal Medicine/Hematology (2005/2012). FAMH certification in Hematology Laboratory Analyses (2014). Venia Docendi (2017). Since 2015 Head of the MDS Centre of Excellence, since 2018 Senior Attending Physician and Head of the Clinical Study Management, Patient Registries and Biobank UKH-HZL. Personalized treatment for patients with myeloid malignancies.

aims to improve care in patients with thromboembolic and bleeding disorders with a focus on heparin-induced thrombocytopenia, anticoagulation treatment, and secondary prevention of venous thromboembolism.

Long term survivorship after stem cell transplantation

Bone marrow failures and cytopenias
This group conducts clinical and registry-based research, including within the European Group of Blood and Marrow Transplantation (EBMT) collaborating actively with the Transplant Complications Working Party (TCWP) and CIBMTR Working committee on Late Effects and Quality of Life.

In 2018, this group set up a platform for diagnostics, research, clinical care, and counseling for patients with bone marrow failure and unclear cytopenias. Using NGS, this group managed to identify or exclude diagnoses, thus allowing a precise clinical decision making.

Innate immunity in hematological diseases

This group focusses on the role of damage-associated molecular patterns (DAMPs) in systemic inflammation, the mechanism for how DAMPs are released, the regulation of this process, and the effects of released DAMPs. By understanding these processes, the aim is to design therapeutic strategies to neutralize DAMPs' proinflammatory effects.

Group Members

Other group members (no master students) with function and title (Research Associate, Postdoctoral Fellow, Laboratory Technician, PhD Student) Group members with start and/or end of employment in 2018: please insert corresponding month (e.g.: Jan. to Dec./since Apr./until Apr.)

Inflammation and Hematopoiesis
Prof. Dr. Ramanajneyulu Allam, Group Leader
Dr. Nicola Andina, Postdoctoral Fellow
Giuseppe Bombaci, PhD Student
Martina Stilinovic, PhD Student
Aubry Tardivel, Research Associate

Mouse models of hematophysiology and hematopathology and their translation to human hematological disorders
Prof. Dr. Anne Angelillo-Scherrer, Group Leader
Dr. Sara Calzavarini, Postdoctoral Fellow
Dr. Raja Prince, Postdoctoral Fellow
Claudia Quarroz, Laboratory Technician
Desiré Reina Caro, Laboratory Technician

Targeted diagnostics in hematological malignancies
Prof. Dr. Vera Ulrike Bacher, Group Leader
Dr. Raphael Joncourt, Research Associate
Dr. Naomi Porret, Research Associate
Dr. Gertrud Wiedemann, Research Associate
Dr. Evgeny Shumilov, Resident
Eva Gfeller, Laboratory Technician
Myriam Legros, Laboratory Technician

Hematopoiesis and molecular genetics
Dr. Michael Daskalakis, Senior Attending Physician
Dr. Monika Haubitz, Postdoctoral Fellow
Ingrid Helsen, Laboratory Technician
Daniela Steiner, Laboratory Technician

Personalized treatment for patients with myeloid malignancies
Mahmoud Hallal, PhD Student
Dr. Annatina Schnegg Kaufmann, Postdoctoral Fellow, since April 2018
Kristina Stojkov, Research Associate, since June 2018
Jovana Jankovic, Data Manager, since June 2018

Hemostasis
Prof. Dr. Johanna A. Kremer Hovinga, Group Leader
Prof. Dr. Kenneth J. Clemeston, Senior Scientist
PD Dr. Monica Schaller, Senior Scientist
PD Dr. Anette van Dorland, Senior Scientist
Isabelle Aebi-Huber, Laboratory Technician
Silvan Heeb, PhD Student
Irmela Sulzer, Laboratory Technician
Dr. Erika Tarasco, Research Associate

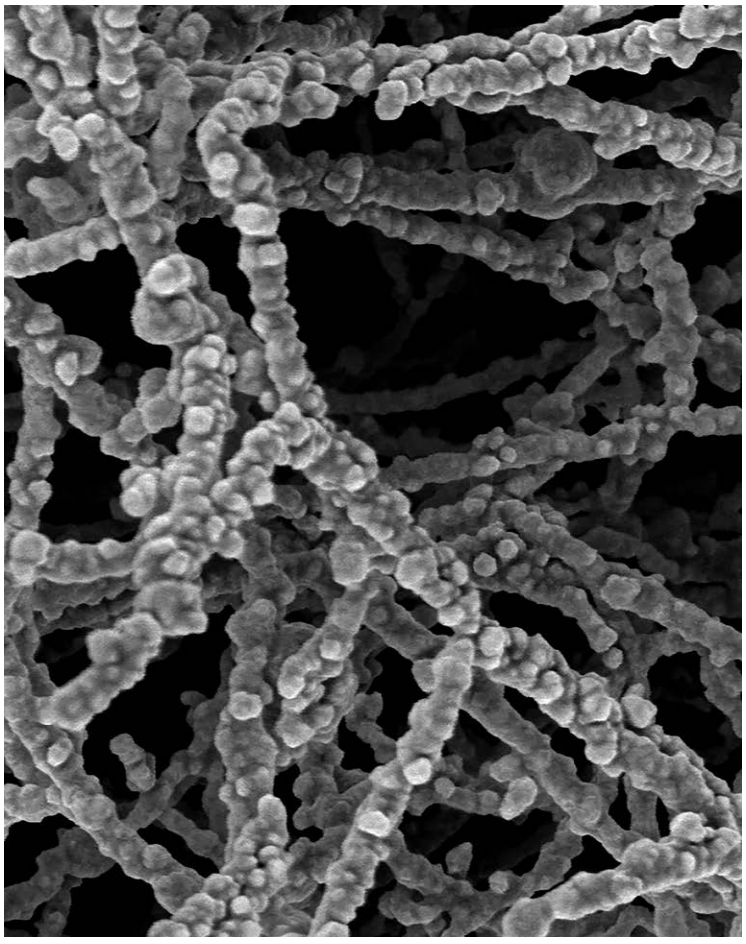
Epidemiology, laboratory medicine, vascular medicine, bleeding disorders
Anja Stalder, Data Manager
Vincent Benites, Laboratory Technician

Long term survivorship after Stem Cell Transplantation
Bone marrow failures and cytopenias
PD Dr. Alicia Rovó, Group Leader
Dr. Naomi A. Porret, Research Associate
Dr. Ekatarina Chigrinova Rebmann, Deputy Senior Attending Physician
Dr. Linet Njue, Research Assistant

Innate immunity in hematological diseases
Prof. Dr. Sacha Zeerleder, Group Leader
Laura del VAsto Nunez, PhD Student
Myrrdin Verjeij, PhD Student
Yasmin de Wit, PhD Student

Selected Collaborators

Esmon CT, Oklahoma Medical Research Foundation, Oklahoma, USA
George JN, Oklahoma Medical Research Foundation, Oklahoma, USA
Gjertsen B, Department of Clinical Science, Bergen University, Norway
Heinis C, EPFL, Lausanne (CH)
Heller M, DBMR, University of Bern (CH)
Hoang T, University of Montreal (CA)
Pabst T, Dept. of Oncology, Inselspital Bern (CH)
Rössler J, Hematology/Oncology (Pediatrics), University of Bern (CH)
Sankaran V, Harvard Medical School, Boston, MA (US)
Savage S, DCEG National Institutes of Health, National Cancer Institute, Rockville, Bethesda (US)
Ten Cate H, Maastricht University (NE)
Tichelli A, Hematology/University of Basel (CH)
van der Poll T, Academic Medical Center, Amsterdam (NL)



Prof. Dr. Johanna A. Kremer Hovinga
Johanna.kremer@insel.ch

MD (1990) at University of Bern; FMH certification (1999 and 2004). Postdoc (1999–2001) at Academic Medical Center, Amsterdam (NL). Venia docendi (2009). Since 2007 research group leader and since 2013, head, Hemophilia Consultation, Department of Hematology and Central Hematology Laboratory, Inselspital. Associate Professor of Hematology (2015). Hemostasis.

