UNIVERSITÄT BERN

DEPARTMENT FOR BIOMEDICAL RESEARCH
www.dbmr.unibe.ch

Jahresbericht Annual Report 2020

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A copy of this report can be obtained online at:
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Cover:
Primary myocardial cells derived from mouse embryos are shown. Cardiomyocytes are marked yellow using an antibody against smooth-muscle actin. Nuclei are stained blue.
Image: Dr. Marco Osterwalder

Contents

Department for BioMedical Research (DBMR) at a Glance

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

The DBMR 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. There are 47 independent research groups affiliated to the DBMR, covering almost all fields of biomedical research.

The DBMR aims to bridge laboratory-based biomedical and patient-oriented clinical research through scientific support of its research groups and the operation of core facilities having state-of-the-art technology and specialized animal facilities. In addition, a strong emphasis is placed on the development of translational approaches and the use of omics technologies.

Department for BioMedical Research (DBMR) auf einen Blick

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

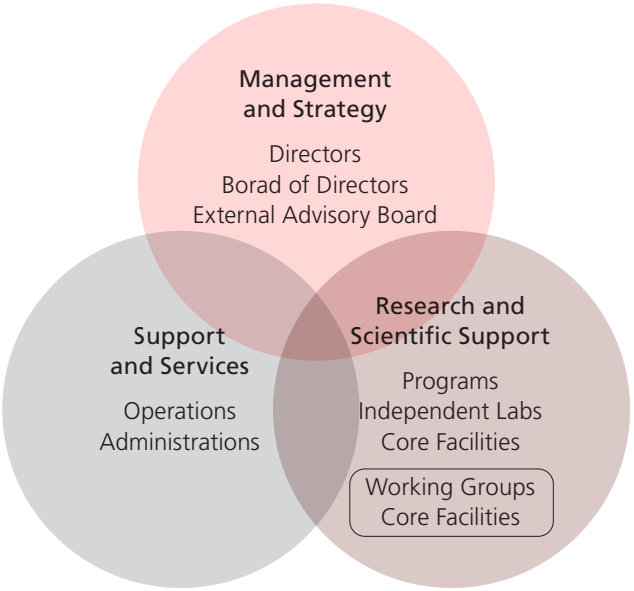
Es wurde 1994 mit dem Auftrag gegründet, Forschenden vom Inselspital, Universitätsspital Bern und von der Medizinischen Fakultät eine optimale Infrastruktur zur Verfügung zu stellen. 47 unabhängige Forschungsgruppen waren dem DBMR angeschlossen, die zusammen fast alle Bereiche der biomedizinischen Forschung 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.

Foreword – Director's Report

The Newly Organized DBMR

The current DBMR structure has served the research community of the University of Bern and Inselspital well and we are grateful to those who have led for the past 25 years. The migration of animal experimentation to the newly established EAC and the much-anticipated opening of the new building planned for 2021, allowed us the opportunity to re-think the structure of the DBMR to one that would reflect trends and changes in research needs and would consolidate the space allocation across all DBMR sites. We have worked closely with the Dean and the Dean's leadership group to coordinate these changes.



During 2019, we invited the research groups to team together to propose thematic Research Programs. The idea then was to try, whenever possible, to spatially cluster the labs belonging to the same Program to promote and incentivize collaboration among them. Each Research Program appointed a contact PI to represent the other PIs in the Program. The few laboratories that chose not to be part of a Program, are jointly represented by one of the independent Laboratory PIs.

Besides scientific collaboration, we find that it is important to have active research members of the DBMR involved in the inter-workings of the department. As such, we implemented in this new structure, a Board of Directors, composed of the Director, the Deputy Director and three Board Members, who are elected by our DBMR membership to serve at the Board for a period of two years with the possibility of re-election. We are proud to welcome our first Deputy Director Prof. Dr. med. Anne Angelillo-Scherrer and three Board Members Ass. Prof. Dr. Carsten Riether, PD Dr. phil. Marianna Kruithof-de Julio, and Ass. Prof. Volker Enzmann. They were elected by the DBMR PIs and will represent the interests of all Programs and researchers in the DBMR.

We have also envisioned the establishment of two new core facilities – Biomedical Genomics (BMG) and the Translational Organoid Resource (TOR), that will offer specialized in-house services that were thus far unmet needs. These new facilities will soon start to operate with the opening of the new building. One important aspect of the core facilities is to assist the DBMR community with state-of-the-art services, that reflect and respond to the needs of the researchers and also technology changes. Accordingly, we have created Working Groups for each Core, composed of three or four of the main users and the core leadership. Their mission will be to define the strategic vision and future plans for each core; they will also be able to provide critical feedback to the core leaders and leadership of the DBMR. Our idea is that by involving all stakeholders, we will have a more comprehensive plan that reflects the diversity of needs and experience.

PMSCF	FCCS	LCI
Chair: PD. Dr. Michele Bernasconi	Chair: Ass. Prof. Dr. Carsten Riether	Chair: PD Dr. Marianna Kruithof-de Julio
Prof. Dr. Oliver Mühlemann	PD Dr. Philippe Krebs	Prof. Dr. Olivier Guenat
Prof. Dr. Norbert Polacek	Prof. Dr. Mirjam Schenk	Prof. Dr. Verena Schröder
Prof. Dr. Beat Suter	Prof. Dr. Deborah Stroka	Prof. Dr. med. Sabine Kässmeyer
Prof. Dr. Mariusz Nowacki	Prof. Dr. Ralph Schmid	Prof. Dr. Martin Zinkernagel

One important mission of the DBMR is to ensure that our members have access to adequate space and that the infrastructure runs effortlessly and efficiently. With this in view, we have created two new positions – the Operations Manager (Dr. Stephan Christen) and the Deputy Operations Manager (Dr. Raschid Setoud). This central and dedicated management of research activities will ensure a more efficient and consistent approach to how the

DBMR runs its daily operations. Stephan and our Lead Grant Advisor (Dr. Mariana Ricca) will both sit on the Board of Directors as non-voting members and will regularly communicate with the Director during the weekly Director's meetings.

Finally, we will establish an External Advisory Board (EAB), that will convene and review the DBMR every two years and thus provide objective oversight of the department from an international perspective. With this external input, we will be able to identify strategic areas where efforts should be invested and which processes could be streamlined. The EAB members can also help us with future recruitment of faculty to the University of Bern and Inselspital.

We are excited to see this *new* DBMR in action and hope that our changes lead to a more efficient, but more importantly, creative scientific environment.

Sincerely,
Prof. Mark A. Rubin, MD
On behalf of the DBMR Board of Directors

Prof. Mark A. Rubin, MD

Prof. Dr. med. Anne Angelillo-Scherrer

Ass. Prof. Dr. Carsten Riether

PD Dr. phil. Marianna Kruithof-de Julio

Ass. Prof. Dr. Volker Enzmann

Information and updates can be found on the DBMR homepage – www.dbmr.unibe.ch

Key People

Management

Prof. Mark A. Rubin, MD
Director DBMR

Heads of Core Facilities

PD Dr. Fabian Blank
Live Cell Imaging (LCI)

Prof. Dr. Manfred Heller
Mass Spectrometry and Proteomics Laboratory

Dr. Stefan Müller
Cytometry Laboratory, FACS Lab

Administration and Central Services

Administrator/Finances and DBMR Secretaries
Basak Ginsbourger, Administrator
Ana Radovanovic, Secretary (until Apr.)
Marla Rittiner, Secretary
Beatrix Stalder, Secretary
Uyen Vo, Secretary

Secretary of Director
Cornita Rohda
Jasmine Stiefel

Human Resources
Rahel Tschudi (since Mar.)
Silvia Rösselet (until Mar.)
Marla Rittiner

Facility Manager
Bernhard Grossniklaus (until Nov.)
Raschid Setoud

Occupational Safety, Health Protection and Environmental Safety (OHE)
François Achermann

IT Support
Michael Ackermann
Ilker Romann
Thomas Späti (until Aug.)
Luca Sulmoni

Bioinformatics
Dr. Irene Keller (until Aug.)

Technical Services
Patrick Furer, Head Maintenance
Nivetha Ravindran, Intern

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

sitem

10

Murtenstrasse 24
(under construction)

Flow Cytometry and Cell Sorting, FCCS

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

Ph.D. (Microbiology), University of Bern, Switzerland (1996). Postdoctoral fellow (Intestinal mucosal immunology), School of Cellular and Molecular Medicine, University of Bristol, United Kingdom (2000–2001). Head, Flow Cytometry Laboratory, School of Cellular and Molecular Medicine, University of Bristol, United Kingdom, (2001). Senior Scientist, Gastroenterology (2004–2011) at DBMR. Since 2010, Head, DMBR Cytometry Laboratory / FACS Lab Core Facility.

Achievements 2020

A notable achievement during this year amidst the SARS-CoV-2 pandemic was the efficient distribution of the facility's instruments between the four individual rooms/laboratories to reduce the number and duration of personal contact between the users. This is an impressive achievement since no SARS-CoV-2 transmission has been reported in our premises despite considerable activity during the second wave of infections.

The first issue of our modular-type FACS course had a promising start but was heavily impacted by the pandemic. The course is yet to be completed.

Performance Report 2020

The shutdown of all non-SARS-CoV-2-related research activities in early spring resulted in a drastic decrease in the usage of both staff-operated cell sorters and user-operated analyzers in 2020. This decrease was reflected in the usage statistics for Q1 (-14.5 % analysis, -24.3% sorting, relative to Q1 2019), and was more pronounced in Q2 (-58.9 % analysis, -66.3 % sorting, relative to Q2 2019). Despite the second wave of SARS-CoV-2 infections in autumn and winter, the usage statistics of our analyzers recovered to normal levels for the most part, while there was a huge increase in the demand for sorting towards the end of the year (+45.8 % relative to Q4 2019). Overall, for the entire year, user-operated usage of our analyzers decreased by 23.9 % and staff-operated sorting decreased by 17.1 %, as compared to that in 2019.

FACS measurements by researchers from Inselspital clinics constituted 58.8 % of the usage while 39.8 % usage was attributed to the University of Bern institutes. Measurements by or for external parties accounted for 1.4 %. Regarding cell sorting, 71.7 % sorting experiments were performed for Inselspital clinics, 27.9 % for university institutes, and 0.4 % for external parties. A total of 60.2 % of measurements and 70.8 % of cell sorting experiments were performed by or for the DBMR groups.

Finances 2020

The FACS Lab had started the year 2020 with a negative account balance, and ended the year with a negative balance as well due to the decreased demand for our services.

Outlook 2021

In addition to the ongoing pandemic, a key event in 2021 will be the transfer of the FACS Lab, along with the other DBMR technical core facilities, to the new building at Murtenstrasse 24–28 (Insel Nord) in late autumn. The FACS Lab will then be known as the Flow Cytometry and Cell Sorting Core Facility (FCCS CF).

With the assistance of two BMA-diploma students (Biomedical analyst students), the FACS Lab is projected to complete the development of two methods that were interrupted due to the shutdown in spring 2020, before relocation. These methods, fluorescent in situ hybridization in flow (flow FISH) and the design and testing of a 17-color flow cytometry panel, are of great interest and benefit to our users.

Staff Members

Dr. Stefan Müller, Head
Bernadette Nyfeler, Laboratory technician and operational lead
Dr. Thomas Schaffer, Scientific and educational support, technical assistance
Isabelle Gsponer (M.Sc.), Laboratory technician, quality control (QC) and standard operating procedures (SOP)
Dr. Claudio Vallan, Scientific and educational support

www.dbmr.unibe.ch/services/core_facilities/flow_cytometry_and_cell_sorting/index_eng.html

Live Cell Imaging (LCI)

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

M.Sc. (Cell Biology), University of Bern, Switzerland (2003). Ph.D. (Structural Biology), University of Bern, Switzerland (2006). Postdoctoral fellow, Institute of Anatomy, University of Bern, Switzerland (2007–2008). Postdoctoral fellow, Telethon Institute for Child Health Research, Perth, Australia (2008–2009). Senior Scientist, Pulmonary Medicine (Adults), DBMR (2009–Present). Commission member, Microscopy Imaging Centre (2010–Present). Head, Live Cell Imaging (LCI) Core Facility, DBMR, University of Bern, Switzerland (2012–Present). Venia Docendi (2016)

Achievements 2020

Similar to other facilities/laboratories in DBMR, the LCI Core Facility also faced several challenges throughout 2020 in order to sustain training, services, and support at an acceptable rate and to minimize any delays due to necessary restrictions imposed by the university. Despite ongoing restrictions on in-person and further-education courses, LCI succeeded in organizing practical courses focusing on microscopy, histology, and image processing as in previous years, but optimized content for distance learning, where appropriate. This training was possible due to the long lasting and close collaboration with the Microscopy Imaging Centre (MIC).

