Department of Biomedicine
Report 2017–2020

Departement
Biomedizin
Basel


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Basel


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Department of Biomedicine
Report 2017–2020

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Preface

The Department of Biomedicine (DBM) unites the laboratory-based research of the faculty of medicine of the University of Basel. In the DBM, the laboratories of the former "pre-clinical institutes" as well as the clinical divisions of the University Hospitals are brought together under a common leadership with the goal to focus their efforts and to strive for excellence in biomedical research. In the 20 years since the department was founded, we enjoyed continuous growth and flourishing of our research. By providing a bridge between basic science and clinical medicine, the DBM is an important component in the University of Basel's strategic plan for the Life Sciences and a key player in the national "Swiss Personalized Health Initiative" (SPHN). The DBM concentrates on research in four focal areas: Oncology, Immunology, Neurobiology, and Stem Cells & Regenerative Medicine.

DBM's research groups are to a large part supported by their own research funds from competitive grants by national foundations, the EU and other countries. More than 50% of the positions are funded by third parties. The DBM has attracted individual grants as well as synergy grants from the European Research Council (ERC), the Swiss Initiative in Systems Biology (Sys- temsX.ch) and the Swiss National Science Foundation (SNSF). We are particularly proud of hosting a substantial number of young research group leaders supported by competitive career development grants by the ERC, the SNSF, and private foundations.

This report summarizes the activities of over 60 DBM research groups during the period of 2017-2020. The reports are grouped thematically according to the four focal areas. Each research group has selected their most relevant publications from this period. A complete list of all publications can be found in the annex of this report. The DBM and our research groups are regularly evaluated by the Scientific Advisory Board that consists of nine internationally recognized experts. During their yearly visits, the Advisory Board members evaluate and make recommendations on how to improve the organization of the department. They also provide an important basis for decisions, including promotions and changes in future directions. Key to the success of the DBM has been the enthusiasm of our scientists and clinicians from over 40 countries to communicate and to perform inter- and transdisciplinary work resulting in benchmark biomedical research. The research is supported by a growing number of Core Facilities. While some Core Facilities are for the DBM only, others are joint ventures between our department with the Biozentrum (Faculty of Natural Sciences) and also the D-BSSE Institute of the ETH Zürich in Basel. The access to these key technologies is of immeasurable value to us.

A major milestone is the project for a new DBM building, which will replace the old Biozentrum located at Klingelbergstrasse 70. The new DBM building is scheduled to be inaugurated in 2028 and will unite all DBM research groups in a single location situated in close vicinity of the new Biozentrum and the new D-BSSE of the ETH. This new campus will provide an excellent basis for expanding collaborative re- search between clinical and basic science at the highest competitive level.

The DBM is committed to the highest quality and innovation in research. This report portraits the scientific excellence and enthusiasm of our research groups. It also coincides with the closure of my term as head of the DBM. Starting in June 2021, Ivan Martin will become the new head and will lead the DBM during the transition to our new DBM building and the years to come.

Prof. Dr. Radek Skoda
Head of the Department of Biomedicine

Departement Biomedizin Basel

Mission Statement

The mission of the Department of Biomedicine (DBM) at the University of Basel is to promote integrated research excellence in biomedical science.

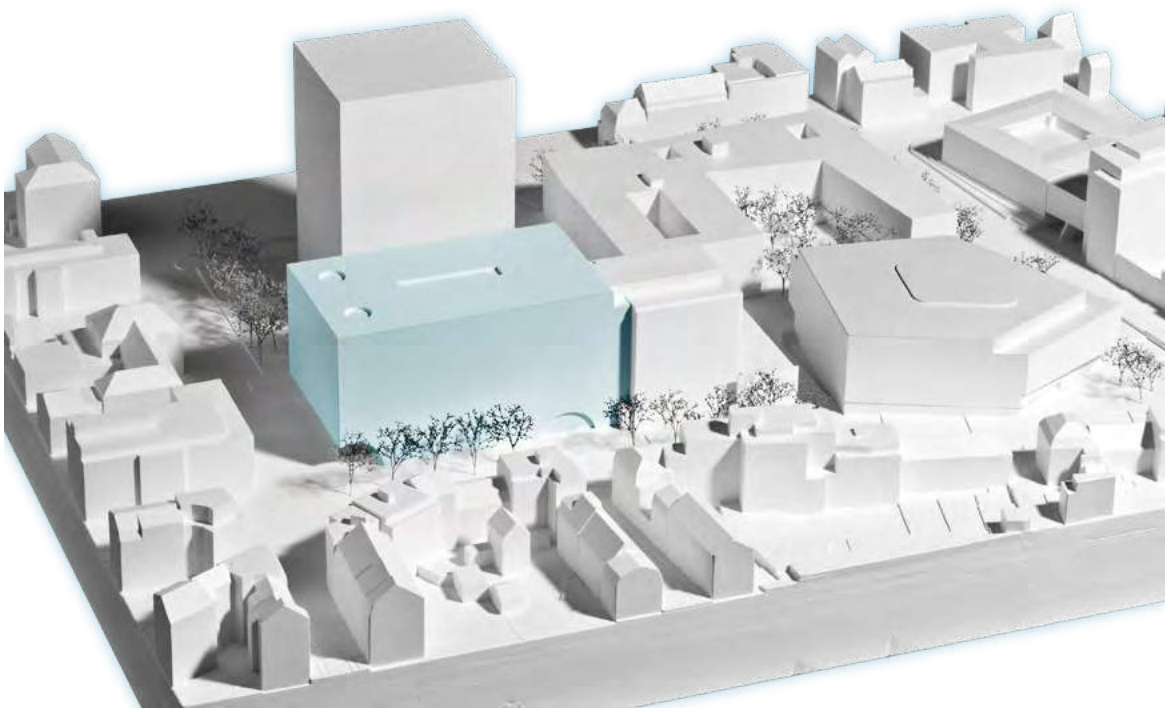
We emphasize research in neurobiology, infection and immunity, cancer, and stem cell biology and regenerative medicine.

The DBM provides a stimulating environment with state-of-the-art facilities, enabling biomedical research of the highest quality, while also training the next generation of leaders in basic and clinical research.

Central to our mission, non-clinical and clinical scientists work side by side to foster a translational environment across all of our disease-relevant scientific themes, benefiting the lives of patients in areas of unmet need.

Translational research:
Developing novel therapeutic approaches to fulfill the unmet medical need of our patients. ▶

New DBM Building



Modell: © Joseph Riegger

By 2028, all DBM researchers will work in a new building on the Schällemätteli Life Sciences Campus.

To further grow together as one department, all research groups, core facilities and staff of today's five locations will move under the same roof. The new DBM will complete the ongoing developments on the Schällemätteli Campus by joining the new buildings of the Biozentrum (2021) and the ETH Department of Biosystems Sciences and Engineering (2021) – creating a magnet for life science research in the Basel area with international reach. It will allow DBM researchers to interact more closely within the department but also with researchers of the neighbouring institutions. These interactions are further strengthened by jointly operated research core facilities, providing access to key technologies.

Visualisation: Caruso St John Architects

Foremost, the proximity of the DBM research labs to the University Clinics of the USB and UKBB will facilitate exchange and collaborations between scientists and physicians working on different disease areas, using complementary approaches and methodologies. This interdisciplinary exchange is the basis for a quick translation from bench to bedside in order for newly generated knowledge to be rapidly used in the development of new diagnostics or therapies for the benefit of patients.

The new DBM building will create synergies that lead to the professionalization of technical and research services and a more efficient operation. These are the key for creating a competitive environment, where researchers can work more efficiently in state-of-the-art laboratories, core facilities and infrastructures.

The new nine-storey building for the Department of Biomedicine will provide space for around 800 DBM employees and 200 students. The laboratory building will provide the DBM with six research floors, one floor for the core facilities and one floor with a science lounge and meeting rooms. On the public ground floor, the building will additionally offer laboratory course rooms as well as teaching rooms for university use.

The building will be owned by the University of Basel and is being planned by the Basel-based architectural firm Burckhardt + Partner. After the construction phase by a total contractor, the building is scheduled to go into operation at the beginning of the semester in autumn 2028 at the earliest.

Organization

HEAD OF DEPARTMENT
Prof. R. Skoda

COORDINATOR
Dr. T. Geiger

EXECUTIVE COMMITTEE

Chair
Prof. R. Skoda

University of Basel
Prof. B. Bettler, Prof. V. Taylor, Prof. D. Pinschewer, Prof. M. Wymann

University Hospital
Prof. Ch. Hess, Prof. A. Navarini, Prof. I. Martin, Prof. S. Cichon

Univ. Children's Hospital
Prof. D. Finke

Coordinator
Dr. T. Geiger

The Department of Biomedicine (DBM) is led by the Head of the Department who is supported in all organizational and administrative matters by a DBM-Coordinator and staff of the Central Services.

The overall strategy is defined by the DBM Executive Committee, which is composed of 10 members: the Head of the Department (chair), plus four representatives from the pre-clinical disciplines of the University of Basel, four representatives from the divisions of the University Hospital, and one representative form the University Children's Hospital.

CENTRAL SERVICES

Controlling
G. Brunner

Human Resources
H. Hoyermann

Dept. Assistant
M. Bernasconi, X. Banholzer

DBM-IT
N. Vogt

Student Affairs
Prof. N. Schaeren-Wiemers

CORE FACILITIES

Microscopy
Dr. M. Abanto, P. Lorentz

Flow Cytometry and Cell Sorting
D. Lopes

Bioinformatics
Dr. R. Ivanek

GMP
Dr. W. Krenger

Histology
Dr. D. Calabrese

LOCAL SERVICES (5 DBM LOCATIONS)

Operations Managers
Organization Safety
Controlling
Mouse User Groups
Administrative Assistants

RESEARCH GROUPS
(details see page 24)

FOCAL AREAS

Oncology
Prof. G. Christofori, Prof. Ch. Rochlitz

Immunology
Prof. G. De Libero, Prof. Ch. Hess

Neurobiology
Prof. B. Bettler, Prof. L. Kappos

Stem Cells and Regenerative Medicine
Prof. R. Zeller, Prof. J. Passweg

Key Data 2020

RESEARCH GROUPS	**69**
CORE FACILITIES	**12**
DBM Core Facilities	5
Joint Core Facilites	7
SPACE	
Locations	5
Effective area	13’608 m²
PERSONNEL	
Employees total	821
FTE (total)	636
FTE (third-party funded)	338
Research group leaders	69
Tenured Professors	40
SNSF Professors	7
Titular- and Tenure track-assistant professors	12
PD and SNSF Ambizione SCORE	10
PhD Students	140
FINANCES (in CHF)	
Personnel	26’936’113
Supplies	6’546’473
Investments (equipment)	4’457’448
Income (total)	-219’254
Third-party funds (grants etc.)	29’268’000

Pipette carousel with pipettes ▶

Executive Committee

Prof. Radek Skoda
Head of the Department

Prof. Bernhard Bettler

Prof. Alexander Navarini

Prof. Sven Cichon

Prof. Daniel Pinschewer

Prof. Daniela Finke

Prof. Verdon Taylor

Prof. Christoph Hess

Prof. Matthias Wymann

Prof. Ivan Martin

Dr. Thomas Geiger

Council of the Department

(DBM Rat)

Prof. Primo Schär (Chair)
Dean of the Faculty of Medicine,
University of Basel

Dr. Werner Kübler
Director,
University Hospital Basel

Prof. Torsten Schwede
Vice President,
University of Basel

Marco Fischer
Director,
University Children's Hospital Basel

Christoph Tschumi
Executive Director,
University of Basel

Dr. Kaspar Traub
Head of Administration
of the Faculty of Medicine,
University of Basel

Scientific Advisory Board

The Scientific Advisory Board is composed of internationally renowned scientists who are based outside of Basel. Members of the Advisory Board cover with their expertise both basic and clinical aspects of the research addressed in the focal areas of the DBM and at least two members are assigned to each focal area. The Advisory Board organizes itself independently and appoints one of its members as chair.

The Scientific Advisory Board visits the DBM once a year and evaluates research quality of individual research groups and organizational aspects of the department. It writes a report for the attention of the DBM Executive Committee and the DBM Council, which is composed of members of the Rectorate, the Dean's Office and the directors of the University Hospitals that participate in the DBM. The Advisory Board can also be consulted during the year on specific issues.