PD Dr. Michael Nagler
michael.nagler@insel.ch

MD (2003) at University of Hamburg, Germany; board certification in General Internal Medicine (2010), Hematology (2014), and Laboratory Analytics (2013); PhD (2014) at Maastricht University; MSc in Epidemiology (2016) Maastricht University; Postdoctoral fellowship at Maastricht University (2014–2016); Venia docendi (2018); Since 2016, Senior Attending and Head of Hemostasis Laboratory. Epidemiology, laboratory medicine, vascular medicine, bleeding disorders.

PD Dr. Elisabeth Oppliger Leibundgut
elisabeth.oppliger@insel.ch

MSc in Pharmacy (1986); PharmD (1996). Postdoc (1997–1999) at University of Bern. FAMH certification in Medical Genetics (2004). Venia docendi (2013). Head, Molecular Diagnostics, Department of Hematology, Inselspital Bern (1999–2017). Since 2017, Head, Research and Development, Molecular Diagnostics, Department of Hematology, Inselspital Bern. Hematopoiesis and molecular genetics.

PD. Dr. Alicia Rovó
alicia.rovo@insel.ch

MD at University of Buenos Aires (1984); Hematology certification Buenos Aires (1990); Disertation University of Basel (2008), FAMH certification 2008, FMH certification (2011), Venia Docenti, University of Basel (2011), Venia Docenti, University of Bern (2016). Since 2017, Senior Attending/Deputy Physician-in-Chief and Head of the Clinical Unit Hematology, Inselspital. Long term survivorship after Stem Cell Transplantation & bone marrow failures and cytopenias.

Prof. Dr. Sacha Zeerleder
sacha.zeerleder@insel.ch

MD at University of Bern (1997); Doctoral thesis 1999 (Prof. B. Laemmle). FMH certification Internal Medicine (2007) and Hematology (2018). Dutch Medical Association—specialization degree for Internal Medicine (2007) and hematology (2010). PhD graduation in 2007 at the University of Amsterdam, The Netherlands (Prof. C.E. Hack/Prof. W.A.Wuillemin). Postdoc at Sanquin research in Amsterdam 2005–2008 (Prof. L.A. Aarden). Principle investigator at Sanquin Research and Staff member, senior resident, department of hematology, Academic Medical Center, Amsterdam, the Netherlands (2010–2018); functions: Medical head transfusion laboratory and special hematology laboratory (2010–2018) and Director stem cell transplantation program (2014–2018). In 2016 appointed Professor for translational Immunohematology. Innate immunity in hematological diseases.

Selected Publications

Pitfalls in the molecular follow up of NPM1 mutant acute myeloid leukemia. Bacher U, Porret N, Joncourt R, Sanz J, Aliu N, Wiedemann G, Jeker B, Banz Y, Pabst T. Haematologica. 2018; 103(10):e486-e488. doi: 10.3324/haematol.2018.192104.

Bürki S, Brand B, Escher R, Wuillemin WA, Nagler M. Accuracy, reproducibility and costs of different laboratory assays for the monitoring of unfractionated heparin in clinical practice: a prospective evaluation study and survey among Swiss institutions. BMJ Open. Jun 9, 2018; 8(6):e022943. doi: 10.1136/bmjopen-2018-022943. PubMed PMID: 29886450; PubMed Central PMCID: PMC6009553. Ribonuclease inhibitor 1 regulates erythropoiesis by controlling GATA1 mRNA translation. Chennupati, V et al (2018) in: J Clin Invest,v128(4), p.1597-1614.

Engel, R., L. Delvasto-Nunez, D. Roem, G. van Mierlo, S. Holst, A. L. Hipgrave Ederveen, J. D. van Buul, M. Wuhrer, D. Wouters and S. Zeerleder (2018). "alpha1-Antichymotrypsin Present in Therapeutic C1-Inhibitor Products Competes with Selectin-Sialyl LewisX Interaction." Thromb Haemost 118(12): 2134-2144.

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

Saussele S, Hehlmann R, Fabarius A, Jeromin S, Proetel U, Rinaldetti S, Kohlbrenner K, Einsele H, Falge C, Kanz L, Neubauer A, Kneba M, Stegelmann F, Pfreundschuh M, Waller CF, Oppliger Leibundgut E, Heim D, Krause SW, Hofmann WK, Hasford J, Pfirrmann M, Müller MC, Hochhaus A, Lauseker M. Defining therapy goals for major molecular remission in chronic myeloid leukemia: results of the randomized CML Study IV. Leukemia. May 2018; 32(5):1222-1228. doi: 10.1038/s41375-018-0055-7. Epub Feb 26, 2018.

Schnegg-Kaufmann A, Calzavarini S, Limacher A, Mean M, Righini M, Staub D, Beer JH, Frauchiger B, Osterwalder J, Kucher N, Matter CM, Husmann M, Banyai M, Aschwanden M, Mazzolai L, Hugli O, Nagler M, Daskalakis M, Rodondi N, Aujesky D, Angelillo-Scherrer. High Gas6 in plasma predicts venous thromboembolism recurrence, major bleeding and mortality in the elderly. A prospective multicenter cohort study. J Thromb Haemost 2018, 17:306-318

Improvement of relative survival in elderly patients with acute myeloid leukemia emerging from population-based cancer registries in Switzerland between 2001 and 2013. Schnegg-Kaufmann A, Feller A, Baldomero H, Rovo A, Manz MG, Gregor M, Efthymiou A, Bargetzi M, Hess U, Spertini O, Chalandon Y, Passweg JR, Stussi G, Arndt V, Bonadies N; NICER Working Group.

Cancer Epidemiol. Feb 2018; 52:55-62. doi: 10.1016/j.canep.2017.11.008. Epub Dec 7, 2017. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, Metjian A, de la Rubia J, Pavenski K, Callewaert F, Biswas D, De Winter H, Zeldin RK; HERCULES Investigators. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2019 Jan 24; 380:335-346

André Tichelli, MD1; Eric Beohou; Myriam Labopin, MD2; et al Gérard Socié, MD3; Alicia Rovó, MD4; Manuela Badoglio; Anja van Biezen; Peter Bader, MD6; Rafael F. Duarte, MD7; Grzegorz Basak, MD8; Nina Salooja, MD9; for the Transplant Complications Working Party of the EBMT . Evaluation of Second Solid Cancers After Hematopoietic Stem Cell Transplantation in European Patients. JAMA Oncol. 2018; doi: 10.1001/jamaoncol.2018.4934 (online first).

Hepatology

Prof. Annalisa Berzigotti
annalisa.berzigotti@insel.ch

MD (1998), Internal medicine specialist (2004) and doctorate in ultrasound in medicine (2009) at the University of Bologna, Italy. Doctorate in hepatology (2012), University of Barcelona, Spain. Since 12/2014, she has been working at the Inselspital, University of Bern, where she is now Associate Professor of Hepatology (2016) and Senior Attending Physician (2016).

Prof. Andrea de Gottardi
andrea.degottardi@insel.ch
andrea.degottardi@dbmr.unibe.ch

MD (1999) University of Lausanne and Heidelberg, PhD in Pharmacology (2002), University of Bern, FMH in Gastroenterology, 2004, Venia docendi (2010): CAS in Research Management (2012), FMH Hepatology as a subtitle (2013), Associate Professor of Hepatology (2016).