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

Performance Report 2020

The total number of hours booked for the use of LCI equipment decreased to 4073 in 2020 from 5445 in 2019. These hours do not include systems that need to be booked on a daily basis, such as the IncuCyte S3 System. In 2020, LCI staff spent a total of 91 hours for introduction training on LCI microscopes (236 hours in 2019). Working hours spent on collaborations with other research groups from the DBMR decreased considerably to 61 (577 hours in 2019). Hours spent for technical assistance decreased to 185.5 (265 hours in 2019). As mentioned above, the facility contributed to advanced microscopy lectures and practical modules organized by the MIC. A total of 15 students were trained in the practical modules of the LCI in 2020.

Finances 2020

Due to decreased activity during the lockdown in 2020, revenues decreased slightly compared to 2019. Maintenance contracts for two important devices, the Zeiss LSM710 and IncuCyte S3, were signed in order to guarantee trouble-free usage for the coming years. As in previous years, the facility received a working credit of CHF 6000 from DBMR for general maintenance and repairs. The LCI Core Facility pays for a yearly subscription of the IMARIS software for a floating license. This software is installed on the workstations available for booking and is available to users of the facility for free.

Outlook 2021

The focus in 2021 will lie on relocating the LCI to Murtenstrasse 24 and starting operations as quickly as possible. Furthermore, the purchase of a backup/replacement system for Zeiss LSM710 is planned for 2021. The new single-point confocal system will provide state-of-the-art performance regarding resolution and scanning speed and will be installed in the new premises of the LCI Core facility at Murtenstrasse 24.

Staff Members

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

www.dbmr.unibe.ch/services/core_facilities/live_cell_imaging/index_eng.html

Mass Spectrometry & Proteomics Laboratory (Core Facility)

Protein & Cell Biology (Research Group)

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

Ph.D. (Biochemistry), University of Bern, Switzerland (1994). Postdoctoral fellow, University of Auckland, New Zealand (1995–1997). Postdoctoral fellow, University of Washington, Seattle, USA (1998). Senior assistant, University of Geneva, Switzerland (1999–2000). Senior scientist, GeneProt Inc., Geneva and DiagnoSwiss, Monthey, Switzerland (2000–2003) Head, Proteomics and Mass Spectrometry Laboratory, a DBMR Core Facility since 2008 (2003–Present). 23 years of experience in mass spectrometry, proteomics, and bioinformatics

Achievements 2020

Mass Spectrometry and Proteomics
The demand for our service continues to be high, as has been the case for several years. We have facilitated a variety of proteomics projects encompassing many different sample types from a range of species. In November, we installed a new mass spectrometry system based on trapped ion mobility technology coupled to a quadrupole time-of-flight detector. This instrument will enable us to support the increase in service requests for more complex proteome analysis. We have also developed a new approach to determine the protein concentration based on size exclusion chromatography-ultraviolet (SEC-UV). We take this opportunity to thank all our customers for their trust in our service.

Protein and Cell Biology
We have developed a method for the analysis of saliva using proteomics, due to interest from other groups. Using a robust, gel-based approach, we quantified approximately 2100 proteins, including some from mycobacterial species and microbiomes, which can indicate whether a person has an oral infection or bad dental hygiene. We have also devoted substantial effort in fine-tuning the instrument platform by optimizing the method of reversed-phase nano-column chromatography.

Outlook 2021

We will continue to work on a manuscript in which we investigate the impact of transport forces on the protein composition of circulating extracellular vesicles in peripheral blood. In October 2021, our laboratory and core facility will relocate to a new research building (Murtenstrasse 24), and much of our time will be devoted in facilitating this relocation.

Performance Report 2020

Mass Spectrometry and Proteomics
We processed approximately 1370 samples submitted by laboratories from the Faculty of Medicine (51 %), Faculty of Science (44 %), Vetsuisse Faculty (4 %), and external institutions (1 %), in 2020. This consisted of 2693 liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) runs for the generation of publishable data. This number is supplemented by 1081 QC standards and 3833 blanks for quality assurance. Despite the Covid-19 lockdown for six weeks in early spring, we were still able to process almost the same number of samples as in 2019, a clear demonstration of the on-going demand for our service.

Finances 2020

Mass Spectrometry and Proteomics
Our financial situation remains sound, in part due to our ability to perform some maintenance work ourselves. The expenses for maintaining the equipment amounted to CHF 22,000. The facility received a working credit of CHF 10,000 from the DBMR to partially cover these costs.

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Staff Members

Prof. 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 head and assistant (Core Facility & Research Group)
Natasha Buchs, Laboratory technician (Core Facility & Research Group)
Ilker Yegit, IT specialist (20 % Core Facility)
Dr. Anne-Christine Uldry, Computational scientist (80 % Core Facility & Research Group)

Collaborators

Bonadies N., University Hospital of Bern, Switzerland
Müller N. & Müller J., Institute for Animal Pathology, Vetsuisse, University of Bern, Switzerland

Teaching activities

- M.Sc. Biomedical Sciences: Tumor Biology – proteomics lecture
- M.Sc. Biology: From Genomes to Metabolomes – proteomics lecture
- M.Sc. Bioinformatics: Mass spectrometry to systems biology – course, practical, M.Sc. thesis supervision, 4-week project supervision

Publications

Heller M, Braga S, Mueller N, Müller J. Transfection with plasmid causing stable expression of a foreign gene affects general proteome pattern in Giardia lamblia trophozoites. *Frontiers: Cellular and Infection Microbiology.* 2020;10:602756. doi:10.3389/fcimb.2020.602756.

Cyrta J, De Filippo MR, Prandi D, Thienger P, Benelli M, Cooley V, Bareja R, Wilkes D, Chae SS, Cavaliere P, Dephoure N, Uldry AC, Lagache SB, Roma L, Cohen S, Jaquet M, Brandt LP, Alshalalfa M, Puca L, Sboner A, Feng F, Wang S, Beltran H, Lotan T, Spahn M, Kruithof-de Julio M, Chen Y, Ballman KV, Demichelis F, Piscuoglio S, Rubin MA. Role of specialized composition of Swi/Snf complexes in prostate cancer lineage plasticity. *Nat Commun.* 2020;1(1):5549. doi:10.1038/s41467-020-19328-1.

Duman M, Vaquie A, Nocera G, Heller M, Stumpe M, Siva D, Sankar D, Dengjel J, Meijer D, Yamaguchi T, Matthias P, Zeis T, Schaeren-Wiemers N, Hayoz A, Ruff S, Jacob C. Eef1a1 deacetylation enables transcriptional activation of remyelination. *Nat Commun.* 2020;11(1):3420. doi:10.1038/s41467-020-17243-z.

Winzer P, Müller J, Imhof D, Ritler D, Uldry AC, Braga-Lagache S, Heller M, Ojo KK, Van Voorhis WC, Ortega-Mora LM, Hemphill A. *Neospora caninum*: Differential proteome of multinucleated complexes induced by the bumped kinase inhibitor Bki-1294. *Microorganisms*. 2020;8(6):801. doi:10.3390/microorganisms8060801.

Muller J, Braga S, Uldry AC, Heller M, Muller N. Comparative proteomics of three *Giardia lamblia* strains: investigation of antigenic variation in the post-genomic era. Parasitology 2020;147(9):1008–18. doi:/10.1017/S0031182020000657.

Briand ML, Gebleux R, Richina F, Correro MR, Grether Y, Dudal Y, Braga-Lagache S, Heller M, Beerli RR, Grawunder U, Corvini PF, Shahgaldian P. Partially shielded enzymes capable of processing large protein substrates. *Chem. Commun*. 2020;56:5170–5173. doi: 10.1039/d0cc01150a.

Cosgrove J, Novkovic M, Albrecht S, Pikor NB, Zhou Z, Onder L, Morbe U, Cupovic J, Miller H, Alden K, Thuery A, O'Toole P, Pinter R, Jarrett S, Taylor E, Venetz D, Heller M, Uguccioni M, Legler DF, Lacey CJ, Coatesworth A, Polak WG, Cupedo T, Manoury B, Thelen M, Stein JV, Wolf M, Leake MC, Timmis J, Ludewig B, Coles MC. B Cell Zone Reticular Cell Microenvironments Shape Cxcl13 Gradient Formation. *Nat Commun.* 2020;11(1):3677. doi:10.1038/s41467-020-17135-2.

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

Oncogenomics

Dr. Charlotte KY Ng
charlotte.ng@dbmr.unibe.ch

Ph.D., University of Cambridge, Cambridge, United Kingdom (2012). Postdoctoral fellow, Institute of Cancer Research, London, United Kingdom (2008–2012). Postdoctoral fellow, Memorial Sloan Kettering Cancer Center, New York, USA (2013–2016). Postdoctoral fellow, University Hospital Basel, Basel, Switzerland (2016–2018). Head, Oncogenomics lab, DBMR (2019–Present)

Research highlights 2020 / Outlook 2021

The Oncogenomics lab focuses on developing and applying computational approaches to address challenges in precision oncology. In particular, we are interested in leveraging the abundance of omics data derived from clinically annotated samples in computational frameworks to discover novel biomarkers and therapeutic targets.

Systematic identification of novel cancer genes from perturbation screens

Systematic perturbation screens provide comprehensive resources for the elucidation of cancer driver genes. We developed a method, called APSiC, to analyze perturbation screens for the identification of novel cancer genes, and demonstrated its robustness in identifying genetic drivers and effectors in perturbation screens even with few samples. Applying APSiC to a deep shRNA screen, we identified well-known and novel putative mutational and amplified cancer genes across all cancer types and also in specific cancer types. Using APSiC, we also discovered tumor-promoting and tumor-suppressive effectors involved in cell cycle control, the Wnt/β-catenin, and the Hippo signaling pathways. The analysis of DRIVE using APSiC is provided on a web portal and represents a valuable resource for the discovery of novel cancer genes.

Towards more accurate mutational analysis with the Ion Torrent sequencing platform

Ion Torrent is the most used sequencing platform for diagnostics in Switzerland, but proprietary software for data analysis requires extensive manual review of the results and lacks optimized workflows for custom sequencing panels. We have developed PipeIT and demonstrated its superior positive predictive value compared to proprietary software for identifying somatic mutations from matched tumor-normal sequencing data, substantially reducing the need for manual curation of results. We are extending PipeIT to accommodate a more clinically relevant scenario in which sequencing data are only available for the tumor, but not the matched germline. PipeIT is currently being integrated into the SPHN/PHRT-funded SOCIBP infrastructure and tested using real-world data.

Proteogenomic characterization of liver cancer

Over the past decade, numerous studies have characterized the genomic and transcriptomic features and diversity of hepatocellular carcinoma (HCC), identifying molecular subgroups of HCC that differ in the expression of genes related to proliferation, stemness, metabolism, hepatocyte differentiation, and liver function. We performed proteogenomic analysis of HCCs across clinical stages and etiologies. We identified pathways that are differentially regulated at the genome, transcriptome, proteome, and phosphoproteome levels. These pathways are involved in the regulation of cellular components, cell cycle control, epithelial-to-mesenchymal transition, signaling pathways, transcriptional and translational control, and metabolism. Integrative clustering identified subgroups of HCCs that showed distinct regulation of biological processes, metabolic reprogramming, and kinase activation.

Dissecting the ecosystem of liver cancer and the cellular interactions involved

Carcinogenesis is governed by the complex interplay of the accumulation of somatic (epi)genetic alterations, transcriptional and translational regulation,

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and cell of origin and its microenvironment. The tumor microenvironment is composed of many different cells, including immune cells, fibroblasts, and endothelial cells. The complexity of this microenvironment is the result of the interaction of many factors, such as the presence of different cell types, the hierarchical structure between cells, and transcriptional activity in response to changes in the microenvironment. In a Swiss Cancer League-funded project, we profiled the transcriptome of HCCs at the single-cell level to elucidate the complexities of the tumor microenvironment of liver cancer, the extent of intra-tumor and inter-tumor cell-to-cell variability, and the interaction between cell types, all of which are crucial for a systematic understanding of the tumor ecosystem. We anticipate that our project will reveal tumor-extrinsic and tumor-intrinsic factors that shape the tumor ecosystem of liver cancer. We are currently profiling additional cancerous livers as well as normal livers to define the biological processes and cellular interactions that are disrupted in liver cancer.