Oncology and Cancer Research

Prof. Ivo Touw (chair)
Department of Hematology,
Erasmus University Medical Center,
Rotterdam, The Netherlands

Prof. Jim Norman
Beatson Institute, Cancer Research UK, University of Glasgow,
Glasgow, UK

Neurobiology

Prof. Klaus-Armin Nave
Department of Neurogenetics,
Max Planck Institute of Experimental Medicine, Göttingen, Germany

Prof. Christian Rosenmund
Charité Neurowissenschaftliches Forschungszentrum, Max Delbrück Center for Molecular Medicine,
Berlin, Germany

Stem Cells and Regenerative Medicine

Prof. Giulio Cossu
Constance Thornley Professor of Regenerative Medicine, The University of Manchester, UK

Prof. Karl-Heinz Krause
Departments of Pathology, Immunology and Clinical Pathology, Faculty of Medicine & University Hospitals of Geneva, Geneva, Switzerland

Immunology and Infection

Prof. Bernard Malissen
Centre d'Immunologie de Marseille-Luminy, Marseille, France

Prof. Judith E. Allen
Lydia Becker Institute for Immunology and Inflammation, Wellcome Trust Centre for Cell-Matrix Research, The University of Manchester, UK

Prof. Pamela Ohashi
Campbell Family Institute for Breast Cancer Research, Princess Margaret Cancer Centre Toronto, Ontario, Canada

Prof. Federica Sallusto
(starting 2021)
Institute for Research in Biomedicine Università della Svizzera italiana Bellinzona, Switzerland

Left during report period:

Kathryn Wood
Brigitta Stockinger
Christian Lüscher

Scientific Advisory Board
Former Members

We are very grateful to the following former members of our Scientific Advisory Board for their important contributions to shaping and improving the organization of the DBM and for their very valuable scientific input and advice to the researchers at the DBM.

Neurobiology

Greg Lemke
2009–2016 (chair)

Christian Lüscher
2009–2017

Stem Cells and Regenerative Medicine

Paolo Bianco
2009–2015

Immunology and Infection

Dimitris Kioussis
2009–2010

Kathryn Wood
2009–2017

Brigitta Stockinger
2011–2019

Oncology and Cancer Research

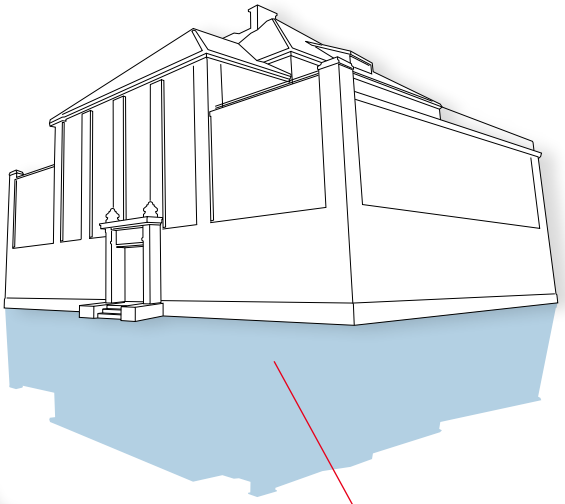
Bob Löwenberg
2009–2013

Margaret Frame
2011–2016

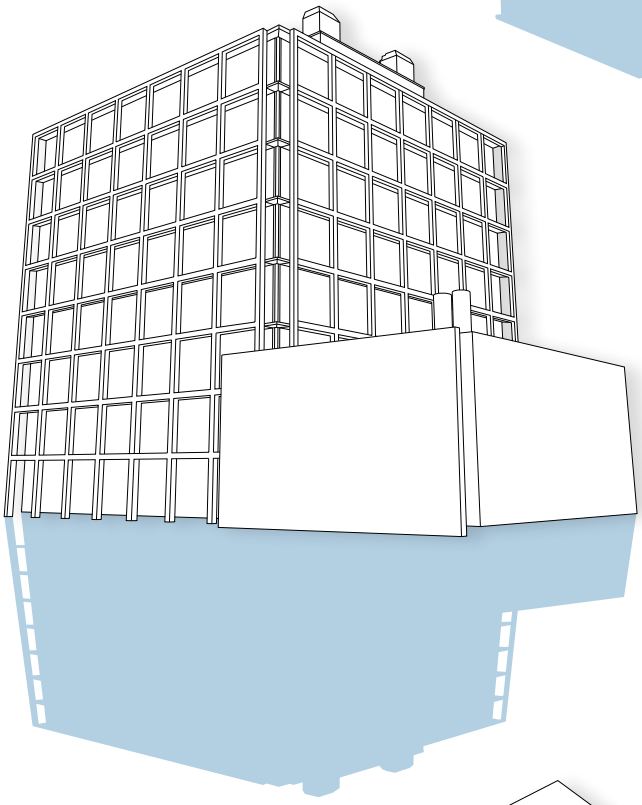
Mariano Barbacid
2009–2010

Adrian Ochsenbein
2017

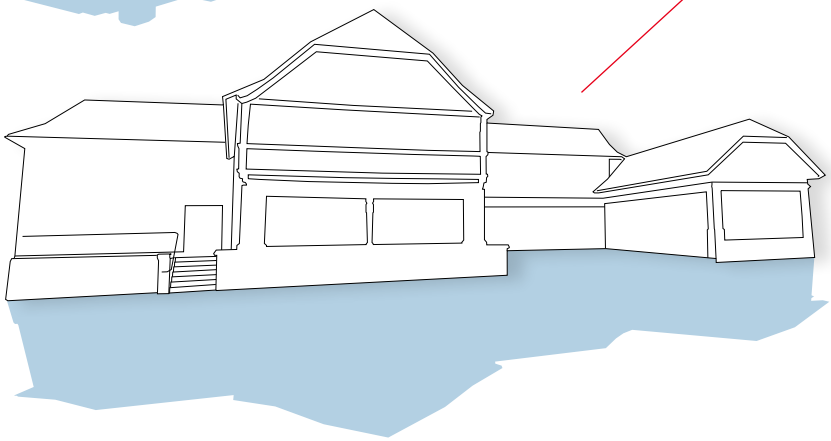
Locations



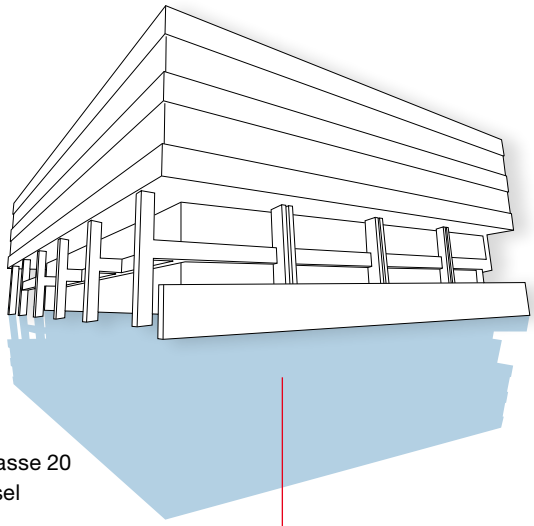
Pestalozzistrasse 20
4056 Basel



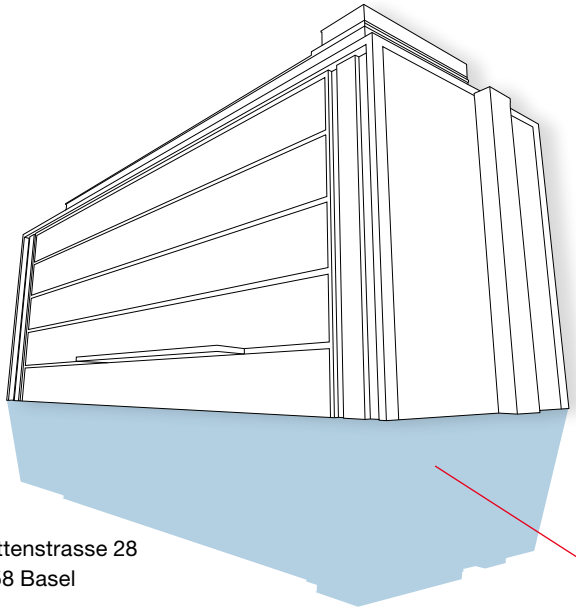
Klingelbergstrasse 50/70
Pharmazentrum (7th floor)
4056 Basel