Dr. Jordi Gracia Sancho
jordi.gracia@dbmr.unibe.ch

MSc in Biochemistry at the Rovira i Virgili University, ES (2003); PhD in Biomedicine at the University of Barcelona (2007). Postdoc at Harvard University, Boston, US (2008–2010); Postdoc at the Hospital Clínic de Barcelona (2011). Fellow at IDIBAPS, Barcelona (2012–2016). Since 2017, Head of the Liver Vascular Biology Research Group, IDIBAPS & Associate Researcher in Hepatology, Inselspital.

www.dbmr.unibe.ch/research/research_groups/hepatology/index_eng.html

Research Highlights 2018 / Outlook 2019

Fatty liver associated with cellular damage and inflammation defines non-alcoholic steatohepatitis. We are studying the mitochondrial Histidine Triad NucleoTide-binding-2 (HINT-2) protein. HINT2-/-mice show hepatic steatosis associated with a decrease in activity of the β-oxidation as well as impaired hepatocellular respiration and ATP production. The phenotype can be partly linked to the increased acetylation status of individual mitochondrial proteins in HINT2-/-livers. Absence of HINT2 increases liver susceptibility to nutritional stress, such as high fat diet and calorie restriction. Recently, we identified binding partners of HINT2: Mic60 and Mic19 (2 components of the mitochondrial contact sites and cristae) and glucose-regulated protein 75, which tethers the mitochondrial Ca2+ channel VDAC to the ER Ca2+ channel IP3R.

The non-invasive quantification of histological features of chronic liver disease, such as fibrosis and fat, is key in patients' management. We are interested in novel ultrasound-based methods.

Controlled Attenuation Parameter (CAP) in patients with compensated advanced chronic liver disease. We have demonstrated that CAP values reliably reflect liver fat content and are associated with the development of infections and clinical decompensation. This parameter is being tested in patients with cirrhosis and obesity.

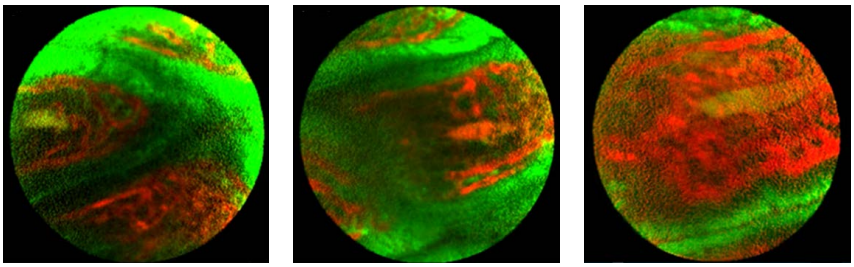
Computed Ultrasound Tomography in Echo mode (CUTE) and spatial distribution of speed-of-sound (SpOSo) reflect liver fat content. We are conducting a collaborative research with PD Dr. Jaeger and Prof. Frenz of the Applied Physics department of the University of Bern to develop this novel ultrasound technique to quantify liver fat. As shown in the figure below, CUTE imaging markedly differs in normal (panel a) and fatty livers (confirmed by CAP and MR spectroscopy) (panel b). This technique could be complementary to existing ultrasound methods.

Portal hypertension (PHT) is a hallmark of advanced chronic liver disease. In liver disease, gut-derived bacterial metabolites and inflammatory cytokines in the splanchnic and systemic circulation contribute to the progression of chronic liver diseases. We are investigating the role of intestinal microbiota along the gut-liver axis in models of cholestasis and cirrhosis.

Gut-liver axis in the development of portal hypertension and fibrosis "Protective role of microbiota during fibrogenesis": We are studying if gut microbiota could affect the progression of liver fibrosis and portal hypertension. We observed that liver fibrosis and PHT were attenuated in SPF-mice compared to ASF-mice. The Role of Paneth cells in PHT and angiogenesis: Paneth cells are long-lived secretory epithelial cells residing at the base of the crypts in the small intestine. We showed that their number is increased in PHT mice. Our results suggest that microbial-derived factors activate Paneth cells to secrete not only antibacterial peptides, but also proangiogenic signaling molecules. Image showing vessels in villi.

Prof. Dr. Jean-François Dufour
jean-francois.dufour@insel.ch
jean-francois.dufour@dbmr.unibe.ch

MD at University of Geneva (1986) Master in Mathematics at University of Geneva (1984) FMH internal medicine (1993) FMH Gastroenterology Hepatology (2003) Postdoc at Tufts University, Boston (USA) (1991–1997) Venia docendi (2000) Since 2011 Head, Hepatology, Co-director at the University Clinic for Visceral Surgery and Medicine Professor of Hepatology (2011).



Group Members

Prof. Dr. Med. Jean-François Dufour, Chief of Hepatology, Co-Chair of Department
Prof. Dr. Med. Annalisa Berzigotti, Senior Attending Physician
Prof. Dr. Med. Andrea De Gottardi, Senior Attending Physician
Dr. Jordi Gracia Sancho, Associate Researcher
Prof. Dr. med. Nasser Semmo, Senior Attending Physician
Dr. med. Guido Stirnimann, Senior Attending Physician
Marco Amsler, Lab Technician
David Bélet, Lab Technician
Prof. Dr. Med. Jaime Bosch, Visiting Professor
Dr. Med. Stefania Casu, Senior Physician
Mirjam Conrad, Study Nurse
Dr. Med. Maria Gabriela Delgado, Deputy Senior Physician
Alice Gilg, Study Assistant
Dr. Med. Maria Guarino, visiting PhD Student (until Nov.)
Dr. Sergi Guixé-Muntet, Postdoc
Mohsin Hassan, PhD Student
Philipp Kellmann, Lab Technician
Rita Mäder, Deputy Assistant to Clinic Director (since Apr.)
Olivier Maurhofer, Head of Laboratory Logistics
Dr. Med. Yuly Mendoza, Clinical Research Associate
Dr. Sheida Moghadamrad, Research Associate
Giuseppe Murgia, Deputy Senior Physician
Dr. Med. Pompilia Radu, Clinical Research Associate
Raviprasadh Rajasekaran, PhD Student (until Aug.)
Susana Gomes Rodrigues, PhD Student
Stefanie Rothen, Study Nurse
Patcharamon Seubnooch, PhD Student (from Aug.)
Dr. Marie St-Pierre, Research Associate
Tamara Tauss, Study Nurse
Dr. Isabelle Vögeli, Research Associate
Tao Wan, visiting PhD Student
Cong Wang, PhD Student

Selected Collaborators

Garcia-Pagan JC, University of Barcelona (ES)
Anstee Q, University of Newcastle (UK)
Sebastiani G, Mc Gill University, Montreal (CA)
Petta S, University of Palermo (IT)
Rautou PE, Hôpital Beaujon, Paris (FR)

Selected Publications

The histidine triad nucleotide-binding protein 2 (HINT-2) positively regulates hepatocellular energy metabolism. Rajasekaran R, Felser A, Nuoffer JM, Dufour JF, St-Pierre MV. FASEB J. Sep 2018; 32(9):5143-5161. doi: 10.1096/fj.201701429R. Epub Apr 18, 2018

Anti-tumoral effects of exercise on hepatocellular carcinoma growth. Saran U, Guarino M, Rodríguez S, Simillion C, Montani M, Foti M, Humar B, St-Pierre MV, Dufour JF. Hepatol Commun. 2018 Mar 22; 2(5):607-620. doi: 10.1002/hep4.1159. eCollection May 2018

Patients with Signs of Advanced Liver Disease and Clinically Significant Portal Hypertension Do Not Necessarily Have Cirrhosis. Rodrigues SG, Montani M, Guixé-Muntet S, De Gottardi A, Berzigotti A, Bosch J. Clin Gastroenterol Hepatol. 2019 Jan 5. pii: S1542-3565(19)30011-4. doi: 10.1016/j.cgh.2018.12.038. [Epub ahead of print]

Prognostic Significance of Controlled Attenuation Parameter in Patients with Compensated Advanced Chronic Liver Disease. Margini C, Murgia G, Stirnimann G, De Gottardi A, Semmo N, Casu S, Bosch J, Dufour JF, Berzigotti A. Hepatol Commun. July 24, 2018; 2(8):929-940. doi: 10.1002/hep4.1201. eCollection Aug. 2018.