Group Members

Dr. Charlotte K Y Ng, Group Leader
Dr. Andrej Benjak, Senior Bioinformatician
Désirée Schnidrig, Bioinformatician (since Jul.)
Dr. Izabela Biedroń, Master student (since Sep.)
Maryam Abdipourbozorgbaghi, Master student (since Sep.)

Collaborators

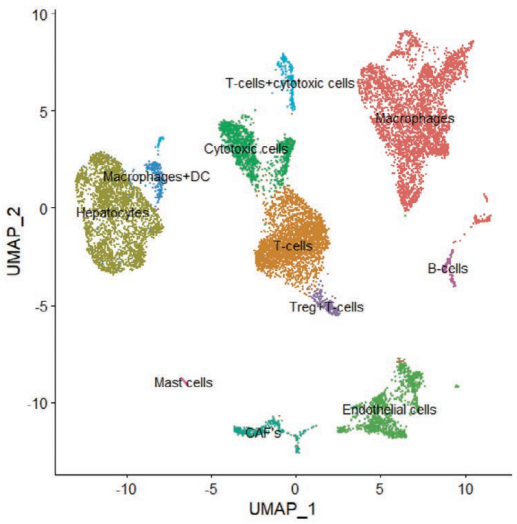
Hall MN, University of Basel, Basel, Switzerland
Heim MH, University of Basel, Basel, Switzerland
Necsulea A, University of Lyon, Lyon, France
Piscuoglio S, University of Basel, Basel, Switzerland
Powell S, Memorial Sloan Kettering Cancer Center, New York, USA
Reis-Filho JS, Memorial Sloan Kettering Cancer Center, New York, USA
Roma G, Novartis, Basel, Switzerland
Terracciano LM, Humanitas University, Milan, Italy

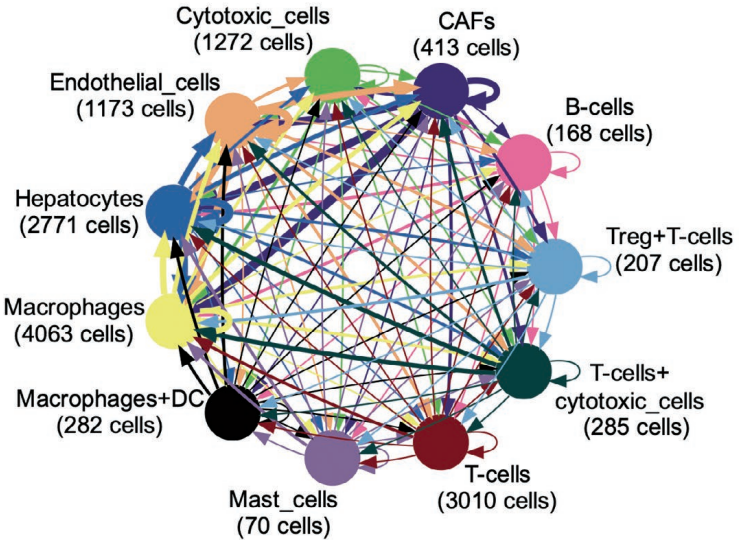
Teaching Activities

- Certificate of Advanced Studies in Personalized Molecular Oncology, University of Basel, Switzerland
- M.Sc. Program in Bioinformatics & Computational Biology, University of Bern, Switzerland

Publications

Link to publication list:
https://publons.com/researcher/3306695/charlotte-k-y-ng/publications/





Bone Biology & Orthopaedic Research

Prof. Dr. Willy Hofstetter
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M.Sc. (Biochemistry), ETH Zurich, Zurich, Switzerland (1975). Ph.D. (Biochemistry), Children's Hospital, Inselspital, DBMR, Basel, Switzerland (1979) (Supervisor: Prof. N. Herschkowitz). Postdoctoral fellow, University of Georgia, USA (1983) (Supervisor: Prof. D. DerVartanian). Postdoctoral fellow, Institute of Pathophysiology, University of Bern, Switzerland (1986) (Supervisor: Prof. H. Fleisch). Head of the DBMR Research Group for Bone Biology and Orthopedic Research (2007–Present)

Research highlights 2020 / Outlook 2021

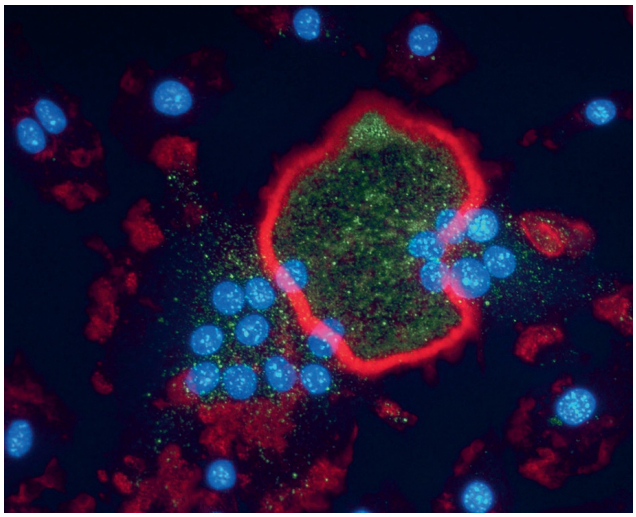
Our research group was focused on the following projects in 2020:
For several years, the study of the mechanisms of bone healing and of the modulation of bone healing by osteogenic growth factors has been a major focus of our research group. Previously, we used a mouse femora osteotomy model to assess the effects of osteoporosis, treatment with bisphosphonates, and stability of osteosynthesis on the healing process. In a new project, the same pathophysiological model was adapted to critical-size bone defects that were filled with CaP ceramic implants as carriers for growth factors. The healing process is being investigated using histological and molecular technologies. After performing a pilot study, as reported in the 2019 annual report, we started the main study, collected data, and will analyze it in the forthcoming months. This work is performed by Franziska Strunz (Ph.D. student), in collaboration with Prof. Marc Bohner, RMS Bettlach, and PD Dr. Nikola Saulacic (Maxillofacial Surgery, Inselspital, Bern).

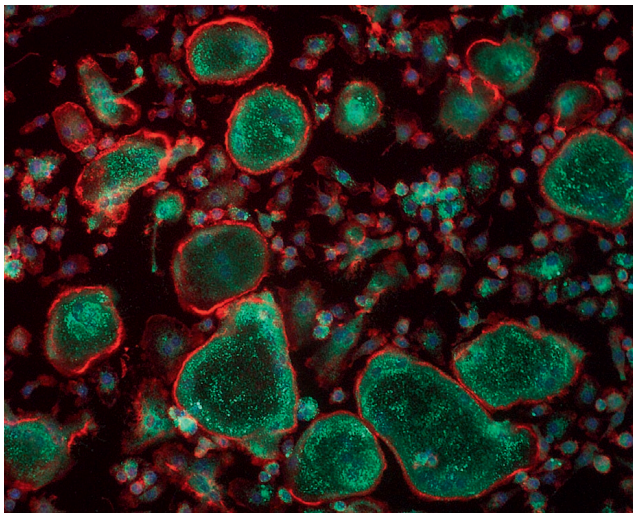
We continued with our studies on iron metabolism in osteoclasts in 2020. For this purpose, we investigated the subcellular distribution of iron and proteins modulating iron metabolism in osteoclasts. In particular, the kinetics of subcellular trafficking of iron was monitored. Iron was found to be distributed mainly in two pools, a cytoplasmic labile iron pool that disappeared within 4 hours, and a membrane vesicle associated with a stable iron pool. Furthermore, transferrin was found to be recycled within 4 hours, while the distribution of transferrin receptor did not visibly change. To corroborate these findings, the subcellular localization of the components of iron metabolism will be assessed microscopically in intact cell, by Cécile Mosimann and Silvia Dolder, Group for Bone Biology & Orthopedic Research.

The skeletal phenotype of Styx mice (serine/threonine/tyrosine-interacting protein) is being investigated in collaboration with PD Dr. Philippe Krebs and Wen Jie Yeoh (Institute of Pathology, University of Bern). Preliminary data demonstrated that Styx mice are osteoporotic. The vertebral and long bones differed in their microarchitecture. In the vertebrae of Styx mice, Bone Density (BV/TV) decreased despite an increase in the number of trabeculae, while BV/TV and the number of trabeculae were both reduced in the metaphyses of long bones. Studies in cell cultures addressing the development of osteoclasts have not revealed striking differences between Styx and wt mice in the capacity of osteoclast progenitor cells (OPCs) to develop into osteoclasts. In future studies, the role of the hematopoietic and stromal microenvironments in the development and activation of bone cell lineages will be further elucidated by Fatemeh Safari, in collaboration with Prof. Dr. Frank Klenke (University Clinics of Orthopedic Surgery, Inselspital, Bern).

Gadolinium (Gd) is widely used as a contrast agent in radiologic diagnostics. To address the potential effects of long-term storage of Gd in bone, we investigated the effects of Gd on the development and activity of osteoblast and osteoclast lineage cells *in vitro*. In these studies, the effects of Gd on the growth and differentiation of osteoblast lineage cells in relation to their binding molecules (complex formation) were analyzed. Furthermore, the differences in the effects of free Gd as compared to complexed Gd were elucidated by Franziska Strunz (Ph.D. student) in collaboration with Dr. Rainer Egli (Department for Radiology, Inselspital, Bern and the RMS, Bettlach.

www.bonebiology.dbmr.unibe.ch
www.dbmr.unibe.ch/research/individual_research_labs/bone_biology_amp_orthopaedic_research/index_eng.html





Group Members

Prof. Dr. Willy Hofstetter, Group leader
Silvia Dolder, Laboratory technician
Mark Siegrist, Laboratory technician
Fatemeh Safari, Ph.D. student
Franziska Strunz, Ph.D. student
Margaux Bringardner, Master student
Roman Weber, Intern (until May)
Cécile Mosimann, Intern (since Nov.)

Clinicians in collaboration with the group
PD Dr. Rainer Egli, Project leader
Prof. Dr. Frank Klenke, Project leader

Collaborators

Bohner M, RMS Foundation, Bettlach, Switzerland
Bonny O, Universite de Lausanne, Lausanne, Switzerland
Fuster D, Albano G, Inselspital, Bern, Switzerland
Saulacic N, Inselspital, Bern, Switzerland
Siebenrock KA, Inselspital, Bern, Switzerland
Philippe Krebs, Wen Jie Yeoh, Pathology, Bern, Switzerland

Grants

- Alfred & Anneliese Sutter-Stöttner Foundation (to Dr. Willy Hofstetter)
- RMS Foundation (to Dr. Willy Hofstetter)
- CTU Forschungsgrant Inselspital (to Dr. Rainer Egli)
- Bangerter-Rhyner Stiftung (to Dr. Rainer Egli)

Teaching Activities

- M.Sc. Biomedical Engineering: Osteology course (Hofstetter/ Saulacic)
- 2nd year medical students: Kidney block – Calcium and phosphate metabolism (Hofstetter)
- Master thesis Margaux Bringardner (M.Sc. Biomedical Engineering) "Investigation of the contribution of SHIP1 and immune cells to bone cell lineages"

Publications

May RD, Frauchiger DA, Albers CE, Hofstetter W, Gantenbein B. Exogenous stimulation of human intervertebral disc cells in 3-dimensional alginate bead culture with Bmp2 and L51p: cytocompatibility and effects on cell phenotype. *Neurospine*. 2020;17(1):77–87. doi.org/10.14245/ns.2040002.001.

Saulacic N, Munoz F, Kobayashi E, Chappuis V, Gonzales-Cantalapiedra A, Hofstetter W. Effects of local application of alendronate on early healing of extraction socket in dogs. *Clin Oral Investig*. 2020;24:1579–89. doi.org/10.1007/s00784-019-03031-7.

Brigger D, Riether C, van Brummelen R, Mosher KI, Shiu A, Ding Z, Zbaren N, Gasser P, Guntern P, Yousef H, Castellano JM, Storni F, Graff-Radford N, Britschgi M, Grandgirard D, Hinterbrandner M, Siegrist M, Moullan N, Hofstetter W, Leib SL, Villiger PM, Auwerx J, Villeda SA, Wyss-Coray T, Noti M, Eggel A. Eosinophils regulate adipose tissue inflammation and sustain physical and immunological fitness in old age. *Nat Metab*. 2020;8:688–702. doi.org/10.1038/s42255-020-0228-3.