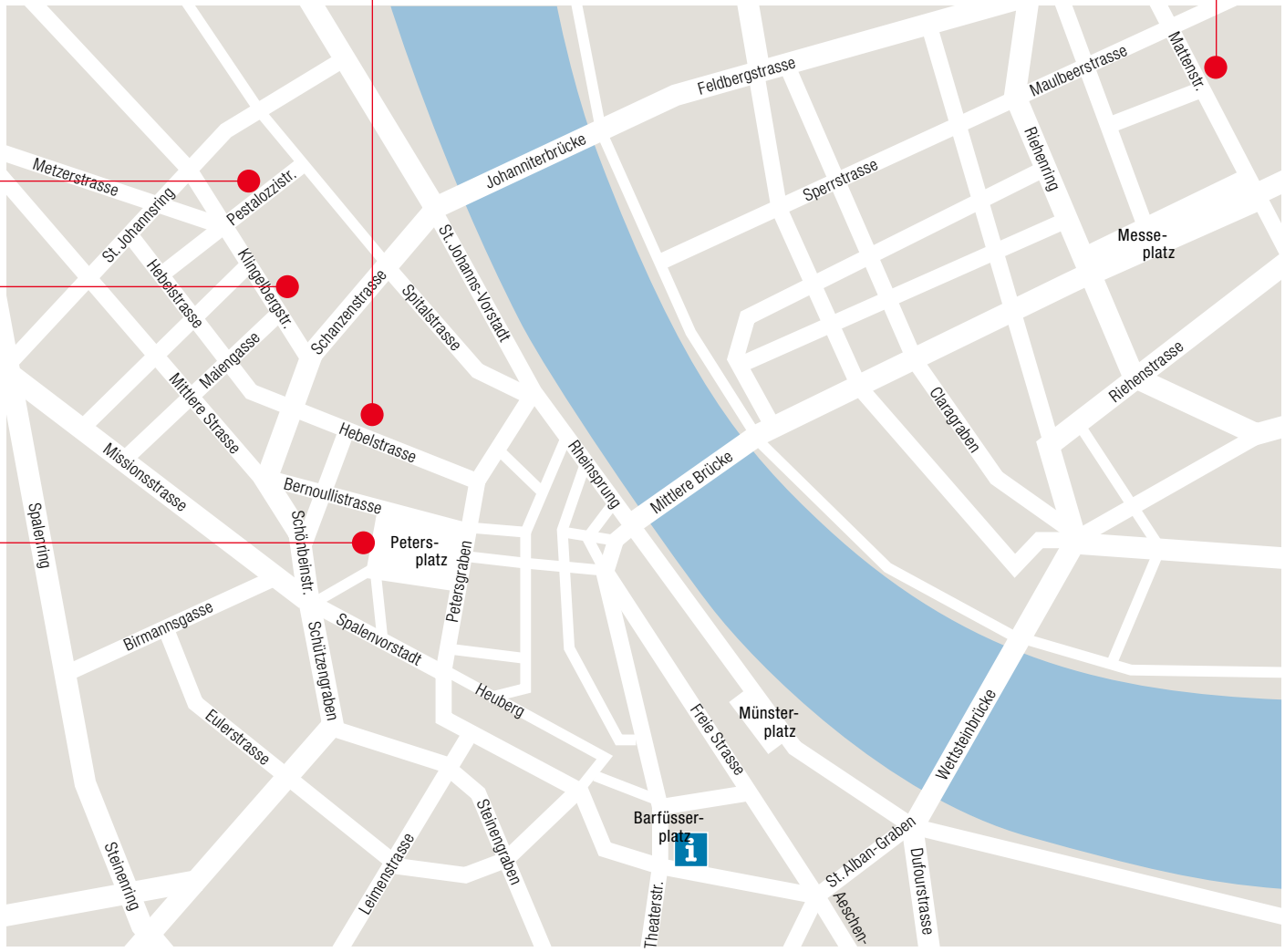
Petersplatz 10
4001 Basel



Hebelstrasse 20
4031 Basel



Mattenstrasse 28
4058 Basel



Research Groups

Overview according to location
and focal area

Department of Biomedicine
Hebelstrasse 20

PD Dr. Andreas Banfi
Cell and Gene Therapy

Prof. Andrea Barbero
Cartilage engineering

Prof. Mohamed Bentires-Alj
Tumor Heterogeneity,
Metastasis and Resistance

PD Dr. Christoph Berger
Translational Immunology

PD Dr. Christine Bernsmeier
Translational Hepatology

Prof. Daniel Bodmer
Inner Ear Research

Prof. Marijke Brink
Cardiobiology

PD Dr. Claudia Cavelti
SNF Ambizione SCORE
Translational Diabetes

Prof. Sven Cichon
Human Genomics

Prof. Christian De Geyter
Gynecological Endocrinology

Prof. Gennaro De Libero
Experimental Immunology

Prof. Tobias Derfuss
Prof. Jens Kuhle
Clinical Neuroimmunology

Prof. Marc Donath
Diabetes Research

Prof. Dr. Adrian Egli
Applied Microbiology Research

PD Dr. Magdalena Filipowicz Sinnreich
SNF Ambizione SCORE
Liver Immunology

Prof. Raphael Guzman
Brain Ischemia and Regeneration

Prof. Karin Hartmann
Allergy and Immunity

Prof. Markus H. Heim
Hepatology

Prof. Viola Heinzelmann
Ovarian Cancer Research

Prof. Christoph Hess
Immunobiology

Prof. Gregor Hutter
SNF Professorship
Brain Tumor Immunotherapy

Prof. Lukas Jeker
Molecular Immune Regulation

Prof. Beat Kaufmann
Cardiovascular Molecular
Imaging

Prof. Nina Khanna
Infection Biology

Prof. Carolyn King
SNF Professorship
Immune Cell Biology

Prof. Gabriela Kuster Pfister
Myocardial Research

Prof. Heinz Läubli
Cancer Immunotherapy

Prof. Claudia Lengerke
Stem Cells and Hematopoiesis

Prof. Matthias Liechti
Psychopharmacology Research

Prof. Luigi Mariani
Brain Tumor Biology

PD Dr. Anna Marsano
Cardiac Surgery and Engineering

Prof. Ivan Martin
Tissue Engineering

PD Dr. Matthias Mehling
SNF Ambizione SCORE
Translational Neuroimmunology

Prof. Sara Meyer
SNF Ambizione SCORE
Myeloid Malignancies

Prof. Alexander Navarini
Skin Biology

PD Dr. Albert Neutzner
Prof. Hendrik Scholl
Ocular Pharmacology
and Physiology

Prof. Jan Hendrik Niess
Gastroenterology

Dr. Salvatore Piscuoglio
Visceral Sugery

Prof. Mike Recher
SNF Professorship
Immunodeficiency

Prof. Michael Roth
Prof. Michael Tamm
Pneumology

Prof. Nicole Schaeren-Wiemers
Neurobiology

Prof. Arnaud Scherberich
Bone regeneration

Prof. Jürg Schwaller
Childhood Leukemia

Prof. Radek Skoda
Experimental Hematology

Prof. Marten Trendelenburg
Clinical Immunology

Prof. Susan Treves
Skeletal Muscle Disorders

Prof. Alfred Zippelius
Prof. Christoph Rochlitz
Cancer Immunology and Biology

Department of Biomedicine
Mattenstrasse 28

Prof. Nicola Aceto
SNF Professorship
Cancer Metastasis

Prof. Gerhard Christofori
Tumor Biology

Prof. Daniela Finke
Developmental Immunology

Prof. Georg A. Holländer
Pediatric Immunology

Prof. Primo Schär
Genome Plasticity

Prof. Verdon Taylor
Embryology and Stem Cell Biology

Prof. Roxane Tussiwand
SNF Professorship
Immune Regulation

Prof. Matthias Wymann
Cancer- and Immunobiology

Prof. Rolf Zeller
PD Dr. Aimée Zuniga
Developmental Genetics

Department of Biomedicine
Pestalozzistrasse 20

Prof. Josef Bischofberger
Cellular Neurophysiology

Prof. Josef Kapfhammer
Developmental Neurobiology and Regeneration

Prof. Magdalena Müller-Gerbl
Musculoskeletal Research

Prof. Eline Pecho-Vrieseling
SNF Professorship
Neuronal Development and Degeneration

Prof. Volker Spindler
Cell Adhesion

Department of Biomedicine
Klingelbergstrasse 50/70

Prof. Bernhard Bettler
Molecular Neurobiology
Synaptic Plasticity

Prof. Jan Gründemann
SNF Professorship
Sensory Processing and Behaviour

Prof. Tania Barkat Rinaldi
Brain and Sound

Prof. Michael Sinnreich
Neuromuscular Research

Department of Biomedicine
Petersplatz 10

Prof. Hans H. Hirsch
Transplantation and Clinical Virology

Prof. Thomas Klimkait
Molecular Virology

Prof. Diego Kyburz
Rheumatology

Prof. Daniel Pinschewer
Experimental Virology

Core Facilities

Microscopy
Dr. Mike Abanto
Pascal Lorentz

Flow Cytometry and Cell Sorting
Telma Lopes

Bioinformatics
Dr. Robert Ivanek

GMP Facility
Dr. Werner Krenger

Histology
Dr. Diego Calabrese

Anatomy Museum
Prof. Magdalena Müller-Gerbl

Legend

- Neurobiology
- Stem Cells and Regenerative Medicine
- Oncology and Cancer Research
- Immunology and Infection

Newly Apppointed Professors 2017–2020

Alexander Navarini

Born 1976 in Basel, Switzerland, graduated from Medical School at the University of Baden in 2002. After a dissertation on cutaneous lymphomas, he trained as an immunologist with Prof. Zinkernagel and Hengartner at Experimental Immunology in Zurich and obtained his PhD degree with studies on neutrophil granulocyte dynamics. During his training in dermatology at the University Hospital Zurich, he specialized in immunodermatology, especially biologics treatment of inflammatory dermatoses. After habilitation, he became a senior visiting research fellow for pustular psoriasis and acne at St. John's Institute of Dermatology at King's College London. Subsequently, he was awarded the Promedica-Bruno Bloch assistant professorship for immunodermatology and developed his research group in Zurich with a focus on genetics of inflammatory skin diseases. In 2018, he was appointed professor of dermatology at the University of Basel. His research is focused on mechanisms of cutaneous inflammation.

Volker Spindler

Born in 1980 (Würzburg, Germany) studied Medicine in Würzburg with stays in universities in US, UK and Tansania. After a postdoc at the Institute of Anatomy and Cell Biology at the University of Würzburg, he was appointed as tenure track Assistant Professor at Institute of Anatomy of the LMU Munich in 2011, where he was tenured as Associate Professor in 2017. He was appointed as Associate Professor of Anatomy at the Department of Biomedicine of the University of Basel in Oktober 2017 and is co-heading the prosection unit of the Institute of Anatomy. His research focuses on the roles of adhesion molecules during development and under pathologic conditions such as autoimmune bullous skin diseases and cancer.

Junior Faculty

Christine Bernsmeier

Born 1977 (Kiel, Germany), studied Medicine at the Universities of Halle/Saale and Kiel (1996-2002) and obtained a MD (University of Kiel, 2002) and a PhD (Cell Biology, University of Basel, 2008). She completed specialist training in Internal Medicine, Gastroenterology & Hepatology. During a Postdoctoral Fellowship (EASL) she worked at the Institute of Liver Studies, King's College London, UK (2012-2014). As Consultant Hepatologist and Research Group Leader (St. Gallen) she received the Venia docendi, University of Basel in 2016. Christine returned to Basel as Hepatologist & Clinician Scientist in 2018. Her SNF granted research focuses on monocyte & macrophage biology in chronic and end stage liver disease.

Jan Gründemann

Born 1981 (Bad Frankenhauen, Germany) studied Human Biology at the University of Marburg (Germany) and obtained a PhD in Neuroscience from University College London (UK). After a postdoc and Ambizione Fellowship at the Friedrich Miescher Institute in Basel (CH) and a short stay as a visiting scientist at Stanford University (USA) he joined the Department of Biomedicine in 2018 as a SNF Professor. Jan's research focusses on the neural circuit computations of sensory integration and emotional learning and state representations in mouse models using advanced deep brain imaging techniques.

Gregor Hutter

Born 1978 (Uznach, Switzerland) graduated from the University of Zurich in 2008 with a joint MD-PhD degree in Molecular Biology and Immunology. He completed his neurosurgery residency in Basel and Lucerne and obtained his board certification in 2013. In 2014, he joined Stanford University Medical School where he studied tumor-associated microglia and macrophages in malignant brain tumors as well as their therapeutic modulation *in vivo*. He returned back to Basel in 2017, and, after receiving a SNSF-professorship, started the "Brain Tumor Immunotherapy" research group at the DBM in 2018. As a physician-scientist in clinical neurosurgery and brain tumor immunotherapy, he aims to find novel treatments against malignant glioma.

Heinz Läubli

Born 1978 in Horgen, Switzerland, graduated 2004 from Medical Schools in Zurich and Lausanne. He obtained his PhD in 2008 from the University of Zurich and completed his Internal Medical Residency in Horgen and the University Hospital in Basel. After his postdoctoral research fellowship at the University of California in San Diego in 2014, he returned to the University Hospital in Basel for a fellowship in Medical Oncology. Since 2016, he is working as an attending physician in Oncology. In 2019, he started his own research group focusing on cancer immunotherapy at the DBM and he was appointed as an Assistant Professor for Cellular Cancer Immunotherapy in 2020 by the Faculty of Medicine.

Salvatore Piscuoglio

Born 1982 in Naples, Italy, obtained his PhD from the University of Basel (Department of Biomedicine) in 2012, with a thesis on the discovery and characterization of novel biomarkers in colorectal cancer. He then moved to the Memorial Sloan Kettering Cancer Center where he worked on the identification and characterization of biomarkers and genetic drivers in breast and other cancers using a high-throughput genomics and transcriptomics profiling. He was then awarded the Ambizione fellowship by the Swiss National Science Foundation to start his own group in Basel. In 2019 he was appointed as Group Leader of the Visceral Surgery and Presicion Medicine Research laboratory at the Department of Biomedicine. His research program combines patient samples, patient derived organoids, molecular and computational biology to identify new molecular targets in human cancer.

International PhD Program in Biomedicine

Dissertations 2017–2020

As of 2015 all PhD students of the DBM are part of the International PhD program in Biomedicine. Within this interdisciplinary environment, more than 120 PhD students from 28 countries are trained on the post- graduate level aiming the PhD degree from the Faculty of Science. Our program provides in-depth experimental competences and scientific knowledge in a wide range of disciplines of basic and clinical research. Our interdisciplinary PhD Program is associated with the PhD Program in Molecular and Cellular Biology offered by the Biozentrum. Every PhD student at the DBM receive theoretical and practical training, and conduct a research project under the supervision of a DBM research group leader recognized by the Faculty of Science, and monitored by a PhD thesis advisory committee. A rich program of courses, lectures, workshops and conferences organized by the Department of Biomedicine and the Biozentrum are offered to the PhD students. PhD fellows attend yearly scientific meetings (DBM PhD scientific retreat) and have the opportunity to organize seminar series and career guidance events.

The DBM PhD Club creates a department-wide student's club organizing various activities for the PhD students at the DBM with the aim to establish a basis for enhanced scientific networking and exchanges between students of the DBM. They organized the DBM PhD Scientific Retreat, which takes place in general in the spring semester as it did in Quarten (2017), Einsiedeln (2018), Schwarzenburg (2019) and in Fall 2020 in Schwarzsee, and is an excellent platform to form new collaborations in form of knowledge, methodological and technical transfer.

They organize the Career Day inviting speakers talking about future career development. This can be either for a scientific track – what kind of financial funding are provided by the Swiss National Science Foundation – or opportunities in Private Industry.

The PhD Program of the DBM aims to provide a scientific as well as an educational platform for PhD students allowing them to shape on one side their individual scientific career but on the other side to establish their first scientific network.