Risk of bleeding in cirrhotic patients treated with rivaroxaban. De Gottardi A, Garcia-Pagan JC; VALDIG Investigators. Liver Int. Oct 2017; 37(10):1575-1576. doi: 10.1111/liv.13543.

Marie Skłodowska-Curie Actions (MSCA) Individual Fellowship Precision Oncology, DBMR Lab of Prof. Dr. Mark A. Rubin

Dr. Joanna Triscott
Postdoctoral Associate, Precision Oncology
joanna.triscott@dbmr.unibe.ch

PhD in Experimental Medicine, University of British Columbia, Vancouver, BC, Canada (2010–2015). Postdoc in Englander Institute of Precision Medicine, Weill Cornell Medicine, New York City, NY, USA (2016–2018).

Research Highlights 2018 / Outlook 2019

Towards understanding non-canonical phosphatidylinositol kinases in the maintenance of prostate metabolism.
1 in 7 men will develop prostate cancer (PCa) with many progressing to advanced castrate-resistant disease (CRPC). A need exists to better understand the mechanisms that control the transition of prostate cells from a hormone-dependent to castrate-resistant state. Androgens strongly influence the metabolic state of PCa cells to favor sustained cellular growth. We hypothesize there are effectors working in conjunction with androgen receptor (AR) signaling to coordinate alterations to androgen-dependent metabolism that are linchpins in the orchestration of the transition to CRPC. Leading candidates are members of phosphoinositol (PI) pathways, which have a high frequency of alteration in PCa (i.e. phosphoinositide 3-kinase [PI3K]). Herein, we will explore a family of poorly understood lipid kinases called the type II phosphatidylinositol-5-phosphate 4-kinases (PI5P4Ks) and predict them to be critical regulators of cancer cell survival. PI5P4Ks are druggable targets that act by phosphorylating the lipid phosphatidylinositol-5-phosphate (PI 5-P) at the 4 position of the inositol ring to generate phosphatidylinositol-4,5-bisphosphate (PI-4,5-P2; PIP2). Analysis of transcript data revealed expression of PIP4K2A, B and C in primary PCa patient samples, which was correlated with an AR activation gene signature and hotspot tumor suppressor deletion. In addition, isoform expression was assessed for differential expression in relation to an integrated neuroendocrine prostate cancer mRNA score (TCGA; n=333). PI5P4Kα protein was detected in primary and advanced prostate cancer using optimized antibodies for patient tissue TMAs (n= 72). Using in vitro LNCaP cell models, siRNA knock-down systems were tested to evaluate the molecular consequence of targeting PIP4K2A and PIP4K2B in androgen dependent systems. Stable knockdown using fluorescently labeled lentiviral shRNA constructs significantly reduced the proliferation of shPIP4K2 treated cells. We have also developed a prostate-specific PI5P4K knock out mouse model by expressing Probasin-driven Cre in a homozygous 129/SvEv Pip4k2aflx/flx murine strain. These data implicate a fundamental role for PI5P4Ks in prostate biology and PCa androgen signaling.

Selected Collaborators

Cantley L, Weill Cornell Medicine, New York City (US)
Emerling B, Sanford Burnham Prebys, La Jolla (US)
Kruithof-de Julio M, University of Bern (CH)

Selected Publications

Triscott, Joanna, and Mark A. Rubin. Prostate Power Play: Does Pik3ca Accelerate Pten-Deficient Cancer Progression? Cancer Discovery 8.6 (2018): 682-685.

Link to publication list:
www.ncbi.nlm.nih.gov/pubmed/?term=Joanna+triscott

Precision Oncology, DBMR
Lab of Prof. Dr. Mark A. Rubin

Dr. Kellie Cotter
kellie.cotter@dbmr.unibe.ch

PhD in molecular biology, cell biology, and biochemistry at Boston University (USA) (2014). Postdoc at Weill Cornell Medicine (USA) (2014–2017). Since 2017, postdoc at the DBMR.

Research Highlights 2018 / Outlook 2019

m^{6}A methylation of mRNAs is known to alter transcript stability, translation efficiency, and patterns of alternative splicing. Recent studies in several cancer types have demonstrated that m^{6}A regulates both the expression and translation of known oncogenes and tumor suppressors. While epigenetic changes in the context of prostate cancer (PCa) are well defined, no study to date has explored the role of epitranscriptomic modification of RNAs, nor of their functional consequences in PCa disease progression. In unpublished preliminary work, I have shown that the m6A methyltransferase METTL3 is overexpressed in PCa and is important for cell growth. I generated the first epitranscriptome map of m^{6}A in PCa cell lines, and by combining this data with ribosome foot printing and RNA-Seq in the context of METTL3 knockdown, I demonstrated that m^{6}A regulates the expression and translation of many important transcripts and pathways. This work established the basis for my PCF Young Investigator Award in which we will attempt to:

1) Understand the role of m^{6}A methylation in the control of PCa cell migration and invasion;
2) Define the interaction between m^{6}A and androgen signaling, including the effects on the splicing of androgen receptor; and
3) Integrate m^{6}A maps from patient samples with RNA-Seq, ribosome profiling, and proteomics in order to both delineate the m^{6}A landscape in PCa with the goal of defining potential m^{6}A-regulated biomarkers in both coding and non-coding genes.

Selected Collaborators

Jaffrey S, Weill Cornell Medicine, New York City (US)

Selected Publications

https://orcid.org/0000-0002-2574-815X

Inner Ear Research Lab

Marta Roccio PhD
Marta.roccio@dbmr.unibe.ch

MSc in Biology at University of Milano (IT) (1996–2001); PhD at University of Utrecht (NL) in Molecular & Cell Biology (2003–2007). Postdoctoral fellow at the University Medical Center of Utrecht in Stem Cell Biology (2007–2008); Postdoctoral fellow at the Federal Institute of Technology in Lausanne (EPFL) in Stem Cell Bioengineering (2009–2012). Senior Scientist and Principal Investigator at the University of Bern at the laboratory of Inner Ear Research (2012-to date) Lab Co-head with Dr. Med Senn (2012–2107). Venia Docendi (2017).

Research Highlights 2018 / Outlook 2019

Sound perception relies on the function of specialized mechano-sensitive hair cells located within the cochlear sensory epithelium. Hair cells function as primary sound receptors and in turn activate the sensory neurons of the spiral ganglion, which relay the signal to the brain for interpretation.

Due to the lack of proliferative and regenerative capacity of the sensory organs, loss or damage of hair cells and spiral ganglion neurons results in permanent hearing impairment. Disabling hearing loss affects 360 million people worldwide, has a negative impact on the quality of life of those affected, and presents a high socio-economic burden.