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

Link to DBMR Network for Bone & Joint Research:
https://www.dbmr.unibe.ch/unibe/portal/fak_medizin/ber_insklin/dept_bmr/content/e39405/e40552/e691896/files691909/180611ClusterDBMR_BoneJoint_eng.pdf

Cardiac Development and Reprogramming

Marco Osterwalder, Ph.D.
SNSF Eccellenza Assistant Professor
marco.osterwalder@dbmr.unibe.ch

Ph.D. (Cell Biology), Department for Biomedicine of the University of Basel, Switzerland (2012). Postdoctoral researcher, Department for Biomedicine of the University of Basel, Switzerland (2012–2014). Postdoctoral fellow, Mammalian Functional Genomics Group at Lawrence Berkeley National Laboratory (LBNL), Berkeley, California, USA (2014–2018). Project scientist, Mammalian Functional Genomics Group at Lawrence Berkeley National Laboratory (LBNL), Berkeley, California, USA (2018–2019). SNSF Eccellenza Professorial Fellowship (2019). Group leader, DBMR, Cardiac Development and Reprogramming (May 2020–Present)

Research Highlights 2020

We are a new group at the DBMR and our main research focuses on understanding the gene regulatory mechanisms driving cardiac differentiation and the formation of the four-chambered mammalian heart. We also explore novel strategies based on epigenome editing for the induction of cardiac reprogramming in non-myocytes, a process with potential for in situ heart repair. We leverage a combination of genome engineering, genetics and functional genomics in mice and embryonic stem (ES) cells to define *cis*-regulatory modules with critical functions in mammalian heart development, which carry potential as driver sequences for cardiac tissue engineering and reprogramming.

Transcriptional enhancers underlying heart development and congenital heart disease

Transcriptional enhancers are known as the fundamental *cis*-regulatory elements in mammalian genomes and are required for tight control of spatio-temporal gene expression. Enhancers can be located hundreds of thousands of base pairs apart from their target gene(s), and epigenomic profiling studies currently predict the presence of approximately 1 million enhancers in the human genome. It is our overarching interest to functionally characterize the regulatory domains near important cardiac genes and to study the impact of heart disease-associated (non-coding) genomic variants on enhancers, thereby contributing to resolving the etiology of congenital heart disease.

Dissecting the enhancer landscapes of critical cardiac regulators

In the framework of our SNSF Eccellenza research program, we combine CRISPR/Cas9 applications, fluorescent reporter tagging, and single-cell transcriptome profiling to explore the functional necessity of heart enhancers near the *Hand2 and Gata4* genes, essential regulators of heart morphogenesis, and expressed in multiple cardiac cell types. We have generated a series of cardiac enhancer knockout mouse models to investigate individual cardiac enhancer functions *in vivo*, which will shed light on the *cis*-regulatory complexities underlying the expression of cardiac transcription factors. We are also constructing versatile fluorescent reporter transgenes, which in combination with a novel method for efficient site-directed transgenic knock-in, will eventually allow us to track spatiotemporal enhancer activities at single-cell resolution.

A gene desert essential for cardiac pacemaker function in embryos

In collaboration with other groups, we functionally profiled the extensive gene desert located downstream of the *Shox2* transcriptional regulator. Using epigenomic analysis, transgenic assays, and chromatin capture, we identified critical enhancer elements with defined tissue-specific activities in the developing limb, brain, craniofacial structures, and cardiac pacemaker domain of the heart. In particular, we found that embryos lacking the gene desert are unable to survive, since *shox2* expression is depleted in cardiac pacemaker cells of the sinoatrial node. A preliminary version of this study is available at Biorxiv (see "Link to publication list").

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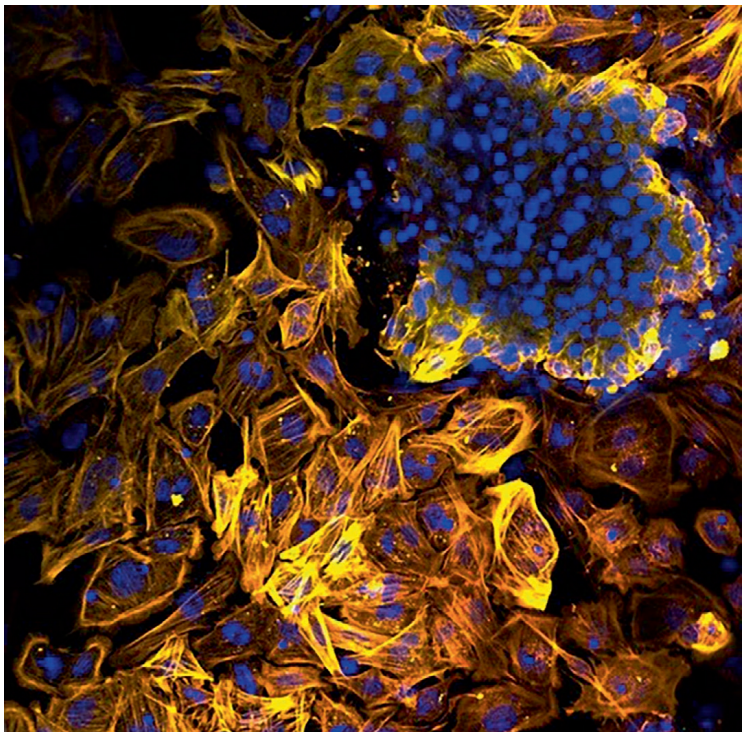

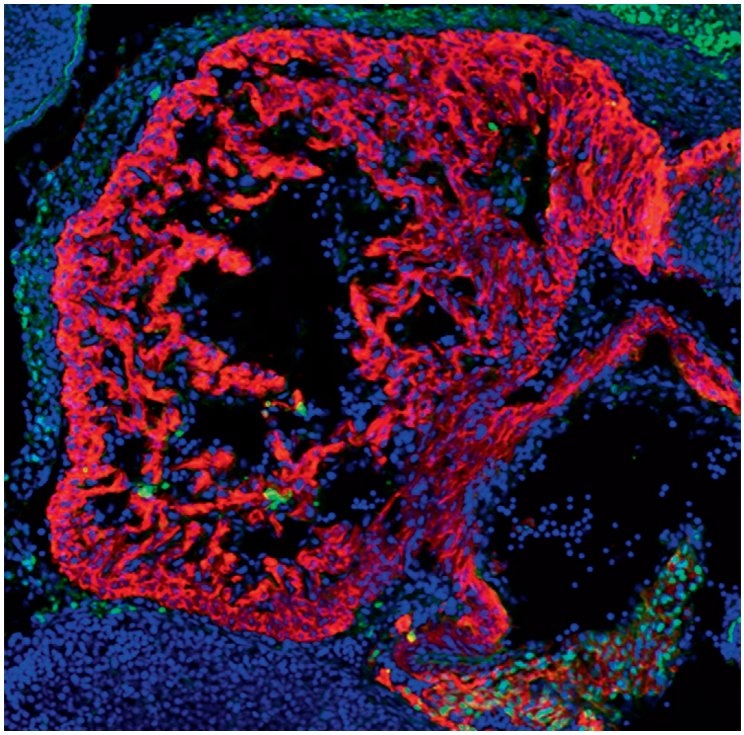

Group Members

Dr. Marco Osterwalder, Group leader (since May)
Dr. Julie Gamart, Laboratory manager and technician (since June)
Virginia Roland Victor, Ph.D. student (since Sep.)
Matteo Zoia, Ph.D. student (since Nov.)

Collaborators

Andrey G, University of Geneva, Geneva, Switzerland
Barozzi I, Medical University of Vienna, Vienna, Austria
Cobb J, University of Calgary, Calgary, Canada
Firulli AB, Indiana University School of Medicine, Indianapolis, Indiana, USA
Lopez-Rios J, CABD, Sevilla, Spain
Mercader N, University of Bern, Bern, Switzerland
Pedrazzini T, University of Lausanne, Lausanne, Switzerland
Pennacchio LA, Visel A, Dickel DE, Lawrence Berkeley National Lab, Berkeley, California, USA
Windecker S, University of Bern & Inselspital, Bern, Switzerland
Zeller R, University of Basel, Basel, Switzerland

Local Research Clusters

- Cardiovascular Disease Program, DBMR, University of Bern, Switzerland
- Cluster for Cardiovascular Research (CVRC), University of Bern, Switzerland

Teaching Activities

- Elective Modules, Master course Biomedical Sciences (BMSc), University of Bern, Switzerland
- BMSc, Master class, Module Heart (HS2021)

Publications

Link to publication list:
https://www.osterwalderlab.com/publications

Cardiovascular Research

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

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

Research highlights 2020 / Outlook 2021

Together with Yvonne Döring (Main applicant, Division of Angiology, Inselspital Bern), Nadia Mercader (Institute of Anatomy, University of Bern), Britta Engelhardt (Theodor Kocher Institute, University of Bern) and 10 project partners: SNSF-funded NRP78 COVID-19 grant (1.95 Mio CHF) "Unravelling consequences of SARS-CoV-2 mediated inflammatory immune responses in heart and vasculature – CoVasc".

Robert Rieben as principle investigator together with Jörg Seebach, Geneva University Hospital, and Eckhard Wolf, Ludwig-Maximilian University, Munich, Germany: SNSF-funded Sinergia-grant (2.656 Mio CHF) for their project "Xeno2Cure – advanced engineering and testing of organ donor pigs". Starting date 01.04.2021.

One new collaborator, Valentina Zollet (PhD-student) joined our team in 2020 to work on our CSL Research Acceleration Initiative Project "The role of citrullination in ischemia/reperfusion injury: identifying new therapeutic targets and biomarkers". The PI of this project is Nicoletta Sorvillo.

Basic science SNF grant "Endothelial cell protection in ischemia / reperfusion injury: Investigation into the roles of the glycocalyx and the plasma cascade systems": We further developed the 3D microfluidic system for endothelial cell culture to investigate the role of the endothelial cell glycocalyx as a scavenger of plasma proteins.

US Department of Defense "Peer-Reviewed Orthopedic Research Project": Extracorporeal pig limb perfusions as well as in vivo reperfusions of long-term ischemic limbs on pigs were performed despite restrictions due to the COVID-19 pandemic. Work performed in close collaboration with the Experimental Surgery Facility, the Clinic of Plastic and Hand Surgery, and the perfusionist's team of the Clinic of Cardiovascular Surgery.

The SNF-funded large animal study on local immunosuppression in vascularized composite allotransplantation (VCA) continued (PI: Radu Olariu, Plastic and Hand Surgery). However, large animal experiments had to be stopped in March 2020 because of the COVID-19 pandemic and the renovation of the Experimental Surgery Facility.