Group Nicola Aceto

Barbara Maria Szczerba (2019)
Single-cell resolution characterization of circulating tumor cell clusters

Manuel Christopher Scheidmann (2020)
In vivo identification of genetic requirements for the generation and colonization of circulating tumor cells

Group Andrea Banfi

Sime Brkic (2017)
Molecular regulation of intussusceptive angiogenesis by ephrinB2/EphB4 signaling and its therapeutic potential

Emmanuela Bovo (2018)
Mechanisms of vascular stabilization by PDGF-BB

Group Mohamed Bentires-Alj

Romain Amante (2019)
SHP2 blockade sensitizes triple negative breast cancers to PI3K inhibition leading to metastatic shrinkage

Federica Zilli (2020)
Unibased piggybac mutagenesis screens identifytumorigenic and mtastatic pathways in breast cancer

Group Christoph Berger

Marc Benjamin E. Bigler (2018)
Cross-reactivity of B and T cells: desired in influenza vaccine responses, feared in autoimmune diseases

Group Josef Bischofberger

Katharina Behr (2019)
Increased NR2B-dependent early network oscillations in a human stem cell-derived model for autism

Meredith Lodge (2019)
GABAergic interneurons control spiking of adult-born hippocampal granule cells via nonlinear alpha5-GABAA receptors

Group Marijke Brink

Sonia Lebboukh (2017)
Cardiac effects of ovarian hormones and gender in a mouse model of obesity

Philippe Heim (2018)
Regulation of glucose uptake in neuronatal rat cardiomyocytes by neuregulin 1beta

Group Claudia Cavelti-Weder

Theresa Rohm (2020)
Targeting colonic macrophages as a potential therapeutic option in metabolic disease

Group Gerhard Christofori

Ayse Nihan Kilinc (2017)
Epigenetic mechanisms regulating epithelial mesenchymal plasticity in breast cancer

David Martin Büchel (2019)
Wnt/beta-catenin signaling in malignant mammary tumor progression and metastasis formation & mechanisms of evasive resistance to sorafenib in hepatocellular carcinoma

Stefanie Nicole Tiede (2019)
Tumour heterogeneity during the progression of metastatic breast cancer and anti-tumour effects of the novel FAK inhibitor BI 853520 in breast cancer

Fabiana Maria Lüönd (2020)
The contribution of partial and full epithelial-to-mesenchymal transition to breast cancer progression

Group Christian De Geyter

Flurina Pletscher (2017)
Assessment of stem cell pluripotency using an *in vitro* 3D perfusion.based culture model

Xinggang Wang (2018)
HECTD1 modulates centrosome duplication, cytokinesis, and ciliogenesis through HAX1

Group Tobias Derfuss

Natalie Rose (2019)
B cells and autoantibodies in Neuroimmunology

Group Marc Donath

Friederike Schulze (2018)
The role of interleukin-1beta in glucose metabolism during pregnancy and in gestational diabetes mellitus

Josua Wehner (2020)
Changes in metabolism via modulation of the interleukin-1 pathway

Group Adrian Egli

Mohammedyaseen Syedbasha (2019)
The immune modulatory role of interferon lambda on human B-cell functions

Group Magdalena Filipowicz Sinnreich

Martin Lett (2020)
Role of liver cells in bacterial antigen metabolism and MAIT cell activation

Group Daniela Finke

Claudia Cornelia Teufel(2020)
mTOR-mediated regulation of group 3 innate lymphoid cell numbers and cytokine responses

Group Raphael Guzman

Urs Fisch (2017)
Characterization of microglia in the rat subventricula zone after neonatal hypoxia-ischemia

Group Markus Heim

Tuyana Boldanova (2017)
Hapatitis C: transcriptional response and interferon signalling in human liver

Tanja Blumer (2018)
Negative regulation of interferon lambda induced JAK-STAT signaling and development of patient-derived xenograft models from fresh human hepatocellular carcinoma biopsies

Sandro Nuciforo (2018)
Liver cancer in a dish: modelling hepato-cellular carcinoma using patient-derived tumor organoids

Aleksei Suslov (2019)
Host-ivrus interactions in chronic hepatitis B

Group Viola Heinzelmann

Shahidul Alam (2017)
Dissecting the molecular function of neutral glycosphingolipids in ovarian cancer progression

Group Christoph Hess

Anne-Valérie Burgener (2018)
B cell metabolic screening in prime antibody-deficiency identifies succination as an inflammatory immunometabolic pathology

Jasmin Grählert (2019)
Iron metabolism dictates NK cell function

Shefaa AlAsfoor (2019)
Imatinib reduces non-alcoholic fatty liver disease in obese mice by targeting inflammatory and lipogenic pathways in macrophages and liver

Jordan Gabriel Löliger (2020)
Metabolic and non-metabolic roles of PHGDH and their impact on T cell function

Jonas Lötscher (2020)
Shaping memory with magnesium – how moderate activation of LFA-1 with magnesium optimizes CD8+ T cell effector function

Group Hans H. Hirsch

Julia Manzetti (2017)
BK polyomavirus replication in primary human renal tubular epithelial cells: Investigating factors in the early and late viral life cycle as determinants of viral

Flavio Christopher Lombardo (2019)
Development of novel strategies to fill the empty drug pipeline for schistosomiasis: from drug sensitivity assay development to preclinical studies

Elvis Tasih Ajuh (2017)
Functional characterization of the non-coding control region of human polyomaviruses

Group Georg Holländer

Hong Ying Teh (2017)
Role of polycomb repressive complex 2 in thymic epithelial development and function

Group Peter Itin

Elias Imahorn (2018)
Development of keratinocyte culture models for epidermodysplasia verruciformis and ichthyosis with confetti

Group Lukas Jeker

Marianne Dölz (2019)
Hierarchical matrix techniques for partial differential equations with random input data

Group Josef Kapfhammer

Pradeep Sherkahane (2018)
Calcium etrusion mechanisms and dendritic development of cerebellar purkinje cells

Sabine Celine Winkler (2020)
PKCy-mediated phosphorylation of CRMP2 regulates dendeitic outgrowth in cerebellar Purkinje cells

International PhD Program in Biomedicine

Dissertations 2017–2020

Qinwei Wu (2020)
Molecules involved in purkinje cell dendritic development and spinocerebellar ataxias

Group Beat Kaufmann

David Steinl (2017)
Non-invasive ultrasound molecular imaging of myocarditis and autoimmune myocardial inflammation

Alexandra Kosareva (2020)
Targeting of vascular cell adhesion molecule 1 with an ultrasound contrast agent bearing designed ankyrin repeat proteins as targeting ligands

Group Nina Khanna

Pascal Forrer (2018)
Diversity in neutrophil biology: from simple foot soldiers to versatile commanders of immunity in infectious diseases

Group Carolyn King

Marco David Künzli (??)
Heterogeneity and plasticity of the CD4 T cell compartment in viral infections

Group Thomas Klimkait

Fabian Otte (2020)
HIV-1 reservoir formation, stability and dynamics during early therapy

Group Stephan Krähenbühl

Madeleine Vollmer (2018)
The role of the sphingosine-1-phosphate pathway in graft-versus-host-disease (GVHD) and T-cell regeneration in murine allogeneic hematopoietic stem cell transplantation

Group Gabriela Kuster Pfister

Giacomo Della Verde (2018)
Role of fms-like tyrosine kinase 3 in cardiac health and disease

Daria Monogiou Belik (2020)
The role of cancer kinome in the healthy and injured heart: focus on Flt3 and Plk2

Group Claudia Lengerke

Anna Maria Paczulla (2018)
Investigation of mechanisms regulating leukemogenesis using mouse xenograft models of human acute myeloid leukemia

Group Matthias Liechti

Dino Lüthi (2018)
Pharmacological and toxicological investigations of new psychoactive substances

Group Javier Lopez-Rios

Virginie Tissières (2019)
Dissection of Ptch1 cis-regulatory obustness in the context of ariodactyl limb evolution

Group Ivan Martin

Chiara Alessandra Noëmi Stüdle (2017)
Towards osteochondral regeneration with human bone marrow derived mesenchymal stromal cells in a functionalized hydrogel system

Alexander Haumer (2018)
Prefabrication of vascularized large bone grafts

Celeste Manfredonia (2018)
Maintenance of primary human colorectal cancer microenvironment using a perfusion bioreactor-based 3D culture system

Sébastien Pigeot (2018)
Hypertrophic cartilage engineering for human bone and bone marrow regeneration

Lina Marcela Acevedo Rua (2019)
Performance of nasal chondrocyte-based engineered tissues in osteoarthritis simulating environments

Thibaut Klein (2020)
Engineering of 3D mesenchymal tissues for bone regeneration and hematopoiesis modeling

Group Matthias Mehling

Corina Frick (2020)
Microfluidics for understanding basic aspects of directed immune cell migration and translational research

Group Albert Neutzner

Ana Catarina de Pinho Ferreira Bento (2018)
UBXD1 and YOD1: p97 cofactors involved in autophagic mitochondrial quality control

Group Jan Niess

Philipp Richard Wasilios Wuggenig (2019)
The branched-chain amino acid transporter CD98 heavy chain facilitates the development of colonic macrophages associated with apoptosis in macrophage progenitors

Berna Kaya (2020)
Lysophosphatidic acid-mediated GPR35 signaling in CX3CR1+ macrophages, regulates the intestinal cytokine milieu

Group Daniel Pinschewer

Mehmet Sahin (2018)
Antibody control and immunopathogenesis of viral infection

Yusuf Ismail Ertuna (2019)
Vectored antibody delivery: impact on and synergy with the host's immune defense in chronic viral infection

PhD Club 2020 (Schwarzsee)

Group Mike Recher

Fabian Sebastian Baldin (2018)
The role of Sp110 in human T cell apoptosis and immunopathology

Florian Marquardsen (2018)
Modulation of T-cell apoptosis by small molecule compounds targeting the nuclear orphan receptor Nur77

Lena Siewert (2019)
Adaptive immunity in murine Bartonella infection

Group Antonius Rolink

Stefan Heiler (2018)
IL-2/anti-IL-2 complexes: the resurrrection of IL-2 as potential treatment for SLE-like murine chronic graft-versus-host disease?

Fabian Klein (2019)
Extrinsic and intrinsic regulation of differentiation and selection events during lymphocyte development

Group Michael Roth/Michael Tamm

Group Nicole Schaeren-Wiemers

Lukas Enz (2020)
Chronic Cortical Pathology in Multiple Sclerosis

Group Jürg Schwaller

Marwa Almosailleakh (2019)
Insights into cellular and molecular mechanisms of normal and malignant hematopoiesis from mouse models

Maria Riera Piqué Borras (2020)
Molecular mechanisms of acute erythroid leukemia: learning from rare chromosomal translocations in pediatric patients

Group Radek Skoda

Ronny Nienhold (2017)
Genetic lesions and clinical implications in myeloproliferative neoplasms

Jakub Zmajkovic (2018)
Genetic studies of hereditary myeloproliferative disorders

Group Giulio Spagnoli

Valeria Governa (2017)
Immunobiology of neutrophils in human colorectal cancer

Group Verdon Taylor

Andrea Erni (2017)
Post-transcriptional regulation of neural stem cell fate by the RNaseIII Drosha

Zahra Ehsaei (2018)
Differentiation potential, lineage commitment and gene expression profile of human cortical neural progenitor cells derived from pluripotent stem cells

Tanzila Mukhtar (2018)
Hippo signalling in mammalian cortical development

Niklas-Frank Iffländer (2020)
Post-transcriptional regulation of neural stem cell fate by non-canonical Drosha functions

Group Susan Treves

Alexis Jesus Ruiz Velez (2018)
Characterization of a transgenic mouse overexpressing SRP35 in their skeletal muscle

Group Roxane Tussiwand

Patrick Fernandes Rodrigues (2019)
Dissecting the development of plasmacytoid dendritic cells

Group Rolf Zeller

Julie Gamart (2017)
SMAD4: a multifunctional regulator of limb bud initiation and outgrowth

Ausra Girdziusaite (2020)
TBX3 and HAND2 controlled gene regulatory networks in establishment of axis polarity in mouse limb buds

Laurène Ramos Martins (2020)
The gremlin1 cis-regulatory landscape: a paradigm to study enhancer cooperation in regulation of transcription dynamics

Group Alfred Zippelius

Vincent Prêtre (2017)
From the regulatory role of PDPN in mTOR/PI3K/Akt signaling to clinical trials

Michal Adam Stanczak (2018)
Targeting sialoglcan – siglec interactions in cancer immunology

Marcel Philipp Trefny (2020)
Resistance mechanisms in cancer immunotherapy

Core Facilities of the Department of Biomedicine

Scientific core facilities are an integral part of the DBM research landscape. They enable cutting-edge research by helping to economically and efficiently take advantage of state-of-the-art technology and collaborate with expert staff.