Our group aims to understand the basic mechanisms that control sensory organ development, degeneration, and regeneration to develop novel therapeutic strategies for hearing loss.

Cochlear development

The lack of knowledge of human sensory cell specifications and the absence of tools to study human hair cells in vitro represent a major bottleneck for the development of causal therapies for hearing loss. To overcome these limitations, we have developed two complementary strategies aiming at deriving sensory cells from stem/progenitor cells.

I) We have established culture conditions, "inner ear organoids," where pluripotent stem cells (PSC) can be efficiently guided through the steps of otic development using small molecules and growth factors, and differentiated into hair cells or spiral ganglion neurons in vitro. Future research will focus on developing inner ear organoids models from human PSC to study in vitro organ development, genetic mutations causing hearing loss, drug ototoxicity and therapeutic strategies.

II) We have recently characterized the molecular signature of the developing human inner ear and developed novel strategies to purify cochlear progenitor cells and optimized 3D culture conditions that allow for their in vitro expansion and differentiation to functional hair cells. We will continue this line of research by refining the culture conditions for the expansion of somatic progenitors and exploit single cell sequencing for a deeper characterization of the developing sensory organs and to benchmark the pluripotent stem cell derived sensory cell types.

Cochlear Regeneration

Despite recent evidence demonstrating that the early postnatal murine sensory epithelium harbors a population of progenitors that could be experimentally triggered to differentiate into hair cells, therapeutic strategies aimed at tissue regeneration are still in their infancy. We have shown that activation of Wnt signaling can induce cell cycle re-entry in supporting cells in the sensory epithelium, while Notch signaling inhibition induced the trans-differentiation of these into hair cells in vitro. Small molecule inhibitors targeting Wnt and Notch signaling are currently being tested in vivo in animal models with sensorineural hearing loss. In collaboration with the institute of infectious diseases at the University of Bern (Group Leib), and the small biotech company Audion Therapeutics, we are currently assessing hair cell regeneration in an animal model with bacterial-meningitis induced hearing loss (Erni et al. In preparation).

Future research directions include a refined molecular analysis of the mechanisms that prevent plasticity and regeneration and the assessment of novel strategies of tissue reprograming and de-differentiation to elicit a regenerative response.

Group Members

Silvia Erni (PhD Student, October 2016-Present)
Michelle Buri (Research Assistant, January 2018-March 2018)
Gabriella Fernandes (Research Assistant, April 2018-October 2018)

Selected Collaborators

Senn P, University of Geneva (CH)
Leib S, IFIK, University of Bern (CH)
Widmer HR, Neurosurgery, University of Bern (CH)
Heller S, Stanford University (US)
Edge A, MEEI, Harvard University, Boston (US)

Selected Publications

Molecular characterization and prospective isolation of human fetal cochlear hair cell progenitors. Roccio M, Perny M, Ealy M, Widmer HR, Heller S, Senn P. Nat Commun. Oct 2, 2018; 9(1):4027. doi: 10.1038/s41467-018-06334-7.

Generation of Otic Sensory Neurons from Mouse Embryonic Stem Cells in 3D Culture.
Perny M, Ting CC, Kleinlogel S, Senn P, Roccio M. Front Cell Neurosci. Dec 19, 2017; 11:409. doi: 10.3389/fncel.2017.00409. eCollection 2017.

Cell cycle reactivation of cochlear progenitor cells in neonatal FUCCI mice by a GSK3 small molecule inhibitor. Roccio M, Hahnewald S, Perny M, Senn P. Sci Rep. Dec 8, 2015; 5:17886. doi: 10.1038/srep17886.
The Severity of Infection Determines the Localization of Damage and Extent of Sensorineural Hearing Loss in Experimental Pneumococcal Meningitis. Perny M, Roccio M, Grandgirard D, Solyga M, Senn P, Leib SL. J Neurosci. Jul 20, 2016; 36(29):7740-9. doi: 10.1523/JNEUROSCI.0554-16.2016.

Response profiles of murine spiral ganglion neurons on multi-electrode arrays. Hahnewald S, Tscherter A, Marconi E, Streit J, Widmer HR, Garnham C, Benav H, Mueller M, Löwenheim H, Roccio M, Senn P. J Neural Eng. Feb 2016; 13(1):016011. doi: 10.1088/1741-2560/13/1/016011. Epub Dec 14, 2015.

Scopus Author ID: 24345169900
https://orcid.org/0000-0001-7568-9429

Gastroenterology/Mucosal Immunology–Subgroup Ganal-Vonarburg

Dr. Stephanie Ganal-Vonarburg
stephanie.ganal@dbmr.unibe.ch

Studied Molecular Medicine (MSc, 2009) at Albert-Ludwigs-University Freiburg (D) and at the University of British Columbia (CAN), and Immunology (PhD, 2013) at Albert-Ludwigs-University Freiburg (D). Postdoc at DBMR, University of Bern (2013–2016). Since September 2016, Group leader at the DBMR, Inselspital, and since July 2016, Clean Mouse Facility Manager at the University of Bern/Inselspital. Winner of the Johanna Dürmüller-Bol DBMR Research Award (2018).

Research Highlights 2018 / Outlook 2019

The role of maternal microbiota in durably shaping immunity and microbiota composition in the offspring through epigenetic mechanisms

A vast number of bacteria, viruses, and fungi inhabit the inner and outer body surfaces such as the intestine, the airways, and the skin of all healthy mammals and contribute to host physiology (digestion, vitamin production, immune maturation). It is currently believed that the changes in an individual's immune system introduced by alterations in the commensal microbiota are due to postnatal colonization with an endogenous microbiota, as the fetus is largely sterile. However, in my postdoctoral work in the Macpherson laboratory, we were able to show that bacterial metabolites derived from the maternal microbiota can reach the offspring via the placenta and the maternal milk and that these metabolites profoundly shape the immune system of the offspring. Intestinal epithelial cells were one of the cell types profoundly affected. Following gestational colonization of germ-free mice, the offspring's intestinal epithelial cells exhibited a significantly altered gene expression profile compared to the offspring born to germ-free control dams. As most of the observed changes in the offspring introduced by gestational colonization were long-lived and could still be observed once the offspring had grown to adulthood, and as the embryonic and fetal development is known to be the most active time in life for epigenetic modifications, I hypothesize that a significant proportion of the effects of gestational maternal microbiota on the immune system of the neonate is mediated through epigenetic modifications in the offspring's genome.

Using a reversible colonization system of pregnant germ-free mice in combination with whole-genome bisulfite sequencing and chromatin immunoprecipitation, I aim to reveal differences in DNA methylation and histone modifications in intestinal epithelial cells between gestationally colonized and control offspring. Additionally, I will identify microbial metabolites with epigenetic modification potential in maternal milk and test if their administration to pregnant germ-free mice can recapitulate the effects of gestational colonization. In 2018, we have established chromatin immunoprecipitation for histone modifications (e.g. H3K-4me3, histone acetylations) of intestinal epithelial cells. A Diagenode Bioruptor Pico is now available in DBMR for accurate chromatin fragmentation by sonication. In addition, we already measured the expression of genes encoding histone modifying enzymes, such as histone methyltransferases or histone deacetylases (HDAC), in the small intestinal tissue of E16 fetuses or P14 pups born to either colonized, gestationally colonized or germ-free control dams. Several histone modifying enzymes were upregulated in the offspring of control dams compared to the offspring of dams either fully colonized with an SPF microbiota or gestational colonized with E. Coli HA107. These data support our hypothesis that maternal microbiota alters epigenetic regulatory programs in the neonatal intestine and may thus contribute to the health of the offspring.