Together with the Department of Cardiology, Inselspital, the Experimental Surgery Facility, and HAYA Therapeutics, Inc., an Innosuisse funding for CHF 835'00 was obtained. The project, entitled "Developing a next-generation targeted anti-fibrotic therapy for heart failure in a porcine model", aims at preventing myocardial fibrosis as a consequence of myocardial infarction.

www.cvrc.unibe.ch/research/ischemia___reperfusion/
www.dbmr.unibe.ch/research/individual_research_labs/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
Anastasia Milusev, PhD Student
Isabel Arenas, PhD Student
Nicoletta Sorvillo, Postdoc
Josip Mikulic, Postdoc until May 2020
Valentina Zollet, PhD Student
Mariafrancesca Petrucci, DVM-PhD Student at ESF (Daniela Casoni)

Collaborators

Garweg J, Zandi S, Berner Augenklinik am Lindenhofspital, Bern (CH)
Guenat O, University of Bern (CH)
Heinis Ch, EPFL, Lausanne (CH)
Jenni HJ, Inselspital (CH)
Langelé B, Duisit J, Université Catholique de Louvain, Brussels (BE)
Luciani P, University of Bern (CH)
Yonglun Luo, Aarhus University (DK)
Olariu R, Constantinescu MA, Inselspital (CH)
Reichart B, Abicht J, Ludwig Maximilian University of Munich (DE)
Schnieke A, Fischer K, Technical University of Munich (DE)
Waskow C, Technical University of Dresden (DE)
Seebach J, Geneva University Hospital (CH)
Spirig R, CSL Behring AG (CH)
Vögelin E, Inselspital (CH)
von Gunten S, Frias Boligan K, University of Bern (CH)
Wolf E, Klymiuk N, Bähr A, Ludwig Maximilian University of Munich (DE)
Döring Y, Inselspital (CH)
Mercader N, University of Bern (CH)
Engelhardt B, University of Bern (CH)
Praz F, Gräni C, Inselspital (CH)
HAYA Therapeutics SA, Lausanne (CH)
CSL Behring AG, Bern (CH)

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

Längin M, Reichart B, Steen S, Sjöberg T, Paskevicius A, Liao Q, Qin G, Mokelke M, Mayr T, Radan J, Issl L, Buttgereit I, Ying J, Fresch AK, Panelli A, Egerer S, Bähr A, Kessler B, Milusev A, Sfriso R, Rieben R, Ayares D, Murray PJ, Ellgass R, Walz C, Klymiuk N, Wolf E, Abicht JM, Brenner P. Cold non-ischemic heart preservation with continuous perfusion prevents early graft failure in orthotopic pig-to-baboon xenotransplantation. Xenotransplantation. 2020 Aug 25:e12636. doi: 10.1111/xen.12636. Epub ahead of print. PMID: 32841431

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Wilbs J, Kong XD, Middendorp SJ, Prince R, Cooke A, Demarest CT, Abdelhafez MM, Roberts K, Umei N, Gonschorek P, Lamers C, Deyle K, Rieben R, Cook KE, Angelillo-Scherrer A, Heinis C. Cyclic peptide FXII inhibitor provides safe anticoagulation in a thrombosis model and in artificial lungs. Nat Commun. 2020 Aug 4;11(1):3890. doi: 10.1038/s41467-020-17648-w. PMID: 32753636; PMCID: PMC7403315

Reichart B, Längin M, Radan J, Mokelke M, Buttgereit I, Ying J, Fresch AK, Mayr T, Issl L, Buchholz S, Michel S, Illgass Reinhard, Mihalj M, Egerer S, Bähr A, Kessler B, Kemter E, Kurome M, Zakhartchenko V, Steen S, Sjöberg, Paskevicius A, Krüger L, Fiebig U, Denner J, Godehardt AW, Tönjes RR, Milusev A, Sfriso R, Rieben R, Walz C, Kirchner T, Ayares D, Lampe K, Schönmann U, Hagl C, Wolf E, Klymiuk N, Abicht JM, Brenner P. Pig-to-non-human primate heart transplantation: the final step toward clinical xenotransplantation? Journal of Heart and Lung Transplantation, 2020. DOI: https://doi.org/10.1016/j.healun.2020.05.004

Sfriso R, Rieben R. 3D Cell-Culture Models for the Assessment of Anticoagulant and Anti-Inflammatory Properties of Endothelial Cells. Methods Mol Biol. 2020;2110:83-97. DOI:10.1007/978-1-0716-0255-3_6

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

Precision Oncology

Prof. Mark A. Rubin, MD
mark.rubin@dbmr.unibe.ch

Prof. Rubin is the Director of the Department of Biomedical Research and heads the Bern Center for Precision Medicine. He is one of the leaders in prostate cancer (PCa) biology and cancer precision medicine research. His landmark studies have defined many molecular features of PCa and their involvement in disease progression. Many of his discoveries have been translated into clinical tests.

Research highlights 2020 / Outlook 2021

Precision oncology applies precision medicine approaches to understand the mechanisms of PCa progression and therapy resistance. In 2020, several projects of the group received further support from Swiss and international fellowships and awards. In 2021, the group will continue to develop additional research projects to investigate the impact of epigenetic and epitranscriptomic events on gene regulation, particularly in the context of advanced PCa.

Defining the heterogeneity of brain metastatic PCa: A pan-Swiss project

In this pilot study within the larger Swiss Personalized Health Network (SPHN)-funded Swiss Oncology and Cancer Immunology Breakthrough Platform for Precision Oncology (SOCIBP) platform sponsored by National Cancer Institute (NCI), matched samples of primary and brain metastatic PCa were collected across seven Swiss cantons. Tumor heterogeneity and its molecular/genomic landscape were defined to better understand this unexplored metastatic location.

Understanding non-canonical phosphatidylinositol kinases in the maintenance of prostate metabolism

In this Swiss National Science Foundation (SNSF) and Marie Skłodowska-Curie Actions (MSCA)-funded project, we posit that PI5P4K lipid kinases influence PCa metabolism. In 2020, we validated findings from multi-omic datasets that characterized changes in cell metabolism using PI5P4K-depleted systems and have continued our work characterizing the first prostate cell-type specific mouse models to target expression in vivo.

Towards precision therapy for speckle-type POZ protein (SPOP) mutant PCa

This project, funded by the Swiss Krebsliga in collaboration with Ruedi Aebersold (ETH Zurich), focuses on identifying the downstream effectors of SPOP by targeted proteomics.

Hijacking transcription-coupled DNA repair for cancer therapy

This SNF Sinergia-funded project in collaboration with Shana Sturla (ETH Zurich) and Orlando Schärer (IBS Korea) integrates chemistry, biology, and precision oncology to explore new therapeutic strategies that exploit vulnerabilities in the transcription-coupled nucleotide excision repair (TC-NER) pathway in PCa patients.

Towards understanding and modulating neuroendocrine transdifferentiation in PCa

This project seeks to understand the lineage plasticity of neuroendocrine PCa (NEPC), which will help create therapeutic approaches that can delay or inhibit this terminal form of PCa and lead to the development of co-targeted therapies which will prevent disease progression.

Understanding the role of aberrant splicing in PCa progression

In PCa, a major clinical challenge is posed by the occurrence of constitutively active androgen receptor splice variants (e.g., AR-V7) which are truncated at the C-terminus and are therefore resistant to AR signaling inhibitors (for example, abiraterone or enzalutamide). This project sought to understand how aberrant splicing participates in therapy resistance in PCa.

www.rubinlab.com

Role of m6A methylation in gene regulation and PCa progression

This Prostate Cancer Foundation (PCF) and National Institute of Health (NIH)-funded project aims to explore the role of m6A modification of mRNAs in PCa. In 2020, we determined the role of reduced METTL3 expression and resistance to androgen-targeted therapy. A manuscript summarizing this research is currently under peer review.

Immune-radiation therapy for metastatic castration-resistant PCa

The aim of this PCF-funded project co-led by George Coukos (CHUV, Centre hospitalier universitaire vaudois) is to expand on current immuno-oncologic approaches and identify potential immunotherapeutic targets for metastatic PCa.

Elucidating the role of metastatic niche

Through the development of novel in vitro models of metastatic PCa, we aimed to identify the mechanisms by which tumor cells metastasize to distant sites.

Development of a platform for genitourinary cancer patient-derived organoids

This 3RCC funded project in collaboration with Marianna Kruithof-de Julio (University of Bern) aims to develop patient-derived organoids from bladder and prostate cancer to study tumor growth, drug response, and resistance to therapies.

Group Members

Prof. Mark A. Rubin, MD, Group leader
Dr. Anke Augspach, Postdoctoral fellow
Dr. Laura Brandt, Postdoctoral fellow
Dr. Kellie Anne Cotter, Postdoctoral fellow
Dr. Joanna Triscott, Postdoctoral fellow
Dr. Alison Ferguson, Postdoctoral fellow
Dr. med. Antonio Rodriguez, Resident pathologist
Dr. Stephan Christen, Lab manager
Matthias Reist, Technician
Muriel Jaquet, Technician
Sina Maletti, Technician
Philip Rubin, Technician
Izzem Gemici, Technician
Phillip Thienger, Ph.D. student
Marika Lehner, Technician (since Aug.)
Lia Mela, NCCR Predoctoral student (June–Dec.)

Selected Collaborators

Emerling B, Sanford Burnham Prebys Medical Discovery Institute, San Diego, California, USA
Aebersold R, ETH Zurich, Switzerland
Moch H, University of Zurich, Switzerland
Coukos G, University of Lausanne, Switzerland
Rätsch G, ETH Zurich, Switzerland
Piscuoglio S, University of Basel, Switzerland
Gerstein M, Yale University, New Haven, Connecticut, USA
Kanadia R, University of Connecticut, USA

Selected Publications

Arriaga J, Panja S, Alshalalfa M, Zhao J, Zou M, Giacobbe A, Madubata CJ, Kim JY, Rodriguez A, Coleman I, Virk RK, Hibshoosh H, Ertunc O, Ozbek B, Fountain J, Karnes RJ, Luo J, Antonarakis ES, Nelson PS, Feng FY, Rubin MA, De Marzo AM, Rabadan R, Sims PA, Mitrofanova A, Abate-Shen C. A MYC and RAS co-activation signature in localized prostate cancer drives bone metastasis and castration resistance. *Nat Cancer.* 2020;1:1082–1096. doi.org/10.1038/s43018-020-00125-0.

Auguste A, Blanc-Durand F, Deloger M, Le Formal A, Bareja R, Wilkes DC, Richon C, Brunn B, Caron O, Devouassoux-Shisheboran M, Gouy S, Morice P, Bentivegna E, Sboner A, Elemento O, Rubin MA, Pautier P, Genestie C, Cyrta J, Leary A. Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) beyond SMARCA4 mutations: A comprehensive genomic analysis. *Cell.* 2020;9(6):1496. doi: 10.3390/cells9061496.

Cyrta J, Augspach A, de Filippo MR, Prandi D, Thienger P, Benelli M, Cooley V, Bareja R, Wilkes D, Chae S-S, Cavaliere P, Dephure N, Uldry A-C, Lagache SB, Roma L, Cohen S, Jaquet M, Brandt LP, Alshalalfa M, Sboner A, Feng F, Wang S, Beltran H, Lotan T, Spahn M, Kruithof-de Julio M, Chen Y, Ballman KV, Demichelis F, Piscuoglio S, Rubin MA. Role of specialized composition of SWI/SNF complexes in prostate cancer lineage plasticity *Nat Commun*. 2020;11:5549. doi.org/10.1038/s41467-020-19328-1.

Janowczyk A, Leo P, Rubin MA. Clinical deployment of AI for prostate cancer diagnosis. *Lancet Digit Health*. 2020;2(8):e383-e384. doi: 10.1016/S2589-7500(20)30163–1.

Liu D, Shoag JE, Poliak D, Goueli RS, Ravikumar V, Redmond D, Vosoughi A, Fontugne J, Pan H, Lee D, Thomas D, Salari K, Wang Z, Romanel A, Te A, Lee R, Chughtai B, Olumi AF, Mosquera JM, Demichelis F, Elemento O, Rubin MA, Sboner A, Barbieri CE. Integrative multiplatform molecular profiling of benign prostatic hyperplasia identified distinct subtypes. *Nat Commun*. 2020;11(1):1987. doi: 10.1038/s41467-020-15913-6.

Lotan TL, Tomlins SA, Bismar TA, Van der Kwast TH, Grignon D, Egevad L, Kristiansen G, Pritchard CC, Rubin MA, Bubendorf L. «www.ncbi.nlm.nih.gov/pubmed/32044806/» Report From the International Society of Urological Pathology (ISUP) Consultation Conference on Molecular Pathology of Urogenital Cancers. I. Molecular Biomarkers in Prostate Cancer. Am J Surg Pathol. 2020 Jul;44(7):e15-e29. doi: 10.1097/PAS.0000000000001450.

Rubin MA, Bristow RG, Thienger PD, Dive C, Imielinski M. Impact of Lineage Plasticity to and from a Neuroendocrine Phenotype on Progression and Response in Prostate and Lung Cancers. Mol Cell. 2020 Nov 19;80(4):562-577. doi: 10.1016/j.molcel.2020.10.033.

Thienger P, Rubin MA SETting Up for Epigenetic Regulation of Advanced Prostate Cancer. Cancer Cell. 2020 Sep 14;38(3):309-311. doi: 10.1016/j.ccell.2020.08.009.

DBMR Research Groups

The following is the list of the 42 research groups from different departments of the institution and other clinics, that were affiliated with the DBMR as of 2020.