The highly trained facility members serve the evolving needs of the DBM research groups by following up with the latest technological advances, giving comprehensive trainings to the users or by coordinating grant applications to purchase new equipment. DBM core facilities are providing their service at no or very little costs, minimizing the administrative burden and leveraging resources to support investigator-driven science. Dedicated steering committees evaluate the services and provide guidance to the core facility heads in order to improve the core facility infrastructure, technology and management for the benefit of the DBM research groups.

While DBM members have access to in-house core facilities for bioinformatics, flow cytometry & cell sorting, light microscopy, histology and for the production of medicinal products according to Good Manufacturing Practices (GMP), the DBM joins forces with other life sciences institutions in Basel to run core facilities for next generation sequencing technologies and genomics research, design and generation of custom transgenic rodent models, preclinical nuclear molecular imaging, electron microscopy, and high-performance computing.

The DBM has a long history in sharing and centralizing common equipment to leverage resources. In the absence of dedicated core facility personnel, these facilities are maintained by members of DBM research groups or by technical staff. Such technologies that are available to all researchers include facilities for robotics, tissue culture, biobanking and other high-end applications.
Together, these core facilities play a central role in creating a competitive research environment and contribute significantly to the scientific success of the Department of Biomedicine.

Medium change in cell culture

Good Manufacturing Practice (GMP)

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Introduction

Good Manufacturing Practice (GMP) is a system to ensure that medicinal products intended for human use are produced according to stringent quality standards. Swiss manufacturers of medicinal products must comply with international GMP guidelines set forth by the European Union (EU). These GMP standards are built on three pillars:

1) Medicinal products for human use have to be manufactured at controlled sites that are adequately equipped,
2) the manufacturer has to demonstrate appropriate professional and technical knowledge that is provided by qualified staff, and
3) a Pharmaceutical Quality System (PQS) system needs to be established by the manufacturer. The DBM is approved by Swissmedic to operate a GMP core facility which is located on the 4th floor of the ZLF.

Service

The “GMP core facility DBM” owns a license for manufacturing of investigational advanced therapy medicinal products (investigational ATMPs); i.e. medicines for human use that are based on genes, cells or tissue engineering and that are used in clinical trials. The core facility offers as “Provider” central services to individual DBM research groups (“Users”) that are affiliated with clinical investigator teams. Training of all staff (both core facility staff and research group staff) is organized by the core facility staff. Interested persons not currently affiliated with research groups working in the facility or planning to do so in the future are also welcome to attend basic training sessions.

Affiliation and Staff

Both the core facility provider and the DBM research group users are required to contribute to the implementation of a fully functional PQS necessary for the certification and release of GMP-compliant ATMPs: the core facility staff forms a “Quality Assurance” unit headed by PD Dr. W. Krenger who also certifies and releases the final product for patient use in his official function of a “Qualified Person”. Additional functions mandated by the PQS need to be provided by members of the individual research teams wishing to manufacture products in the facility. These functions include at minimum a Quality Control manager (QC), a Manufacturing Manager and a Product Manager who is usually the Principal Investigator of the research group or the clinical investigator team.

Activity 2017–2020

The GMP core facility DBM is uniquely suited to contribute to innovations in cellular therapies. In the time period from 2017 to 2020, cartilage tissue was engineered and used in a phase II clinical trial to treat knee cartilage injuries at the USB and also at hospitals abroad. In early 2020, the technical groundwork was laid for a second group to join the facility in order to study cellular therapy with tumor-infiltrating lymphocytes in a new phase I clinical trial.

Bioinformatics

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The Bioinformatics Core Facility provides a centralized resource of expertise in computational biology and statistics, available to all DBM researchers. It offers support for the analysis and visualization of large-scale biological data. The platform also provides training in bioinformatics and facilitates access to high-performance computational resources.

Design and analysis of the high-throughput biological experiments

The aim of the Bioinformatics Core Facility is to implement solutions for the design, analysis, visualization, interactive exploration and interpretation of large-scale genomic and proteomic data. Over the years, the facility has supported more than fifty research groups for genomic projects involving assays such as gene expression (RNA-seq), DNA-protein binding (ChIP-seq), RNA-protein binding (CLIP-seq, RIP-seq), DNA methylation (BS-seq), DNA accessibility (ATAC-seq), mapping of physical contacts between genomic elements (4C-seq), identification of sequence variants (DNA-seq). More recently the facility has developed the expertise to analyze data from newly emerged technologies: single cell expression profiling (scRNAs-eq), high-dimensionality flow cytometry data (CyTOF) and high-throughput proteomics. Beside supporting standardized approaches, the platform also develops customized solutions tailored towards the needs of individual research projects.

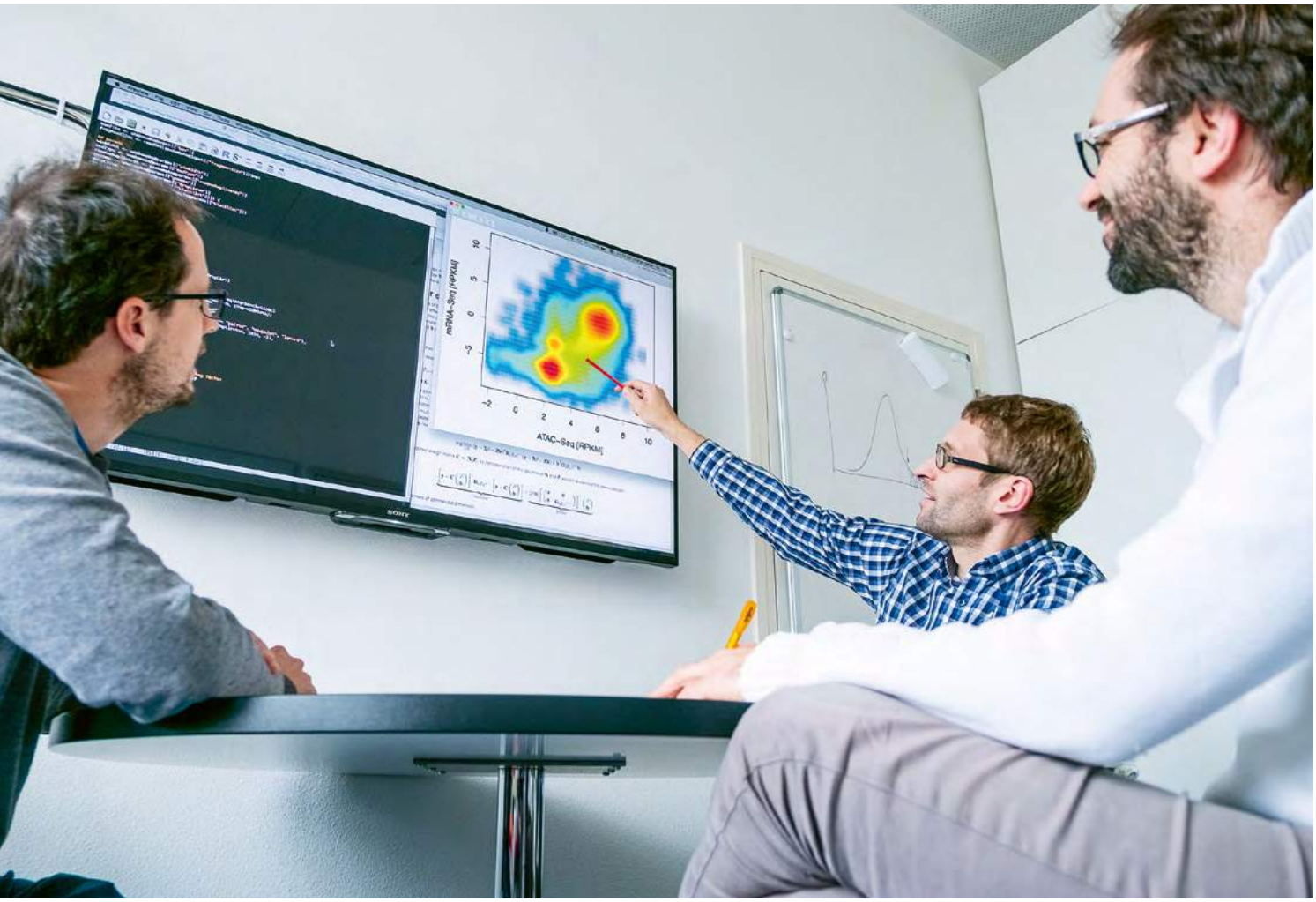
Bioinformatics training

The Bioinformatics Core Facility trains and advises researchers at the DBM. Furthermore, it is a point of contact for the bioinformaticians embedded within the DBM research groups, with whom they meet in bi-weekly seminars.
The facility also organizes bioinformatics teaching at the University of Basel in collaboration with computational biologists from the Friedrich Miescher Institute for Biomedical Research. This comprises two full semester lecture series and exercises:

1. “Introduction to **R**”, a hands-on course on the basic usage of **R** software with a focus on data exploration and visualization, and basic statistics.
2. “Analysis of genomics data with **R** and Bioconductor”, an advanced course giving students an overview of typical Bioconductor based analysis pipelines including: NGS data processing, differential gene expression analysis, single-cell data, DNA binding analysis, working with sequence and annotation packages and visualization of genomic data.

Fostering interactions within and outside of Basel

The platform’s mission is to build and maintain an infrastructure for comprehensive and strong bioinformatics analysis which empowers the biomedical research at the DBM. To keep track with recent technological developments and the increasing number of bioinformatics approaches and tools, the Bioinformatics Core Facility closely interacts with other bioinformatics units in the Basel area (e.g., sciCORE, Biozentrum, FMI). The Bioinformatics Core Facility is a member of Swiss Institute of Bioinformatics (SIB). The facility also actively contributes to the Bioconductor project and are involved in the development of packages Gviz, seqLogo, ExploreModelMatrix and BgeeDB.



Project discussion at the Bioinformatics Core Facility

Microscopy

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The Microscopy Core Facility is a centralized platform that provides cutting-edge microscopes and expert support to all DBM researchers.

Infrastructure and equipment

The facility staff is currently supervising over 30 high-end microscopes, including multiplex, two-photon, super-resolution, confocal, widefield, FRAP, TIRF, high content screening, slide and plate scanning, live-cell imaging, flow cytometer imaging, stereo, and laser capture microdissection. The facility also provides resources for image analysis, including high-end computers, virtual machines, data and image analysis servers, and several commercial and open-source image analysis softwares.

Training and support

The facility trains and advises researchers throughout the entire microscopy process, from initial idea to publication. Support often starts with a conversation about the biology and leads to a robust microscopy experimental design that includes sample preparation, choice of microscope, software for image visualization, and strategy for analysis. Researchers are then trained to work independently at the corresponding microscopes and computers.

Future developments

In order to learn and develop new microscopy technology, the facility is embedded in European and Swiss microscopy networks. In the Basel area, the academic microscopy facilities are organized within the Microscopy Network Basel (MNB, https://microscopynetwork.unibas.ch/home). The MNB facilitates interactions on the levels of sharing resources and knowledge, fostering collaborations and co-organizing courses, equipment demonstrations, seminars or symposia.
While the core facility staff is constantly keeping up with the latest technological developments, a steering committee of DBM research group leaders is providing instrumental guidance. This allows the facility to swiftly adapt to the needs of the DBM research community. For example, several groups at the DBM recognized the importance of multiplex imaging, and the facility was able to react by hiring a multiplex analyst and investing in software and hardware to make the technique accessible to all DBM researchers.


Discovery.V20
ZEISS
SteREO

Flow Cytometry

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Introduction

The Flow Cytometry Facility is a centralized platform that provides advanced instrumentation as well as high-level technical and scientific expertise in multi-dimensional flow cytometry and cell sorting, to facilitate science, improve the quality and advance the scope of DBM research. We have more than 60 research groups, from the four different focal areas of research, using the Flow Cytometry Facility.