www.dbmr.unibe.ch/research/research_groups/gastroenterology___mucosal_immunology/index_eng.html

Group Members

Dr. Stephanie Ganal-Vonarburg, Oberassistentin
Cristina Kalbermatter, PhD Student
Sandro Christensen, Medical student

Selected Collaborators

Diefenbach A, Charité Berlin (D)
Prinz M, Uniklinikum Freiburg (D)
Riether C, DBMR, UniBe (CH)
Sauer U, ETH Zurich (CH)
Watson A, The University of East Anglika, Norwich (GB)

Teaching Activities

- MSc Biomedical Sciences: Gastroenterology block course
- MSc Molecular Life Sciences: Immunology lecture and Master theses
- Bachelor Biology: 3rd year Immunological practical course

Selected Publications

Y. Uchimura, T. Fuhrer, L. Hai, M. Lawson, M. Zimmerman, M. Gomez de Agüero, B. Yilmaz, F. Ronchi, M. Sorribas, S. Hapfelmeier, S. C. Ganal-Vonarburg, K. D. McCoy, U. Sauer, A. J. Macpherson. Antibodies set boundaries limiting microbial metabolite penetration and the resultant mammalian host response. Immunity 49, 545-559 (2018).

D. Bauché, B. Joyce-Shaikh, R. Jain, J. Grein, K. S. Ku, W. M. Blumenschein, S. C. Ganal-Vonarburg, D. C. Wilson, T. K. McClanahan, R. de Waal Malefyt, A. J. Macpherson, L. Annamalai, J. H. Yearley, and D. J. Cua. LAG3+ Regulatory T cells restrain Interleukin-23-producing CX3CR1+ gut resident macrophages during group 3 Innate lymphoid cells-driven colitis, Immunity 49, 342-353 (2018).

C. Mooser, M. Gomez de Agüero, S. C. Ganal-Vonarburg. Standardization in host-microbiota interaction studies: challenges, gnotobiology as a tool, and perspective. Curr Opin Microbiol. Jul 26, 2018; 44:50-60 (2018).

A. J. Macpherson, B. Yilmaz, J. P. Limenitakis and S. C. Ganal-Vonarburg, IgA Function in Relation to the Intestinal Microbiota, Annu Rev Immunol Apr 26, 2018; 36:359-381 (2018).

A. J. Macpherson, S. C. Ganal-Vonarburg. Checkpoints for gut microbes after birth. Nature Aug; 560(7719):436-438 (2018).

Functional Urology Research Group

Prof. Dr. Fiona C. Burkhard
Fiona.Burkhard@insel.ch

MD at Zürich University (1990); FMH certification (2001). Fellowship in Female and Functional Urology at University of Texas Southwestern Medical Center, Dallas (USA) (1997–1998). Habilitation (2006). Associate Professor of Urology University of Bern (2009). Since 2015, Head of Female, Functional and Neurourology, Department of Urology, Inselspital

Prof. Dr. Katia Monastyrskaya
katia.monastyrskaia@dbmr.unibe.ch

D.Phil. in Biochemistry, Wadham College, University of Oxford, UK (1995). Postdoc at the NERC Institute of Virology, Oxford, UK (1994–1997). Senior Scientist at H. Hoffmann-La Roche/Givaudan AG, Switzerland (1997–2001). Senior Research Associate, University of Bern (2001–2011); Habilitation (2007), Associate Professor of Molecular Cell Biology (2014) University of Bern. Since 2011, Group Leader, Functional Urology Group, Urology Research Laboratory, DBMR and Urology Clinic, Inselspital.

Research Highlights 2018 / Outlook 2019

Urgency, frequency, and incomplete emptying are the key symptoms of lower urinary tract dysfunction (LUTD) caused by many non-cancerous diseases of the bladder, including benign prostatic obstruction (BPO), urethral obstruction and neurogenic bladder dysfunction. BPO affects most men as they age, and the resulting urgency/urgency incontinence and bladder failure are the major factors negatively reflecting on the quality of life of the elderly.

Our Functional Urology Group investigates the molecular mechanisms underlying the functional and morphological changes in the bladder during LUTD. Our comprehensive transcriptome sequencing, the first of its kind, of human bladder biopsy samples from BPO patients revealed the activation of immune response and proliferative signaling pathways and suggested an increasing involvement of regulatory small non-coding miRNAs in the control of bladder function. We identified 3 mRNA- and 3 miRNA-biomarker signatures sufficient to discriminate between bladder functional states, validated them in a blinded study and showed the normalization of their expression in patients whose bladder function improved after deobstruction. To evaluate the suitability of urinary miRNAs as biomarkers for BOO, we used NanoSight technology together with miRNA profiling with a Nanostring platform and established reliable isolation strategies to increase the yield and purity of human urinary exosomes for biomarker discovery. In BPO patients, we observed an excellent correlation between the urinary miRNA levels and the symptoms of LUTD. We are currently validating a panel of representative miRNAs, which can be further explored to develop a non-invasive diagnostic test for the recovery potential of bladder function after treatment.

Using cell-based systems, we validated TNF-alpha as the top upstream regulator of bladder remodeling during obstruction and showed that compensatory up-regulation of miR-199a-5p reduced NF-kB signaling and preserved bladder contractility. We developed and experimentally validated bioinformatic tools to predict the impact of dysregulated miRNAs on cell signaling relevant for disease development. Now, we are evaluating the significance of disease-inhibited miRNAs to compensate the aberrant disease-mediated signaling.

Along with recruiting human spinal cord injury (SCI) patients for a longitudinal study of gene expression changes during neurogenic LUTD, we secured SNSF funding for a translational project to perform urodynamic studies in awake mice with obstruction and SCI. The project started in summer 2018 and will continue until 2022, investigating the impact of obstructive and neurogenic LUTD on bladder remodeling. It will accelerate the functional validation of the key regulatory elements (proteins and miRNAs) that we are identifying in the human study.

Overall, in 2018 we generated a wealth of data, advancing our knowledge of LUTD. We established novel technologies and made important observations laying the foundation for future discoveries.

www.dbmr.unibe.ch/research/research_groups/urology/index_eng.html

Group Members

Dr. Ali Hashemi Gheinani, Postdoctoral Fellow
Dr. Marc P. Schneider, Research Associate
Ivonne Koeck, PhD Student until April 2018
Michelle Andrea Küffer, PhD Student since July 2018
Mustafa Besic, Laboratory Technician since October 2018

Selected Collaborators

Adam RM, Harvard Medical School, Boston (US)
Monty Hughes F, Duke University, Durham, North Carolina (US)
Locatelli G, University of Bern (CH)
Kessler T, University of Zürich (CH)
Vassella E, University of Bern (CH)

Selected Publications

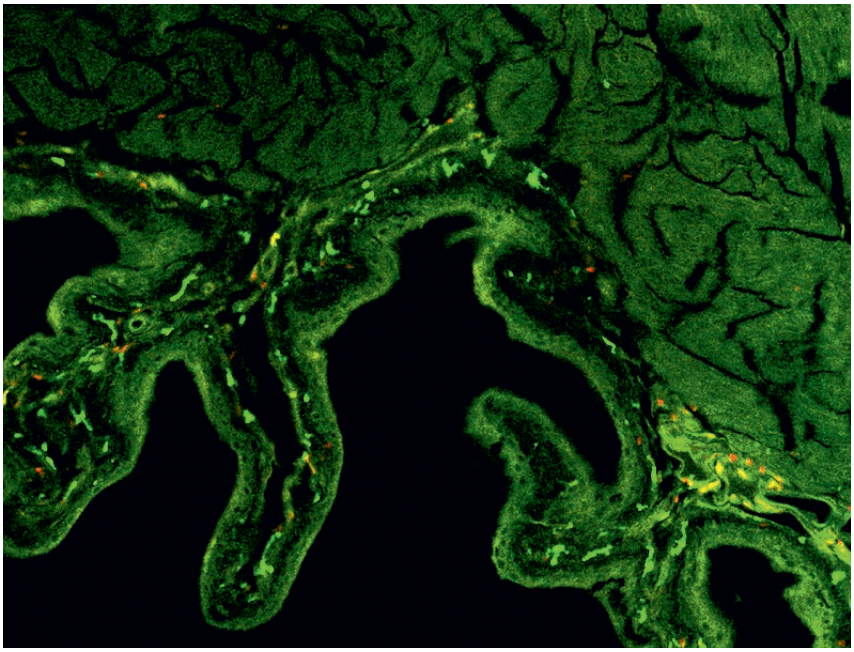
Gheinani AH., et al. (2018) Sci Rep. 2; 8(1):3945. doi:10.1038/s41598-018-22142-x.