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

Angiology: Prof. Dr. Iris Baumgartner, Prof. Dr. Yvonne Döring

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

Cardiology: Prof. Dr. Stephan Windecker, Prof. Dr. Christian Seiler, Prof. Dr. Stefano Rimoldi, PD Dr. med. Stefan Stortecky, Prof. Dr. Thomas Suter, Prof. Dr. Hildegard Tanner, PD Dr. Emrush Rexhaj

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Cranio-Maxillofacial Surgery:
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Endometrium & Ovary:
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Experimental Hemostasis:
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Experimental Radiology:
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Research highlights 2020 / Outlook 2021

In response to the COVID-19 pandemic, we recently initiated research efforts to uncover the biological and pharmaceutical aspects of SARS-CoV-2 infectivity, with the goal of developing new routes toward fighting the disease. We have begun to study the dependence of the predisposition to SARS-CoV-2 infection on the host and viral genetic variants. In addition, we are screening compounds in collaboration with Prof. Jean-Louis Reymond, exploring substances that inhibit the docking of the virus to the host receptor.

Clinically, COVID-19 manifests in many different ways, ranging from very mild or flu-like symptoms to pneumonia, acute respiratory distress syndrome, and death. We posit that genetic variants of both SARS-CoV-2 itself and human SARS-CoV-2 host genes of cells in affected organs (lungs, gastrointestinal tract, and kidneys) have a significant impact on the clinical outcome, along with other risk factors such as age, diabetes, high blood pressure, and immunological determinants.

In our project, we are studying genetic variants of several host genes, including: 1) the angiotensin-converting enzyme 2 gene (ACE2), which encodes the virus receptor; 2) the *TMPRSS2* gene, which encodes the serine protease needed to cleave the viral spike protein; and 3) genes encoding different SLC6 amino acid transporters that are associated with ACE2 and likely affect SARS-CoV-2 infection.

To investigate the factors that affect SARS-CoV-2 infection in epithelial cells of the lung, intestine, and kidney, we used a combination of biochemical assays, such as microscale thermophoresis to determine the binding affinity of SARS-CoV-2 receptor binding domain (RBD) to ACE2, and the SARS-CoV-2 pseudovirus entry assay to reveal viral load. Using these approaches, we aim to clarify the roles of genetic variants of these host and viral proteins in conferring COVID-19 severity, and to screen for inhibitors of viral susceptibility as hit/lead compounds for the development of novel treatment strategies. The understanding of the biochemical effects of genetic variants of the host genes and coronavirus will be correlated with clinical data from large cohorts of COVID-19 patients. We believe that validation of our results from these large cohorts of patients with different clinical manifestations will help to develop risk-adapted safety and treatment strategies based on the genomic profile of patients, in combination with the emerging new coronavirus variants that are more infectious.

Based on our compound screening efforts, we hope to lay the foundations for the development of novel antiviral treatments, such as oral or nasal spray formulations of any antiviral agents that can be identified as an alternative to vaccination.

We acknowledge funding from the Bernese Center of Precision Medicine and the National Research Program NRP78 (https://twitter.com/nrp78_covid19/status/1349752399834058753).

www.bioparadigms.org/hedigerlab/index.html

Group Members

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Dr. Bartlomiej Augustynek, Postdoctoral fellow
Dr. Rajesh Bhardwaj, Postdoctoral fellow
Damian Nydegger, Ph.D. student
Dr. Benjamin Clémençon, Postdoctoral fellow (until Nov.)
Dr. Gergely Gyimesi, Postdoctoral fellow
Dr. Palanivel Kandasamy, Postdoctoral fellow
Dr. Jonai Pujol, Postdoctoral fellow

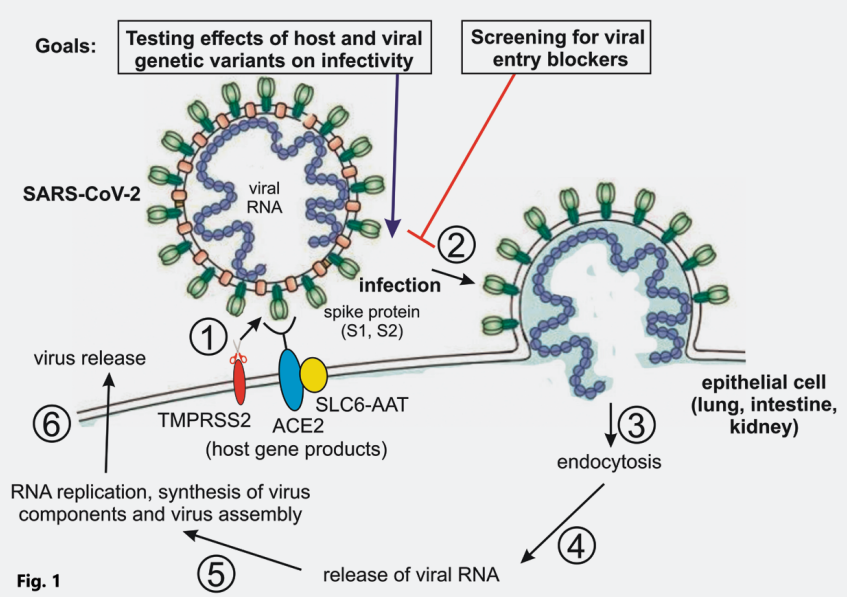

Fig. 1

Collaborators

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Precision Oncology

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Research Highlights 2020

An estimated 1 in 7 men in Europe will develop prostate cancer by the age of 60, ranging from mild to untreatable disease condition. Unlike other cancer types, prostate cancer is heavily influenced by androgen hormone signaling. Androgens activate the androgen receptor (AR), and drives the metabolic state of prostate cells to favor cellular growth and survival. Standard treatment strategies for prostate cancer involve blocking the AR using multiple approaches, including hormone-reducing surgery and AR-targeting drugs. While these approaches have improved the clinical treatment of prostate cancer, patients with hormone-insensitive disease may develop resistance to these therapies. There is a need to better understand the mechanisms that control prostate cell transition from a hormone-driven to resistant disease.

Particular traits of the prostate organ might explain why it is prone to form tumors and how it develops resistance to therapies. Studies have found that lipid production and consumption increase when prostate cancer develops. In addition, molecules that regulate members of the phosphatidylinositol (PI) lipid family are frequently altered in the genome of prostate cancer tumors. There is a direct connection between some PI pathways and AR; however, a great deal remains unknown regarding the large family of PI enzymes.

Exploitation of potential vulnerabilities in aggressive prostate cancer through a better understanding of its cellular metabolism is possible. Dr. Triscott's research involves investigation of a relatively unknown PI enzyme called PIP4K2. PIP4K2 is responsible for generating PIP2 in an alternative way. In her future work, Dr. Triscott will use pre-clinical *in vitro* tumor models to detect the effect of PIP4K2 knockout in prostate cells. This project is the first to investigate the role of PIP4K2 in prostate biology, under conditions when androgen hormones are blocked. Dr. Triscott will use markers to image different prostate cells before and after hormone depletion. She will also implement state-of-the-art single-cell sequencing technology to uncover how PIP4K2 possibly controls metabolic stress when prostate cells no longer depend on AR. Finally, Dr. Triscott's work will directly examine the potential for developing new drugs that target PIP4K2. Her experiments will test whether a decrease in PIP4K2 using genetic tools will impact the growth in established prostate tumor models.

Group Members

Prof. Mark A. Rubin, MD, Group leader
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Dr. Laura Brandt, Postdoctoral fellow
Dr. Kellie Anne Cotter, Postdoctoral fellow
Dr. Joanna Triscott, Postdoctoral fellow
Dr. Alison Ferguson, Postdoctoral fellow (since Jan.)
Dr. med. Antonio Rodriguez, Resident pathologist
Dr. Stephan Christen, Laboratory manager
Marika Lehner, Laboratory technician (since Aug.)
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Selected Collaborators

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Selected Publications

Triscott J and Rubin MA. Prostate power play: Does Pik3ca accelerate PTEN-deficient cancer progression? *Cancer Discov.* 2020;8(6):682–685. doi: 10.1158/2159-8290.CD-18-0369.

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Emerling BM, et al. Depletion of a putatively druggable class of phosphatidylinositol kinases inhibits growth of p53-null tumors. *Cell.* 2013;155(4):844-857. doi: 10.1016/j.cell.2013.09.057.

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Hematology

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Areas of research

Our work is dedicated to determining the role of innate immunity in the pathogenesis of hematological diseases. We investigated the contribution of damage-associated molecular patterns (DAMPs), such as cell-free DNA histones, cell-free heme, and neutrophil activation in the form of neutrophil extracellular traps (NETs) in the pathogenesis of neutropenic sepsis, graft-vs host disease (GvHD), sickle cell disease (SCD), autoimmune hemolytic anemia (AIHA), paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and thrombosis. In addition, we studied the efficacy of therapeutic interventions to neutralize the proinflammatory effects of DAMPs and NETs in these diseases. Another focus are of our research is the role of complement and the therapeutic efficacy of complement inhibitors in diseases such as AIHA, PNH, and aHUS. In our projects, we make use of a translational approach including *in vitro* studies, animal models (xenotransplantation models in rats and mice, knockout models in mice), and studies in humans.

Research Highlights 2020

One of the highlights of 2020 for our group was the publication of our study on the efficacy of compstatin, a complement inhibitor targeting C3, to inhibit intra- and extravascular hemolysis induced by sera of patients with AIHA. The results from this study will form the basis for future clinical intervention studies in patients with AIHA, to halt hemolysis. Another highlight was the establishment of our xenograft hemolysis model in rats to study the efficacy of complement inhibitors *in vivo* as well as in different systemic inflammation models in mice, to study the efficacy of treatments targeting DAMPs. Finally, our NRP78 COVID-19 application entitled "Devils dance: complement, NETs and thrombosis" (SNF 4078P_198255) was granted. In this project, we will address the pathogenesis of microvascular complications, which cause organ dysfunction and ultimately result in fatality in COVID-19 patients. We will investigate in detail the role of complement activation and NETs in the pathogenesis of microvascular thrombosis in COVID-19. We aim to identify the complement pathway(s) involved in COVID-19, study the effect of complement activation on neutrophil activation in the form of NETs, and design treatment strategies targeting both complement and NETs in COVID-19. With the support of this grant, we have been able to expand our research group and welcome Noëlia Schärz as a new member of our team.

Outlook 2021

Anne Jan van de Meer ("Encoding DAMPs: Investigating the intricate crosstalk between host response and collateral damage") and Laura Delvasto Nunez ("it takes two to tango: Neutrophil-extracellular traps and complement activation in the pathogenesis of thrombosis in autoimmune hemolytic anemia") will defend their Ph.D. thesis in 2021 at the University of Amsterdam. We will continue our work on the efficacy of therapeutic interventions in our established DAMP models. In particular, mouse models for GvHD using knockout strains will be operational, and we will investigate the efficacy of DAMP neutralizing strategies in these models. Finally, we are confident about presenting the first data from the NRP78 grant, which would provide insights into the pathogenesis of microvascular complications in COVID19.

Group Members

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Noëlia Schärz, Laboratory technician

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Translational Angiology

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Research Highlights 2020

Basic and translational research in the area of atherosclerosis, lower extremity artery disease (LEAD), thrombosis, and vascular malformations

B-Cell Specific CXCR4 protects against atherosclerosis development and increases plasma IgM levels

Over the last few years, studies focusing on the role of B cells in atherosclerosis have revealed that this cell subset can have both pro- and anti-atherosclerotic properties depending on the specific subset and method of targeting. We revealed that B cell-specific CXCR4 deficiency specifically decreases B1 cells and consequently plasma IgM titers. Our results suggest that the atherosclerotic effects observed upon B-cell CXCR4 deficiency are primarily caused by a B-cell-mediated decrease in IgM levels. Döring et al. Circulation Research, 2020.

SNSF NRP 78: Unravelling consequences of SARS-CoV-2 mediated inflammatory immune r esponses in heart and vasculature (Acronym: CoVasc)

COVID-19 is a global public health challenge, with its rapid spread, high reproductive rates, and a lack of specific treatment. Severe cases are significantly affected by cardiovascular disease (CVD), kidney failure, and symptoms of the central nervous system. The underlying mechanisms of non-pulmonary tissue damage in COVID-19 and associated coagulopathies are poorly understood. Within CoVasc, we combine our complementary expertise in cardiovascular biology to study whether disease progression is dependent on the particular cell type. Analysis of in vitro and animal models will allow us to study acute and long-term outcomes of infection, which are currently unknown. (NRP, together with Profs. Britta Engelhardt, Nadia Mercader, and Robert Rieben.)