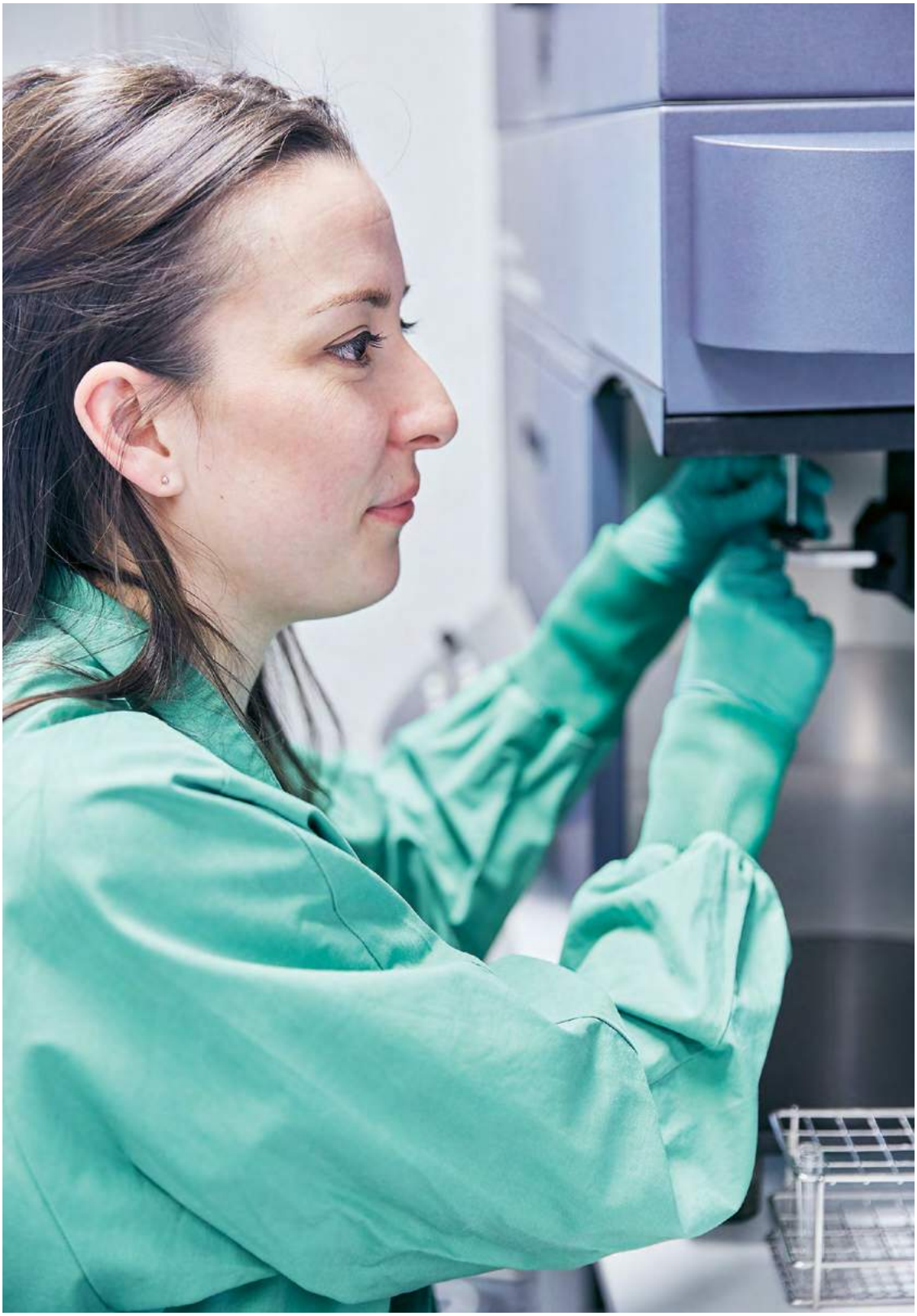
Until recently flow cytometry was limited to the analysis of fluorochromes that had distinct emissions spectra and the instruments were able to separate each with specific filters. For some years that in flow cytometry was possible to analyze the whole emission spectra of the dyes but we were limited with the number of excitation lasers that were available on this specific instrument. Recently, a new instrument with up to 5 lasers and 67 detectors, have opened the field supporting the analysis of the complete emission spectra of each dye. This allowed for the analysis and separation of fluorochromes with very similar spectra. One of the advantages is the detection of simultaneous parameters on the same sample, the limit is always increasing still at the moment it was possible to do 40 parameters simultaneously.

At the DBM we were one of the first in Switzerland to have this technology available for the researchers, opening new possibilities for scientific discoveries. In only a few months, this instrument was being used by more than 8 research groups in the different focal areas.

Service

The facility is responsible for the maintenance and quality control of all instruments, as well as, to give support to the researchers at all steps of the experiment, from the initial idea and experimental design to publication.
The importance of good experimental design will be essential for a robust data analysis, and it includes sample preparation, choice of instrument for acquisition and analysis strategy.
The facility is providing one-to-one training for all researchers in the flow analyzers. This allows a specialized train based on the researcher experience and experiment to acquire, making sure that the later independent use of the instrument is a success.
Then, for any correlation between experiment data sets, the instruments must be in the same conditions as before, this is why is so important to have good maintenance and quality check control.
While the flow analyzers are operated by trained researchers, the high-speed cell sorters are mainly operated by the facility staff.

Researcher working on a flow cytometer in the Flow Cytometry Facility. ▶



Histology

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Histology Specialists

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Introduction
In a scientific world dominated by the high-throughput and -omics methodologies, there is still space for the ancient discipline of histology.
The study of tissue morphology, the interaction between cells, the intra-and extracellular localisation of molecular markers are the bases of this discipline, that over the centuries, does not lose its importance in the basic and translational research.
The Histology Core Facility (HCF) has been established at the DBM in 2019, to support the DBM research activities in the specific field of histology.
The Facility is located at the Anatomy Institute, in Pestalozzistrasse 20. Diego Calabrese is the head of the Facility and he is assisted by Andreas Ochsenbein and, recently, from Mylène Toranelli.

Mission
The primary mission of the HCF is to train and support scientists at the DBM, to enable them to establish and execute histology protocols specific to their individual experimental settings. This also ensures that research groups can maintain and pass-on the corresponding know-how within their groups and/or share them with other groups. Additionally, the Facility provides a fee-based service that can cover every histology protocol, including an image analysis service.

Facility Organization
The facility is currently run on two functional units: the Do It Yourself (DIY) platform and the Service platform.

DIY platform
The Facility staff supports the DIY platform in two ways:
1. The staff provides an in-depth initial training on the basic principles of histology. This mandatory training ensures that each user starts with a minimal fundamental knowledge.
2. After the training, users are supported in their work as follows:
   - assistance in case of equipment failure
   - developing new methods
   - resolving methodological problems

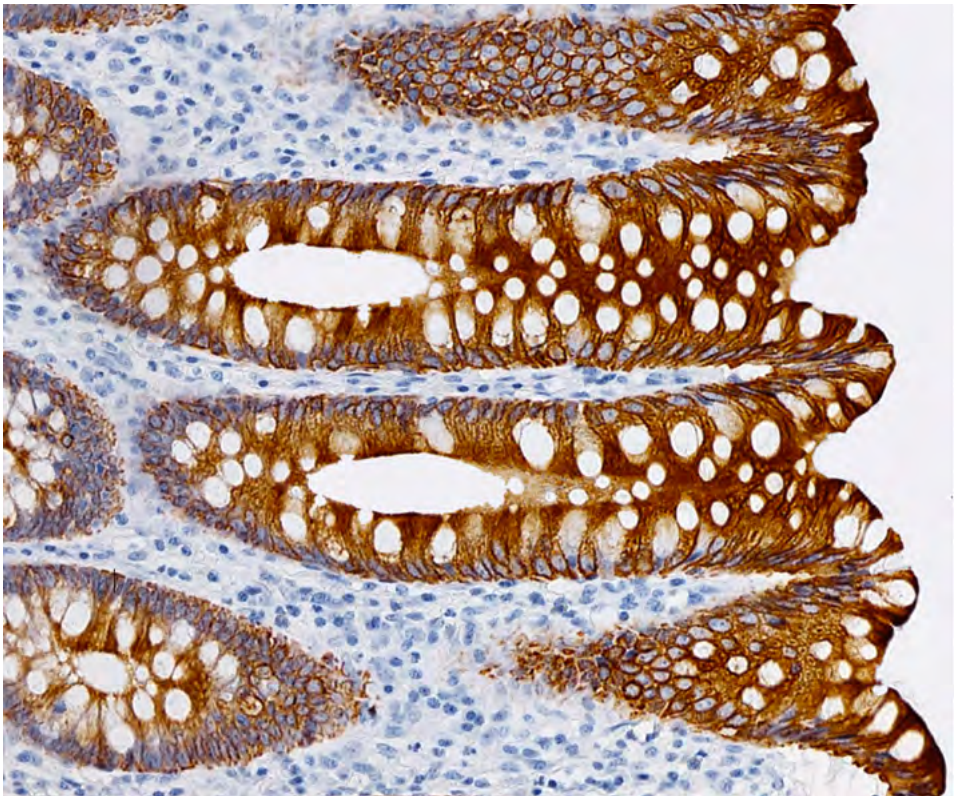
Currently, the DIY platform provides 19 instruments, supporting 343 registered and trained users. The DIY platform is free of charge for DBM/USB/UKBB groups.

Service platform
Since 2019, every established histology protocol (e. g. tissue embedding and cutting, automated immunohistochemistry, immunofluorescence and in-situ hybridization, and imaging analysis with a special focus on the IHC and ISH image analysis) is offered by the HCF on a fee-based service platform.

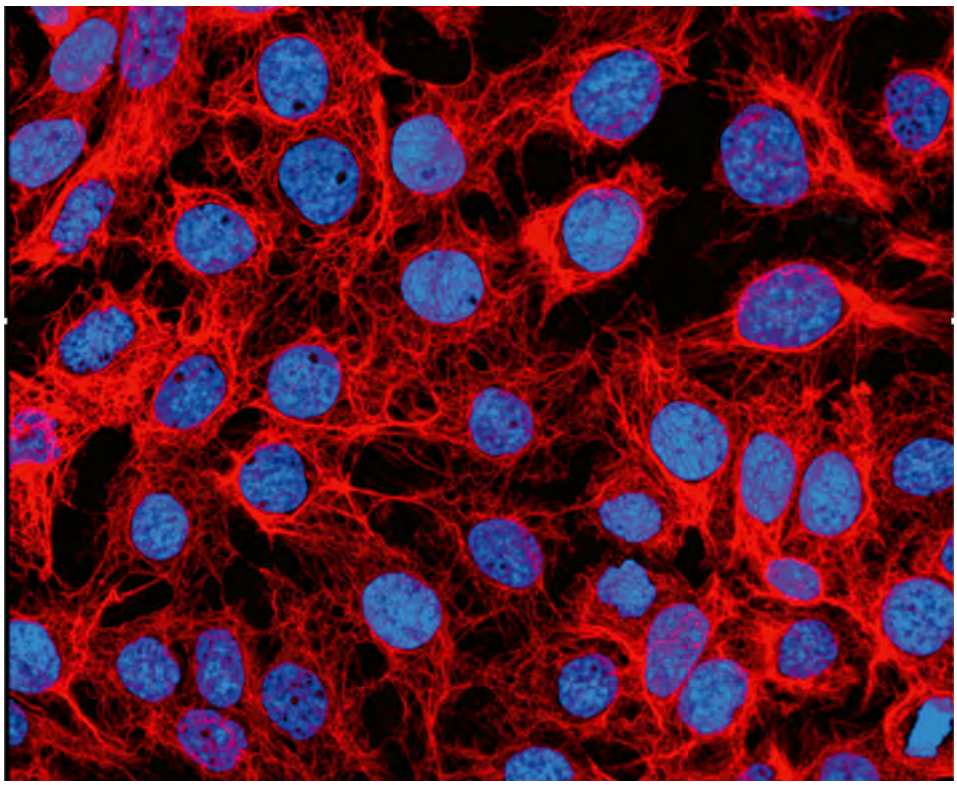
Other HCF responsibilities
The Facility is part of a Phase 3, international, multi-center clinical trial on ovarian cancer providing:
1. centralized IHC service for all the trial sites
2. organizing a centralized biobank
3. digitization and distribution of histology data to an international reference pathologist network

The Facility complies with the GCLP standards for the execution of those activities.