Koeck I., et al. (2018) Am J Pathol. 188(8):1847-1864. doi:10.1016/j.ajpath.2018.05.008.

Gheinani AH, et al (2018) Am J Clin Exp Urol. 6(6):219-233. eCollection 2018.

Baumgartner U et al (2018) Mol Cancer. 17(1):44. doi:10.1186/s12943-018-0781-5

Gheinani AH, et al (2017) JCI Insight, doi:10.1172/jci.insight.89560.



Key Events

Swiss Youth in Science: "Biology and Medicine" Study Week
12–18 Mar.

Info Events DBMR 2018
12 Apr. and 3 Oct.
Around 25 interested DBMR newcomers attended each of these events. The next Info Events will take place in April and October 2019.

Day of BioMedical Research 2018
06–07 Nov.
As usual, a large and interested audience followed the presentations of **Prof. Dr. Arul Chinnaiyan** (Michigan Center for Translational Pathology, University of Michigan, Ann Arbor, MI, United States) entitled "The Application of Integrative Sequencing for Precision Oncology," and **Dr. Uwe E. Jocham** (Insel Gruppe AG, Bern, Switzerland) entitled "Research in Clinical Practice – How the Insel Gruppe Promotes Translation and Innovation."

Five candidates applied for the Johanna Dürmüller-Bol DBMR Research Prize 2018 (funded by the Johanna Dürmüller-Bol Foundation) and 163 abstracts were submitted for the Poster Prizes of the DBMR and the Research Prize Alumni MedBern. The winners were (left to right in photo below): Aleksandra K. Eberhard-Moscicka, Dr. Stephanie Ganal-Vonarburg, Prof. Mark A. Rubin (Director DBMR), Daniel Andres, Elisa Rodrigues Sousa, and Pauline G.V. Zamprogno.

Johanna Dürmüller-Bol DBMR Research Award 2018
Dr. Stephanie Ganal-Vonarburg
Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital and Research Group Gastroenterology/Mucosal Immunology, DBMR, University of Bern

Poster Prizes of the DBMR for:
– *best preclinical project*
Elisa Rodrigues Sousa
Department for BioMedical Research, University of Bern,
Research Group Urology and Department of Urology, Inselspital, Bern University Hospital, University of Bern
– *best clinical project*
Aleksandra K. Eberhard-Moscicka
Department of Neurology, Inselspital, Bern University Hospital, University of Bern
– *best project by a medical student*
Daniel Andres
Department of Neurology, Inselspital, Bern University Hospital, University of Bern

Research Prize Alumni MedBern
Pauline G.V. Zamprogno
Organs-on-Chip Technologies Laboratory, ARTORG Center for Biomedical Engineering Research, University of Bern

The next Day of BioMedical Research will be held on November 13, 2019.

"Clinical Research" symposium for Biomedical Sciences students of the University of Fribourg

29 Nov.

DBMR Research Conferences 2018

With an average of 54 visitors each month, the DBMR Research Conferences continue to be successful. In 2018, we were pleased to present the following speakers:

Feb. 5 – Prof. Dr. Markus Huber-Lang, MD
Institut für Klinische und Experimentelle Trauma-Immunologie, Universitätsklinikum Ulm (DE)
Molecular danger management after polytrauma

Mar. 5 – Prof. Jakob Skou Pedersen
Department of Molecular Medicine (MOMA), Aarhus University Hospital, Aarhus (DK)
Pan-cancer driver discovery in more than 2'500 whole cancer genomes

Apr. 9 – Prof. Dr. Manfred Claassen
Department of Biology, Institute of Molecular Systems Biology, ETH Zurich (CH)
Computational single cell biology in health and disease

May 7 – Prof. Dr. Kilian Eyerich
Department of Dermatology and Allergology, Technical University of Munich (DE)
Chronic inflammatory skin disease: How pathmechanisms translate into novel therapeutic approaches

June 4 – Prof. Dr. Jens Georg Leipziger
Department of Biomedicine, Physiology and Biophysics, Aarhus University (DK)
Secretin, a gastrointestinal hormone with important renal implications

July 2 – Prof. Dr. Jean-Philippe Theurillat
Institute of Oncology Research, USI, Bellinzona (CH)
Uncovering the function of prostate cancer driver mutations

Sep. 3 – Prof. Dr. Joerg Huelsken
ISREC, School of Life Science, Swiss Federal Institute of Technology Lausanne (CH)
Targeting cancer stem cells

Oct. 1 – Prof. Dr. Med. Reinhard Hohlfeld
Institute of Clinical Neuroimmunology, Hospital of the Ludwig-Maximilians-University (LMU) Munich (DE)
What twin studies can tell us about the beginnings of MS

Dec. 3 – Prof. Robert L. Medcalf
Australian Centre for Blood Diseases, Monash University, Melbourne, VIC, (AUS)
Fibrinolysis: beyond clot removal

Personnel Update

Academic Degrees

The following academic degrees where awarded to DBMR group members:

Associate Professor

Prof. Pascal Escher
Augenheilkunde

Prof. Dr. Yitzhak Zimmer
Radiation Oncology

Lecturer (Privatdozent)

PD Dr. Michaela Medová
Radiation Oncology

PD Dr. Nikola Saulacic
Cranio-Maxillofacial Surgery

PhD

(supervisors in brackets)

Mariana Bustamante Eduardo
(Prof. Dr. Rolf Jaggi)
A comparison of molecular signatures for breast cancer and analysis of the role of the progesterone receptor in breast cancer cells

Ivonne Köck
(Prof. K. Monastyrskaya)
TNF-α: Key regulator of bladder remodeling during outlet obstruction-induced lower urinary tract dysfunction

Dr. Claire Micossé
(Prof. Dr. Dr. Christoph Schlapbach)
IL-4- and TGF-β-induced PPAR-γ promotes the IL-9-expressing subpopulation of TH2 cells

Dr. Catherine Mooser
(Prof. Dr. Andrew Macpherson)
A novel gnotobiotic mouse model as a tool to study dietary effects on the microbiota, the host, and their interplay

Eleonora Orlando
(Prof. Dr. Yitzhak Zimmer, Prof. Dr. Ruedi Aebersold)
Proteomic and phosphoproteomic investigations for dissecting the interplay between oncogene addiction and DNA damage response signaling

Michaela Poliaková
(PD Dr. Michaela Medová, Prof. Dr. Yitzhak Zimmer)
A metabolomic discovery approach for identification of metabolic changes associated with MET inhibition and DNA-damaging agents in MET inhibition-sensitive and non-MET inhibition sensitive cellular systems

Raviprasadh Rajasekeran
(Prof. Dr. Jean-François Dufour)
Influence of HINT-2 on mitochondrial protein acetylation: Mechanism and significance.