Investigating the ill-alliance of neutrophil extracellular traps (NETs) and extracellular vesicles (EVs) in LEAD

LEAD is a manifestation of atherosclerosis and arterial thrombosis in the lower extremities and is becoming a health problem worldwide. LEAD lesions exhibit significantly greater calcification and osteoid metaplasia than carotid plaques. Calcification patterns consist of EVs, which further contribute to mineralization and calcification. We will examine the role of NETs in LEAD in combination with EVs as part of the NET scaffold. Readouts will include lesion size measurements, cell phenotyping, and assessment of arterial thrombosis.

SNSF SINERGIA: Disease-targeted NGS for the detection of mutations in congenital vascular malformations to enable personalized therapeutic approaches

We aim to establish a customized disease-targeted gene-sequencing panel ("VASCSeq") to identify (known) malformed genes, which may allow for drug repurposing. We therefore want to consolidate an interdisciplinary collaboration network of vascular physicians, pediatricians, radiologists, and geneticists to enable project harmonization between Bern and Brussels. Further, we aim to develop new standardized imaging techniques to support a truly multiscale trial design. (SINERGIA with Prof. J. Rössler, Prof. H. von Tengg-Kobligk, Prof. M. Vikkula, and PD Dr. U. Amstutz.)

www.dbmr.unibe.ch/research/individual_research_labs/angiology/index_eng.html

Group Members

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Prof. Dr. Yvonne Döring, Group leader/Head of Research
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Selected Publications

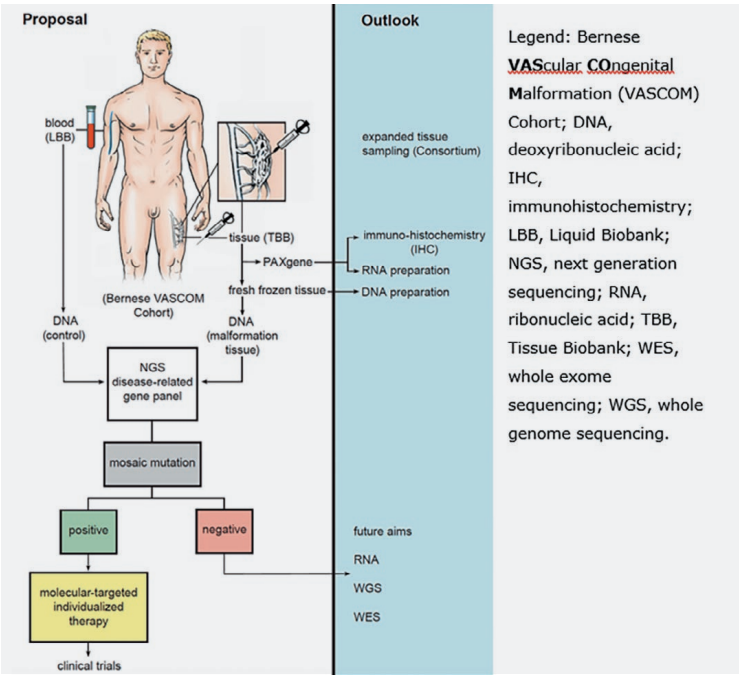
Döring Y, Jansen Y, Cimen I, Aslani M, Gencer S, Peters LJF, Duchene J, Weber C, van der Vorst EPC. B-cell-specific CXCR4 protects against atherosclerosis development and increases plasma IgM levels. *Circ Res*. 2020;126(6):787–788. doi:10.1161/CIRCRESAHA.119.316142.

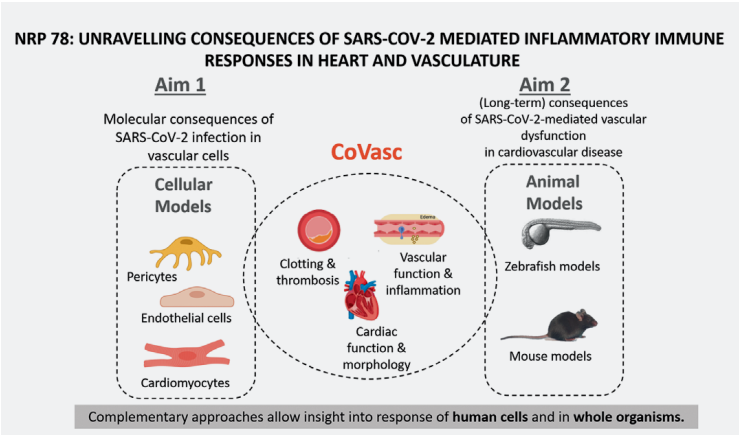
Döring Y, Libby P, Soehnlein O. Neutrophil extracellular traps participate in cardiovascular diseases: Recent experimental and clinical insights. *Circ Res*. 2020;126(9):1228–1241. doi:10.1161/CIRCRESAHA.120.315931.

Gencer S, Lacy M, Atzler D, van der Vorst EPC, Döring Y, Weber C. Immunoinflammatory, Thrombohaemostatic, and Cardiovascular Mechanisms in COVID-19. *Thromb Haemost*. 2020;120(12):1629–1641. doi:10.1055/s-0040-1718735.

Vuillemin N, Bernhard S, Haine A, Schindewolf M, Häberli D, Hügel U, Obrist D, Baumgartner I. Capillary-venule malformation is a microfistulous variant of arteriovenous malformation. *J Vasc Surg Venous Lymphat Disord*. 2021;9(1):220–225. doi:10.1016/j.jvsv.2020.05.012.

Haine A, Kavanagh S, Berger JS, Hess CN, Norgren L, Fowkes FGR, Katona BG, Mahaffey KW, Blomster JI, Patel MR, Jones WS, Rockhold FW, Hiatt WR, Baumgartner I. International Steering Committee and Investigators of the EUCLID Trial. Sex-specific risks of major cardiovascular and limb events in patients with symptomatic peripheral artery disease. *J Am Coll Cardiol*. 2020;75(6):608–617. doi:10.1016/j.jacc.2019.11.057.





University Clinic of Visceral Surgery and Medicine (UVCM)

DBMR Groups: Gastroenterology/ Mucosal Immunology and Visceral and Transplantation Surgery

In early 2020, the world entered into a global pandemic due to the spread of a novel coronavirus SARS-CoV-2. The global response brought together scientists and health care professionals to accelerate the research and development of new practices and standards to contain the spread of COVID-19 disease, care for the affected, and understanding the health consequences of the infection. In response to the exponential increase in the number of COVID-19 cases in Switzerland, there was a quick coordination and collaborative effort between the groups of Gastroenterology and Visceral Surgery and the University Clinic of Visceral Surgery and Medicine involving both the clinical and scientific staff. Here, we established protocols for sampling, RNA extraction, and PCR and obtained ethics approval to implement a testing pipeline to monitor the course of SARS-CoV-2 infection among our personnel. This pipeline served to control the spread of infections among our workforce and to understand the secondary effects, namely B-cell responses, to the virus. This work was made possible by the tireless efforts of our colleagues working on the pipeline, the contribution of all the study participants, and the generous support of the Swiss National Science Foundation, Bern Center for Precision Medicine, and the DBMR who provided us with designated laboratory space and infrastructure to safely perform this work.

SNF Special call on Coronaviruses

1) Andrew Macpherson (Principal Investigator [PI]), Stephanie Ganal-Vonarburg (co-PI)

Title
Longitudinal single B-cell studies across the trajectory of COVID-19 to identify SARS-CoV-2 specific monoclonal antibodies and long-term memory formation

Main discipline
Immunology

Project Partners
Dr. Tim Rollenske

Project collaborators
Ian Young and Sophie Burkhlater (Gastroenterology)
Rajagopal Murugan (German Cancer Research Center, Heidelberg)
Gert Zimmer and Renate Boss (Vetsuisse, Mittelhäusern)

This project was undertaken to study the neutralizing humoral immunity that may be pivotal for protection against COVID-19 and the generation of immunological memory needed for future protection from the disease. We prospectively and longitudinally followed a cohort of approximately 380 healthcare workers from the Clinic of Visceral Surgery and Medicine, University Hospital Bern, by monitoring their SARS-CoV-2 viral status weekly using in-house diagnostic PCR tests to determine an individual's viral status.

With data on viral status, we could then describe the acute and memory B cell responses before, during, and after COVID-19 infection and provide a description of the acute B cell response to SARS-CoV-2 at the single-cell level. Moreover, we determined whether cellular B cell memory is formed during COVID-19 infection. Through weekly PCR testing, determination of SARS-CoV-2-binding serum antibodies and virus neutralization titers in a cohort of health-care workers (n = 382), we identified a subset of non-sero-converted individuals that showed serum SARS-CoV-2 neutralizing capacity. Using fluorescence-labeled antigens as bait in flow cytometry, we identified that these individuals possess pre-existing memory B cells specific to the SARS-COV-2 spike protein. Using single-cell immunoglobulin gene sequencing, we then aimed to derive a panel of monoclonal antibodies against the SARS-CoV-2 spike protein. With this data, we will be able to describe the immunogenic determinants of the B cell response that can discriminate between protected and non-protected individuals and/or severe from non-severe cases. Further, it will create a resource that will contribute to global databases that define potentially neutralizing SARS-CoV-2 monoclonal antibodies.

2) Guido Beldi (PI), Daniel Sanchez Taltavull (co-PI)

Title
Protecting the healthcare workforce during an epidemic outbreak: Modeling a desynchronization strategy from the COVID-19 pandemic

Main discipline
Mathematics

Project Partners
Edgar Roldan (Abdus Salam International Centre for Theoretical Physics)
Alexander Leichtle (Institute for Clinical Chemistry, Inselspital, Bern)
Michael Gerfin (Department of Economics, University of Bern)
Violeta Castelo-Székely (Visceral Surgery, University of Bern)

The second project focused on exploring strategies to protect healthcare providers and maintain the medical workforce needed during a worldwide pandemic. This crucial and challenging task is important as the sustainability of the healthcare workforce is threatened by several factors such as 1) infected patients, 2) infected co-workers, and 3) the infected community. During the course of an epidemic, the healthcare workforce may become a scarce resource, particularly during later phases of the epidemic. Unlike most other professions, social distancing is extremely difficult in medical teams where healthcare workers are required to work in close contact with patients and colleagues.

Therefore, we studied which work organizational strategy in hospitals is most suitable to protect the healthcare workforce and to identify if organizational measures installed during the COVID-19 outbreak were effective in protecting caregivers.

This study has three main aims. The first aim was to determine the difference in the risk of infection between healthcare and non-healthcare workers in a hospital environment. Second was to determine the impact of early testing on healthcare personnel. Here, the intensive strategy of testing twice weekly for SARS-CoV-2 was used to assess the health status of the workforce was compared to the strategy employed in other departments. This also allowed us to determine the relevance of the frequency of asymptomatic healthcare workers. Third was to test the effectiveness of a desynchronization strategy to protect healthcare workers. The staff were divided into two groups and worked alternate weeks with the goal of reducing contact between the teams and decreasing the chance of infection among the workforce.

A major strength of our study is the introduction of a testing regime among our healthcare professionals that was not limited to those presenting symptoms but was open to all personnel. We carried out qPCR-based testing to detect and isolate pre- and asymptomatic individuals and prevent further transmission. Here, we show that nosocomial infection occurs in addition to the household transmission of COVID-19. Moreover, our model was used to study how both regular testing and work shift protocols can prevent infection transmission between co-workers.

To explore preventive measures, we modeled and compared a testing regime with a desynchronization protocol in which workers would be split into two non-mixing groups working alternate weeks. The results of our modeling showed that both strategies alone or in combination are effective in limiting transmission between co-workers to only community transmission. Finally, we compared the testing and work-shift strategies in terms of work productivity and cost effectiveness. We considered work productivity in terms of available personnel and considered both the time devoted to testing as well as the work output that can be done in the home-office by healthcare professionals.

We concluded that regular testing has a minimal impact on work production, whereas a desynchronization strategy would imply an important decrease in work output unless high levels of home-office productivity are achieved.

In summary, our study showed that frequent and widespread testing of pre- and asymptomatic healthcare professionals is effective in detecting infections and preventing transmission between co-workers while maintaining work output and cost-effectiveness. The data we obtained will be used for the simulation and refinement of mathematical modeling to develop strategies that can be adapted for recurrent and future epidemic outbreaks.