The HCF provides support for preparation of histological slides for the anatomy course set up at the University of Basel.



Human colon section
stained by immunohistochemistry
for the pan-keratin protein pool



Microscopic picture
of hepatocellular carcinoma cells
stained by immunofluorescence
for the protein cytokeratin 18

Joint Core Facilities

Joint Core Facilities not only provide services to researchers at the DBM, but also to other life sciences institutions in the Basel area.
They are jointly managed by the contributing partners and form an important pillar in assuring access to state of the art infrastructure and technical expertise to our research groups while keeping up with the rapid technological developments.

Genomics Facility Basel

Providing a central platform for next generation sequencing technologies and genomics research

The Genomics Facility Basel is a joint venture between the Department of Biosystems Sciences and Engineering (D-BSSE) of ETH Zürich and the life sciences departments of the University of Basel. They provide professional expertise and technical support for all steps in the NGS workflow, including library preparation, (single-cell) RNA-seq, genome and exome sequencing and the development of new protocols and applications. The Genomics Facility Basel works in close collaboration with the DBM Bioinformatics Core Facility.

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Center for Scientific Computing (sciCORE)

Facilitating access to high-performance computing infrastructure

The sciCORE at the University of Basel is maintaining and developing high-performance computing infrastructures, large scale storage systems and an up-to-date software stack. sciCORE staff provides training, consulting and direct support to the researchers in the use of these resources and is actively participating in computational projects of national scope. At the DBM, the Bioinformatics Core Facility is closely interacting with sciCORE to provide the researchers optimal access to the required resources.

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Life Sciences Training Facility (LSTF)

Understanding gene function in health and disease

The Life Sciences Training Facility (LSTF) is a technology platform, which is supported by the Department Biozentrum, the Transfaculty Research Platform Molecular and Cognitive Neurosciences and the Department of Biomedicine. The LSTF provides access to deep-sequencing and microarray technologies and contributes to the identification of novel molecular pathways. The LSTF works in close collaboration with the Genomics Facility Basel.

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Mouse Core Facility

Laboratory Animal Care and Husbandry

The University Basel Mouse Core Facility comprises five animal facilities in different locations, including three in DBM. Our highly skilled and knowledgeable animal caretakers support investigators in their research endeavors and assure state of the art animal care and animal welfare. They provide standard services (cage and food/water change, husbandry, timed matings, plug checks, biopsies for genotyping etc.), as well as monitoring of constraint lines, trimming of nails in strained lines and packing of animals for export. We assure high quality veterinary care and maintain SPF hygiene status by supervising animal import, disease prevention and housing. If necessary we initiate treatment, and always take into account animal welfare, the 3R principles and the quality of research.

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Center for Transgenic Models (CTM)

Designing and generating custom transgenic models

The CTM at the University of Basel provides researchers access to the latest transgenic and assisted reproduction technologies, while at the same time implementing the 3R principles for responsible animal experimentation. Their services include DNA pronuclear injection, rapid oocyte injection, embryo cryopreservation, mouse strain rederivation, chimera generation and sperm cryopreservation and transgenic model design. The CTM also provides technical advice on TALENS and CRISPR technology and is developing novel gene delivery techniques.

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BioEM Lab at Center for Cellular Imaging and Nano Analytics (C-CINA)

Electron microscopy for the life sciences

The BioEM Lab of the University of Basel gives researchers access to electron microscopy structural investigations in the life sciences field. The BioEM Lab offers various life sciences high-resolution electron microscopy imaging methods for cellular EM (e.g. TEM imaging and volume reconstructions of tissues) and molecular EM (e.g. high-resolution cryo-EM 3D reconstructions of biological macromolecules). By providing training, consulting and technical support, the facility staff supports researchers in defining their workflow for sample preparation, data acquisition and image processing.

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Small Animal Facility for Preclinical Nuclear Molecular Imaging

In vivo imaging of radiolabelled compounds at high sensitivity

The facility is operated in collaboration with the Divisions of Radiopharmaceutical Chemistry and Nuclear Medicine at the University Hospital Basel. It provides access to SPECT/CT technology for short- and long-term experiments in living rodents and other equipment for the analysis of pharmacokinetic and –dynamic properties of radiolabeled compounds. The different nuclear imaging modalities allow highly sensitive detection of molecules in the femtomolar range in an endogenous setting – a prerequisite to avoid interfering interactions such as receptor saturation effects.

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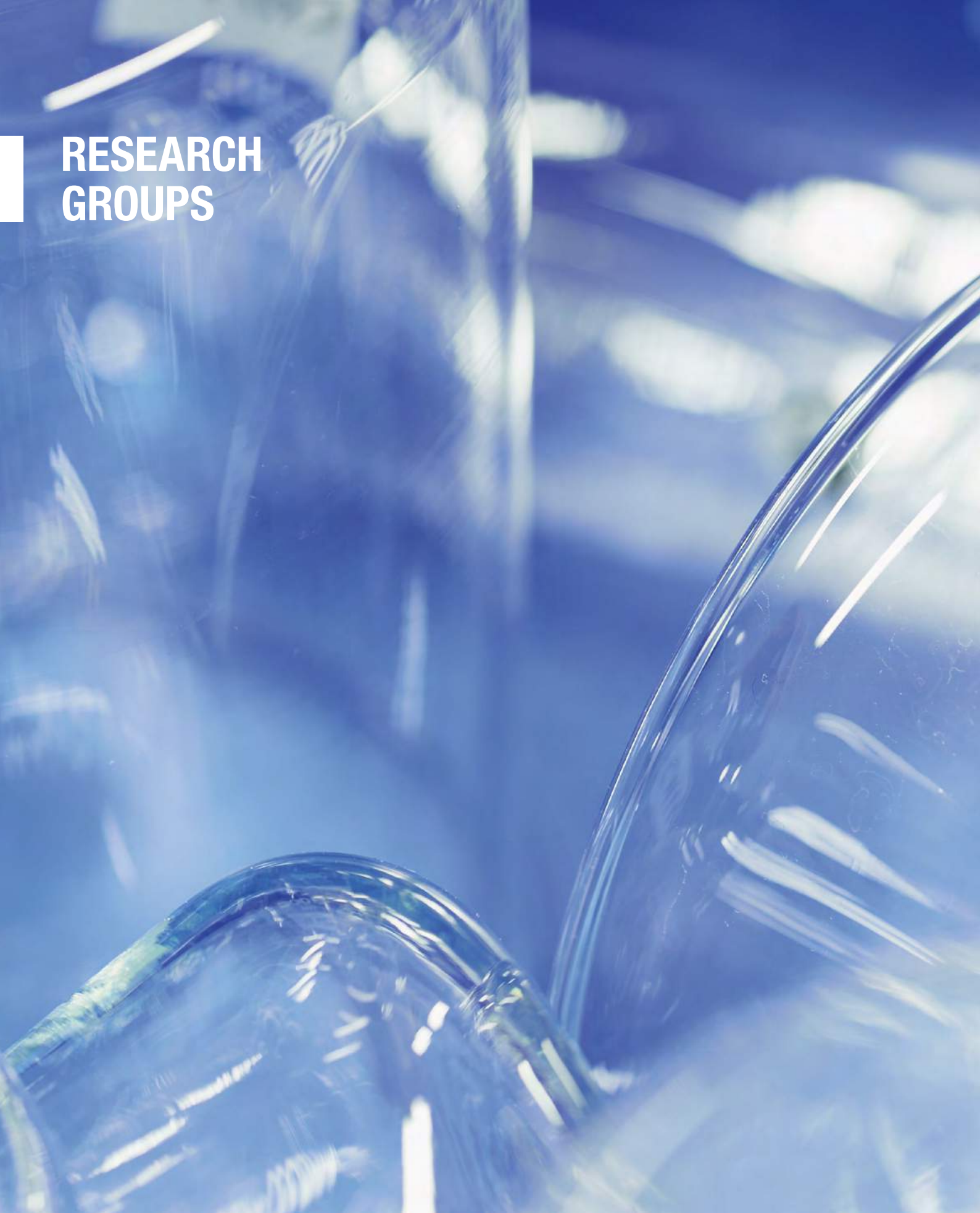

RESEARCH GROUPS

Neurobiology

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Understanding the molecular events underlying diseases of the nervous system and exploiting this knowledge for improving treatment are among the major challenges in the life sciences. In view of the increasing social and financial burden generated by these diseases, especially in the setting of an ageing population, the Department of Biomedicine (DBM) has defined the neurosciences as one of its focal areas.

The Focal Area Neurobiology of the DBM complements parallel efforts at the Biozentrum and at the Friedrich Miescher Institute (FMI) and is part of the Neuroscience Network Basel (NNB), which is acknowledged as a center of competence by the University of Basel since 2008. The NNB aims at promoting translational collaborative research and comprises more than 400 neuroscientists from 40 different laboratories associated with the University, the University Hospitals, the FMI and the Basel Life Science Industry.

Research is conducted at all levels – from molecules and synapses up to complex brain networks and behavior – thus providing outstanding research opportunities and an excellent platform for a strong educational program. The NNB offers weekly research seminars and lecture series at the graduate and postgraduate levels, covering all aspects of basic and clinical neuroscience. The NNB is part of the trinational educational and collaborative NEUREX network along with the neuroscience programs at the Universities of Freiburg (Germany) and Strasbourg (France).

A major aim of the Neuroscience groups at the DBM is to take advantage of the unique expertise in the neurosciences present in the Basel area to pursue translational research projects. Because of these efforts, basic and clinical neuroscientists have already contributed to the development of innovative therapies with leading roles in international collaborations and successfully raised grant support for translational research projects from the Swiss National Science Foundation, the European Union, the Swiss Cancer League, the Swiss MS Society, various private foundations and industry. The focus of these projects is on neuroimmune (see the respective reports under focal area immunology), neurodegenerative and genetically determined neurological, psychiatric and neuromuscular disorders.

To promote the rapid translation of research results into clinical practice the DBM Focal Area Neurobiology co-organizes the Annual Basel Neuroscience Symposium “From Bench to Bedside”. The one-day event provides a platform for exchange of ideas and is regularly attended by more than 150 local neuroscientists, including basic and clinical researchers from Novartis, Roche, Janssen (former Actelion), Santhera Pharmaceuticals, the FMI and the University of Basel.

Molecular Neurobiology Synaptic Plasticity

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From the GABA-B receptor proteome to brain functions and therapeutic concepts

My laboratory studies how the molecular composition of GABA-B receptors (GBRs), the G protein-coupled receptors for the neurotransmitter GABA, influences neuronal activity. Because GBRs are implicated in the pathophysiology of neurological and psychiatric disorders, we also aim at targeting molecularly defined GBR signaling complexes for therapy. In collaboration with Prof. B. Fakler (University of Freiburg, Germany), we identifed 30 GBR-associated proteins (Pin & Bettler, Nature 540, 2016; Bettler & Fakler, Curr. Opin. Neurobiol. 45, 2017). We have mapped the interactions of several of these proteins with each other and with the GBR subunits GB1 and GB2 (Fig. 1). We found that GBR components associate in a modular fashion into a variety of functionally distinct multi-protein complexes. We analyzed several GBR-associated proteins for their effects on receptor signaling, neuronal excitability, brain network activity and behavior. Auxiliary KCTD proteins, for example, regulate the kinetics of GBR-induced currents, explaining kinetic discrepancies between currents observed in different neurons (Fritzius *et al.,* J. Neurosci. 37, 2017). KCTD proteins influence both strength and frequency of thalamic spindle oscillations, showing that kinetic effects of the KCTDs on GBR signaling regulate network activity (Ulrich *et al.,* Neuropharmacol. 136, 2018). Accordingly, lack of KCTD16 in mice also influences behavioral responses (Cathomas *et al.,* Behav. Brain Res. 317, 2017).