Marcel Sorribas
(Prof. Dr. Reiner Wiest)
Intestinal mucus and vascular barrier in liver cirrhosis: entry site for bacterial translocation independent from portal hypertension and lymphatic route

MD, PhD

(supervisors in brackets)

Dr. Michael A. Amrein,
(Prof. Dr. Adrian F. Ochsenbein)
A functional characterization of TNIK in stem cells and cancer stem cells

Elias D. Bührer,
(Prof. Dr. Adrian F. Ochsenbein)
Extrinsic and intrinsic regulation of cancer stem cells

Awards

The following DBMR group members received awards in 2018:

Daniel Andres
Neurology
Poster awards from the Annula Congress of Swiss Society of Clinical Neurophysiology (SGKN) and at the Day of BioMedical Research 2018 for Best Project by a Medical Student for "Diagnostic patterns of sleep and vigilance tests in distinct causes of excessive daytime sleepiness"

Dr. Claudia Böttcher
Pediatric Endocrinology
Poster-Preis für Grundlagen-forschung der Deutschen Gesellschaft für Kinderendo-krinologie und -diabetologie für "Biochemische, genetische und molekulare Charak-terisierung einer neuen P399_E401Dup Mutation im P450 Oxidoreductase Gen eines Kindes mit 46, XX DSD"

Prof. Dr. Christa E. Flück
Pediatric Endocrinology
Research Award from the European Society Pediatric Endocrinology
Award for Research in (pediatric) steroidogenesis

Dr. Kellie Anne Cotter
Precision Oncology
PCF Young Investigator Award from the Prostate Cancer Foundation, USA for "Role of m6A methylation in post-transcriptional regulation and prostate cancer disease progression"

Dr. Stephanie Ganal-Vonarburg
Gastroenterology/Mucosal Immunology
2018 Johanna Dürmüller-Bol DBMR Research Award "The role of maternal microbiota in durably shaping intestinal immunity and gene expression in the offspring through epigenetic mechanisms"

Martina Göldlin
Neurology
Young Talents in Clinical Research grant 2018 (SAMW/Bangerter Foundation)

Dr. Jordi Gracia-Sancho
Hepatology
Novartis Foundation Prize for medical-biological Research, "Discovering new molecular targets for liver cirrhosis: stiffness as a leading cause"

Damian Hertig
Pediatric Endocrinology
Best oral Presentation at the Society of Clinical Chemistry for "NMR for online metabolomics in 3D cell culture"

Magdalena Hinterbrandner
Tumor Immunology
Awardee: Poster Prize, Best Stem Cell Project 2018, Annual SCRM Meeting 2018, Title: "MHC II-dependent activation of regulatory T cells in the bone marrow of leukemia mice leads to immune evasion and disease progression"

Johannes Kaesmacher
Neurology
Swiss Stroke Society Research Fellowship 2018 and Best oral presentation from the Swiss Stroke Society 2018

Jonas Paul Koch
Radiation Oncology
Best Academic Presentation Award, Annual Meeting of the Scientific Association of Swiss Radiation Oncology, Zurich, Switzerland, "DNA-PK regulates the radio-sensitivity of MET-addicted cancer cell lines via a novel MET phosphosite"

PD Gregor J. Kocher
Thoracic Surgery
Best experimental presentation: "Surgical smoke – still a severely underestimated threat" from the Schweizerischen Gesellschaft für Thoraxchirurgie on Thoracic Day 2018.

Dr. Sheida Moghadamrad
Hepatology
Best Knowledge Prize, EASL Basic School of Hepatology: Liver Vascular Biology

Hassan Mohsin
Hepatology
Young Investigator Bursary, EASL International Liver Congress. Poster presentation "Depletion of Paneth cells is associated with decreased portal hypertension and angiogenesis after partial portal vein ligation in mice"

Hassan Mohsin
Hepatology
Travel and Registration Bursary, EASL Basic School of Hepatology: Liver Vascular Biology

Prof. Dr. Katia Monastyrskaya, Dr. Ali Hashemi Gheinani, Ivonne Köck, Prof. Dr. Fiona C. Burkhard.
Urology
Poster Prize from the 33th Congress of the European Association of Urology, Copenhagen 2018 for "MicroRNAs, inhibited by TNF-α, might influence smooth muscle remodeling during outlet obstruction-induced lower urinary tract dysfunction"

Prof. Dr. Mark A. Rubin
Precision Oncology
PCF Challenge Award from the Prostate Cancer Foundation, USA for "Immune-Radiation Therapy for Metastatic Castration-Resistant Prostate Cancer"

Dr. Joanna C. Triscott
Precision Oncology
Marie Skłodowska-Curie Fellowship from EU Horizon 2020 "PCAPIP–Towards understanding non-canonical phosphatidylinositol kinases in the maintenance of prostate metabolism"

Dr. Sameer Udhane
Pediatric Endocrinology
Young Scientist Travel Award; European Society for Pediatric Endocrinology for "Specificity of substrates for human aromatase and their impact on steroid production"

Sonia Verma
Young Scientist Travel Award from the European Society for Pediatric Endocrinology for "Human genetic variations in growth hormone gene"

PD Dr. Ren-Wang Peng
Thoracic Surgery
PREIS 2018 from the Swiss Society of Thoracic Surgery for the best experimental publication: "mTOR mediates a mechanism of resistance to chemotherapy and defines a rational combination strategy to treat KRAS-mutant lung cancer"

Dr. Bahtiyar Yilmaz
Gastroenterology/Mucosal Immunology
2018 Research Encouragement Award from the SGG

Staff Changes

New Staff

Stephan Christen
Research Assistant (100%)
Precision Oncology (since Jan.)

Mariana De Sá Ricca
Grant Advisor (100%)
Grant Advisor (since Aug.)

Muriel Jaquet
Laboratory Manager (100%)
Precision Oncology (since Aug.)

Sidikiba Kaba
House Staff (100%)
Administration (since Jan.)

Max Pelletier
Practical Student (100%)
IT Support (since Aug.)

Nivetha Ravindran
Polymechanic Apprentice (100%)
DBMR Services (since Aug.)

Timo Staub
COO Center for Precision Medicine (100%)
Center for Precision Medicine (since Jan.)

Selina Steiner
Lab Technician (100%)
Life Cell Imaging (since Mar.)

Anne-Christine Uldry
Research Assistant (80%)
PMSCF Mass Spectrometry and Proteomics Laboratory (since May)

Retirements

Eugen Aeby
House Staff (60%)
DBMR Services (until Dec.)

Verena Frazao
Secretariat (20%)
Administration (until May)

Short employment

Mirjam Bergmann
Assistant (10%)
Quality Assurance, Quality Development and Safety (Feb. to May)

Resignations

Mariana Bustamante Eduardo
Lab Technician (50%)
Molecular Biology & Genomics (until Sep.)

Nathalie Schuster
Lab Technician (50%)
Molecular Biology & Genomics (until Oct.)

Murteza Volina
House Staff (20%)
Administration (until Aug.)

Reallocations to the Inselspital

Joël Grosjean
Lab Technician (100%)
Urology (until Dec.)

DBMR Director: Prof. Dr. Mark A. Rubin, MD
Coordination: Basak Ginsbourger & Marla Rittiner
Editing: Editage (www.editage.com)
Photos: DBMR Philipp Kellmann (Hepatology), Bern; Portrait MR John Abbott
Print: Länggass Druck AG Bern