Persons involved

Leadership and Coordination
Prof. Andrew Macpherson
Prof. Guido Beldi
Prof. Daniel Candinas
Prof. Stephanie Ganal
Prof. Deborah Stroka

Pipeline for sample collection and data management
Chiara Ziegler
Elke Beutler
Jeannine Kölliker
Isabel Huber
Kimberly König
Joseba Möri
Michelle Broger

Clinical research fellows
Lilian Salm
Magdalena Eilenberg,
Daniel Spari
Shaira Murugan
M.D. students at the UVCM Clinic

Research personnel for the PCR pipeline
Dr. Hai Li
Dr. Bahtiyar Yilmaz
Dr. Jakob Zimmerman
Dr. Adrian Keogh
Isabel Büchi
Marianna Rentsch
Katharina Bacher
Sophie Burkhlater
Dr. David Young
Dr. Felix Baier
Dr. Jacopo Gavini
Dana Leuenberger
Dr. Nicolas Melin

Data Analysis and reporting
Dr. Tim Rollenske
Dr. Daniel Sanchez-Taltavull
Dr. Violeta Castelo-Székely

Key Events

Info Events at DBMR were not organized in-person due to the COVID-19 pandemic in 2020.

Day of BioMedical Research 2020

04–05 November

This event was hosted virtually this year. As expected, a large audience attended the following presentations: "Circulating tumor cells in lung cancer, biomarkers and biology" by Prof. Dr. Caroline Dive (CRUK Manchester Institute University of Manchester, UK); "Accelerated implementation of DBMR resources for translational research on SARS-CoV-2" organized by Prof. Dr. Debora Stroka (Visceral and Transplantation Surgery, DBMR) with the speakers Prof. Dr. Guido Beldi (Visceral and Transplantation Surgery, DBMR), Prof. Dr. Stephanie Ganal-Vonarburg, and Dr. Tim Rollenske (Gastroenterology/Mucosal Immunology, DBMR).

Fifteen candidates contested for the Johanna Dürmüller-Bol DBMR Research Prize 2020 (funded by the Johanna Dürmüller-Bol Foundation), and 145 abstracts were submitted for the poster prizes of the DBMR and the Research Prize Alumni MedBern. The winners were:

Johanna Dürmüller-Bol DBMR Research Award 2020
Dr. Joanna Triscott
Research Group Precision Oncology, Department for BioMedical Research
"Exploiting metabolic vulnerabilities in advanced prostate cancer"

Poster Prizes of the DBMR for:
- *best preclinical project*
  Kevin Plattner
  Department of BioMedical Research, University of Bern, Research Group Rheumatology and University Hospital for Rheumatology, Immunology, and Allergology, University of Bern, Bern.
  "Glycan-specific IgG anti-IgE autoantibodies contribute to protectivity against allergic diseases"
- *best clinical project*
  Jasmine Lea Jendoubi
  Department of Neurology, University Hospital, University of Bern, Switzerland. "Differential spindle expression dependent upon thalamic nuclei lesioned by stroke"
- *best project by a medical student*
  Marco Sutter
  Department of Pulmonary Medicine, University Hospital Bern, Switzerland and Department of Biomedical Research, Research Group Pulmonary Medicine (Adults), University of Bern. "*In vivo* electroporation-mediated, intrahepatic alpha1 antitrypsin gene transfer reduces pulmonary emphysema in pallid mice"
- *best publication 2019*
  Dr. Bahtiyar Yilmaz
  Research Group Gastroenterology/Mucosal Immunology, Department of Biomedical Research, University of Bern, Bern, Switzerland, and Department of Visceral Surgery and Medicine, Bern University Hospital, University of Bern, Bern
  "Microbial network disturbances in relapsing refractory Crohn's disease"

Research Prize for Alumni MedBern
Vera Lehmann
Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, University of Bern. "HEADWIND: design and evaluation of a vehicle hypoglycemia warning system in diabetes – results from a driving simulator study"

Stem Cell Prize
Pascal Näf
Tumor Immunology, Department for BioMedical Research, University of Bern, Switzerland, and Graduate School for Cellular and Biomedical Sciences (GCB), University of Bern, Switzerland for the project, "IL-33/ST2 signaling promotes steady-state hematopoiesis via IL-6 producing ILC2"

The next event of BioMedical Research will be held in Summer 2022.

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

09 Dec. (online)

DBMR Research Conferences 2020

Due to the pandemic, only four research conferences could be held, of which only one was held in person. Nonetheless, there was great interest in the virtual conferences. In 2020, we were pleased to present the following speakers:

10 Feb. – Prof. Yonglun Luo
Department of Biomedicine, Aarhus University, Aarhus (DK)
Single-cell transcriptome profiling of endothelial cells

07 Sep. – Prof. Dr. Catherine Verfaillie
Head of Stem Cell Institute Leuven (SCIL), KU Leuven (BE)
Multi-engineering approaches to create multicellular liver mimics from PSCs to model liver disease and liver toxicity

05 Oct. – Dr. Marko Nikolic
Division of Medicine, Rayne Institute, University College London, London (UK)
Building the lung: Progress and challenges in human lung development and its relevance to patients

07 Dec. – Prof. Dr. Alexander Bartelt
Klinikum der Institute for Cardiovascular Prevention, Ludwig-Maximilians-University, Munich (DE)
Neither fat, nor flesh – how brown adipocytes control metabolic health

Personnel Update

Academic Degrees

The following academic degrees were awarded to members of DBMR research groups:

Associate Professor

Prof. Dr. Manfred Heller
PMSCF and Protein & Cell Biology

Prof. Dr. Nicolas Bonadies
Hematology (Adults)

Full Professor (Extraordinarius)

Prof. Dr. Fiona C. Burkhard
Urology

Lecturer (Privatdozent)

PD Dr. med. Michael Daskalakis
Hematology (Adults)

PD Dr. Patrick Dron
Thoracic Surgery

M.D., Ph.D.

(Supervisor in brackets)

Dr. med. Federico Storni
(Prof. Dr. Martin Bachmann and PD Dr. Monique Vogel)
Development of a new therapy for peanut allergy

Dr. med. Duo Xu
(Prof. Dr. Ralph A. Schmid and Prof. Dr. Ren-Wang Peng)
New strategies to target malignant pleural mesothelioma

Dr. med. Haitang Yang
(Prof. Dr. Ralph A. Schmid and Prof. Dr. Ren-Wang Peng)
Targeting the mitogen-activated protein kinase signaling cascade in KRAS-mutant lung cancer and malignant pleural mesothelioma

Dr. med. Zhang Yang
(Prof. Dr. Ralph A. Schmid and Prof. Dr. Ren-Wang Peng)
Development of a synergistic combination therapy for non-small cell lung cancer (NSCLC)

Ph.D.

(Supervisors in brackets)

Dr. Giuseppe Bombaci
(Prof. Dr. Ramanjaneyulu Allam).
Understanding the role of ribonuclease inhibitor (RNH1) in inflammation

Dr. Laura Facchin
(Prof. Dr. Claudio L. Basseti).
Slow waves promote sleep-dependent plasticity and functional recovery after stroke

Dr. Yanyun Gao
(Prof. Dr. Ralph A. Schmid, PD Dr. Thomas M. Marti).
Targeting mitochondrial metabolism of chemo-resistant non-small cell lung cancer cells

Dr. Mahmoud Hallal
(Prof. Dr. Nicolas Bonadies)
Development and validation of a phosphoproteomics analysis pipeline for the characterization of targetable kinases in myeloid malignancies

Dr. Efstathios Katharopoulos
(Prof. Dr. Christa E. Flück, Prof. Dr. Genevieve Escher).
Understanding human gene variants involved in steroidogenic pathways

Dr. Lukas Oesch
(Prof. Dr. Antoine Adamantidis).
Optical imaging of hypothalamic circuits across sleep states and feeding behaviors

Dr. Christoph Saner
(Prof. Dr. Markus Juonala, Prof. Dr. Matthew A. Sabin, and Prof. Dr. David P. Burgner)
Nutritional determinants & cardiometabolic risk outcomes in children and adolescents with obesity

Dr. Martina Stillinovic
(Prof. Dr. Ramanjaneyulu Allam).
Understanding the role of ribonuclease inhibitor (RNH1) in erythropoiesis and translation

Awards

The following DBMR group members received awards in 2020.

Isabel Arenas
Cardiovascular Research
"Best Free Communication Research 2020" Prize from 56th Congress SGPRAC-SSCPRE and 8th Congress SGAC-SSCE, Swiss Plastic Surgery

Dr. Anke Augspach
Precision Oncology
SAKK/Astellas Award 2020, Swiss Oncology & Hematology Congress 2020 for "Role of specialized composition of SWI/SNF complexes in prostate cancer lineage plasticity"

Dr. Katarzyna Jalowiec
Hematology (Adults)
"Hematology Research Physician-Scientist Fellowship Award 2020", Swiss Society of Hematology

Prof. Johanna A. Kremer Hovinga
Hematology (Adults)
Günter Landbeck Excellence Award for the International Hereditary thrombotic thrombocytopenic purpura (TTP) Registry

PD Dr. med. Behrouz Mansouri
Hematology (Adults)
Volkmar-Sachs-Medaille in recognition of his services to transfusion medicine and immune-hematology, Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie

Dr. Raja Prince
Hematology (Adults)
Hemostasis Prize, Swiss Society of Hematology, for the abstract entitled: "Targeting protein S using small interfering RNA is well tolerated and protects mice with hemophilia A from acute hemarthrosis"

Prof. Dr. Robert Rieben
Cardiovascular Research
SNSF Singergia Grant: Prof. R. Rieben (main applicant, DBMR, University of Bern), along with Prof. Dr. med. Jörg Seebach, Geneve University Hospital, and Prof. Dr. Eckhard Wolf, Ludwig-Maximilian University, Munich, Germany received a SNSF-funded Sinergia-grant (2.656 Mio CHF) for their project "Xeno2Cure – advanced engineering and testing of organ donor pigs"

Prof. Dr. Robert Rieben
Cardiovascular Research
Co-PI, SNSF NFP78 Project "Unravelling consequences of SARS-CoV-2 mediated inflammatory immune responses in heart and vasculature" (Total CHF 1,951,700)

Dr. Antonio Rodriguez
Precision Oncology
Poster prize of the German Society of Pathology 2020 for "The genomic landscape of prostate cancer brain metastases"

Dr. Antonio Rodriguez
Precision Oncology
2020 Jeff & Loyd Zisk-PCF Young Investigator Award, Prostate Cancer Foundation for "Molecular Pathology-Artificial Intelligence Approach to Therapy Response Prediction for Castration Resistant Prostate Cancer"

Dr. Joanna Triscott
Precision Oncology
Johanna Dürmüller-Bol Research Award, Department of BioMedical Research for
"Exploiting metabolic vulnerabilities in advanced prostate cancer"

Staff Changes

New Staff

Ricardo Miguel Fernandes Filipe
Housekeeping (80 %)
DBMR Services (since Dec.)

Dr. Julie Gamart
Laboratory technician (100 %)
Cardiac Development and Reprogramming (since June)

Scarlet Kohler
Laboratory technician (40 %)
Medical Oncology (since May)

Marika Lehner
Laboratory technician (80 %)
Precision Oncology (since Aug.)

Prof. Dr. Eliane Müller
Research associate (50 %)
Dermatology (since Dec.)

Dr. Marco Osterwalder
Eccellenza SNF Professor (100 %)
Cardiac Development and Reprogramming (since May)

Virginia Roland
Ph.D. student (75 %)
Cardiac Development and Reprogramming (September 2020–Present)

Désirée Schnidrig
Bioinformatician (100 %)
Oncogenomics (since July)

Rahel Tschudi
Human resources assistant (80 %)
Administration (since Mar.)

Matteo Zoia
Ph.D. student (75 %)
Cardiac Development and Reprogramming (since Nov.)

Valentina Zollet
Ph.D. student (75 %)
Cardiovascular Research (since Aug.)

Resignations

Thomas Späti
IT technician (40 %)
IT Support (until Apr.)

Bernhard Grossniklaus
Facility manager (100 %)
Facility Management (until Nov.)

Karin Schmitter
Laboratory technician (40 %)
Medical Oncology (until May)

Ana Radovanovic
Secretary (70 %)
Administration (until Apr.)

Josip Mikulic
Advanced postdoctoral fellow (100 %)
Cardiovascular Research (until Oct.)

Short employment

Lia Mela
Laboratory technician (100 %)
Precision Oncology (until Dec.)

Retirements

Silvia Rösselet
HR assistant (60 %)
Administration (until Mar.)

Re-allocations

Irene Keller
Research associate (90 %)
Bioinformatics (until Aug.)

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Coordination: Basak Ginsbourger & Marla Rittiner
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