Amyloid precursor protein (APP), adherens junction-associated protein 1 (AJAP1) and PILRα-associated neural protein (PIANP) form three mutually exclusive GBR complexes by binding to the N-terminal sushi domain of GB1a (Schwenk *et al.,* Nat. Neurosci. 19, 2016). Because this sushi domain mediates axonal localization, we tested whether axonal trafficking of GBRs is impaired in APP-/-, AJAP1-/- or PIANP-/- mice (Dinamarca *et al.,* Nat. Commun. 10, 2019). Selectively APP-/- mice exhibited a decrease in axonal GBRs (Fig. 2A) and a consequent deficit in GBR-mediated inhibition of neurotransmitter release. Trafficking of APP/GBR complexes in axons was visualized using time-lapse imaging (Fig. 2B-D). APP associates with JIP3 and CSTN3 proteins (Fig. 1) of the axonal trafficking machinery. Complex formation with GBRs stabilizes APP at the cell surface and reduces proteolysis of APP to Aβ, a component of senile plaques in Alzheimer's disease. These findings establish a link between APP/GBR complex formation, axonal trafficking of GBRs and Aβ production.

The SHRM4 protein, which is genetically associated with intellectual disability and epilepsy, controls GBR cell surface expression. Knockdown of Shrm4 in rodents impairs GBR activity, induces anxiety-like behaviors and increases susceptibility to seizures (Zapata *et al.,* Nat. Commun. 8, 2017). Collaborative work further showed that GBRs shape the auditory map (Vickers *et al.,* Neuron 99, 2018), evoke distinct responses in astrocytes (Mariotti *et al.,* Nat. Commun. 9, 2018) and regulate cocaine-induced behaviors (Edwards *et al.,* Nat. Neurosci 20, 2017).

Drug Discovery

Clinical use of GBR drugs is limited to agonists and the treatment of narcolepsy, spasticity and alcohol use disorders. One reason for the limited use of GBR agonists is that global GBR activation results in unwanted side effects. The recognition that GBRs form a variety of multi-protein complexes provides opportunities for targeting cell-type specific functions and individual signaling pathways (Rosenbaum *et al.,* Nat Rev Drug Discov (2020). https://doi.org/10.1038/s41573-020-0086-4). Targeting molecularly defined receptor complexes should reduce side effects and enable new therapeutic applications. In collaboration with the medicinal chemistry group of K. Strømgaard (Pharmaceutical University, Copenhagen), we developed

peptide-based inhibitors of the GBR/KCTD interaction (Sereikaite *et al.,* J. Med. Chem. 62, 2019). These inhibitors are expected to exhibit anxiolytic properties by preventing GBR desensitization. We are currently also developing peptides interfering with defined presynaptic GBR complexes to facilitate glutamate release, particularly for the treatment of cognitive dysfunctions.

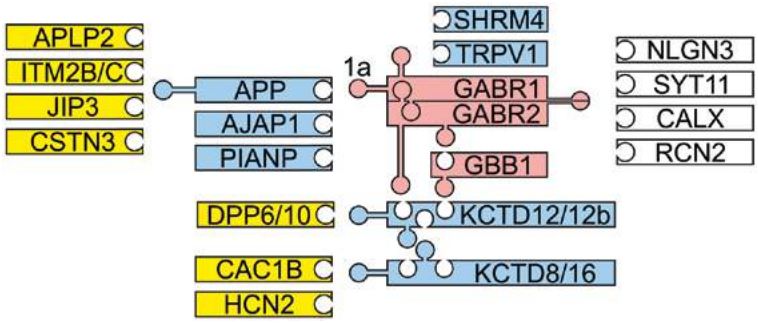

Fig. 1: Structural organization of GBR complexes. GB1 (GABR1) and GB2 (GABR2) receptor subunits constitute fully functional heterodimeric receptors that bind to the β subunit (GBB1) of the G protein (red). Modular association of these receptors with additional components generates multi-protein complexes of varying composition and signaling properties. Primary (blue) and secondary interactors (yellow) as well as receptor components with unknown interaction sites (white) are depicted. Pentamers of auxiliary KCTD proteins bind to GB2 and GBB1 to regulate receptor kinetics. APP, AJAP1 and PIANP bind to the N-terminal sushi domain of GB1a. APP binds to JIP3 and CSTN3, which link the APP/GBR complex to the axonal trafficking motor. APLP2 and ITM2B/C assemble via APP with GB1a. TRPV1 channels bind to GB1a while Cav2.2 (CAC1B) and HCN2 channels bind to KCTD8/16. NLGN3, Neuroligin 3; SYT11, Synaptotagmin 11; CALX, Calnexin; RCN2, Reticulocalbin 2. Adapted from Fritzius & Bettler, Basic Clin. Pharmacol. Toxicol. 126, 2020.

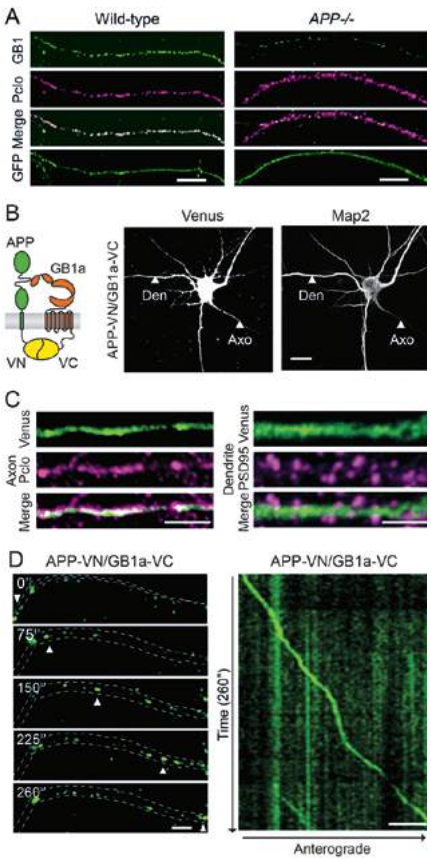

Fig. 2: APP associates with GB1a and mediates axonal trafficking of GBRs. **(A)** Endogenous GB1 protein is reduced by 75% in the axons of APP-/- hippocampal neurons. Neurons were immunostained for GB1 (green) and the presynaptic marker piccolo (Pclo, magenta). GFP served as a volume marker. Merged images show GB1 and piccolo co-localization. Scale bar 5 µm. **(B)** Scheme depicting bimolecular fluorescence complementation (BiFC) using the split Venus fusion-proteins APP-VN and GB1a-VC. Association of APP-VN with GB1a-VC reconstitutes Venus fluorescence. Representative confocal images show hippocampal neurons expressing APP-VN together with GB1a-VC. BiFC is observed in axons (Axo) and dendrites (Den). Microtubule-associated protein Map2 identifies dendrites. Scale bar 10 µm. **(C)** Higher magnification of axons and dendrites expressing APP-VN and GB1a-VC. The BiFC complex (Venus) partly co-localizes with piccolo (magenta) and is also present along dendritic shafts but excluded from spines, identified by PSD-95 (magenta). Scale bar 5 µm. **(D)** Time-lapse images of a well-separated APP-VN/GB1a-VC complex (arrowheads) trafficking anterogradely in the axon (acquisition time in seconds). A kymograph shows the entire time-lapse recording (right). Scale bars 25 µm.

Connection to Clinical Practice

Prof. Murim Choi, Prof. Cyrill Géraud
Seoul National University College of Medicine, Seoul, Republic of Korea (MC), Medical Faculty, University Heidelberg (CG)

GABBR2 and PIANP mutations in neurodevelopmental disorders

Dominant de-novo mutations in the GB2 subunit gene GABBR2 were identified in pediatric Rett (RTT) and epileptic encephalopathy (EE) patients (e. g. Lopes *et al.,* J Med Genet 53, 2016; Yoo *et al.,* Ann Neurol 82, 2017; Vuillaume *et al.,* Ann Neurol 83, 2018). Characterization of RTT and EE mutations revealed that increased constitutive receptor activity reduces the efficacy of GABA. We hypothesize that a reduced efficacy of synaptically released GABA tips the excitation/inhibition balance in the brain towards more excitation. Our collaborator, Prof. M. Choi, has generated mice with inducible RTT and EE mutations in GABBR2. We will study the mechanism of pathogenesis and address how GABBR2 mutations affect synaptic GBR responses to identify possible therapies. A homozygous nonsense mutation in the gene for the GBR-associated protein PIANP leads to global developmental delay and intellectual disability. In collaboration with Prof. C. Géraud, we showed that PIANP-/- mice exhibit autism spectrum disorder-like phenotypes (Winkler *et al.,* Mol. Psych. 2019). Similar to APP-/- mice, PIANP-/- mice exhibit a deficit in GBR-mediated inhibition of glutamate release, supporting that saturation of synaptic plasticity and excitotoxicity contribute to disease pathology.

Selected Publications

Dinamarca MC, Raveh A, Schneider A, Rem PD, Stawarski M, Früh S, Fritzius T, Lalanne T, Turecek R, Choo M *et al.* (2019). Complex formation of APP with $GABA_B$ receptors links axonal trafficking to amyloidogenic processing. Nature Commun. 10 (1), 1331.

Vickers ED, Clark C, Osypenko D, Fratzl A, Kochubey O, Bettler B, and Schneggenbruger R (2018). Parvalbumin-interneuron output synapses show spike-timing dependent plasticity that contributes to auditory map remodeling. Neuron 99(4), 720–735.

Mariotti L, Losi G, Gomez-Gonzalo M, Melone M, Chiavegato A, Lia A, Sessolo M, Bovetti S, Forli A, Zonta M *et al.* (2018). Interneuron-specific signalling unveils unique somatostatin-mediated properties of astrocytes in adult neocortex. Nature Commun. 9(1), 8.2.

Edwards NJ, Zhang S, McDevitt RA, Tejeda HA, Pignatelli M, Bass CE, Bettler B, Morales M, and Bonci A (2017). Circuit specificity in the inhibitory architecture of the VTA regulates behavioral reponses to cocaine. Nature Neurosci. 20(3), 438–448.

Fritzius T, Turecek R, Seddik R, Kobayashi H, Tiao J, Rem PD, Metz M, Kralikova M, Bouvier M, Gassmann M *et al.* (2017). KCTD hetero-oligomers confer unique kinetic properties on hippocampal $GABA_B$ receptor-induced K^+-currents. J. Neurosci. 37(5), 1162–1175.

Cellular Neuro-physiology

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Synaptic integration of young neurons into the adult hippocampus

In the adult hippocampus new neurons are continuously generated throughout life by adult neural stem cells (Fig. 1). The newly generated young neurons show a number of distinct functional properties, including enhanced excitability, reduced GABAergic inhibition and enhanced synaptic plasticity (Lodge and Bischofberger 2019). Based on these cell biological findings it was concluded that the young neurons are hyperactive and hyperexcitable during learning behavior and memory processing. However, on the behavioral level adult neurogenesis improves learning by increasing the brains capability to distinguish between similar memory items, a process called “pattern separation”. During the last research period (2017–2020) we focussed on glutamatergic and GABAergic circuit analysis, to address this apparent paradox of “hyperactive cells” versus “improved pattern separation”.
Synaptic recruitment of adult-born young granule cells. We studied excitatory glutamatergic synaptic transmission from cortical perforant-path fibers onto newly generated young granule cells (GCs) up to 4 weeks post mitosis (wpm, Li *et al.* 2017). We found that the young neurons fire action potentials (APs) as early as 2 wpm in response to a small number of active glutamatergic synapses, due to a high synaptic gain. However, due to small dendritic trees and sparse connectivity, neighboring young neurons are activated by different distinct small subsets of afferent fibers with minimal overlap. As the neurons mature, the increase in synapse number is balanced by a gradual decrease in intrinsic excitability. This indicates that the enhanced excitability in young granule cells does not generate hyperexcitability, but instead compensates for sparse synaptic connectivity in developing young neurons. Using paired whole-cell recordings, we could show that AP firing in neighboring young cells is not unspecific, but rather dependent on small non-overlapping populations of afferent input fibers (Fig. 2). This is due to the sparse connectivity combined with the high synaptic gain, generating differential and highly specific spiking output in neighboring cells. Therefore, perforant-path fibers can recruit young neurons in a sparse and orthogonal manner, well suited to support sparse coding during hippocampal information processing.

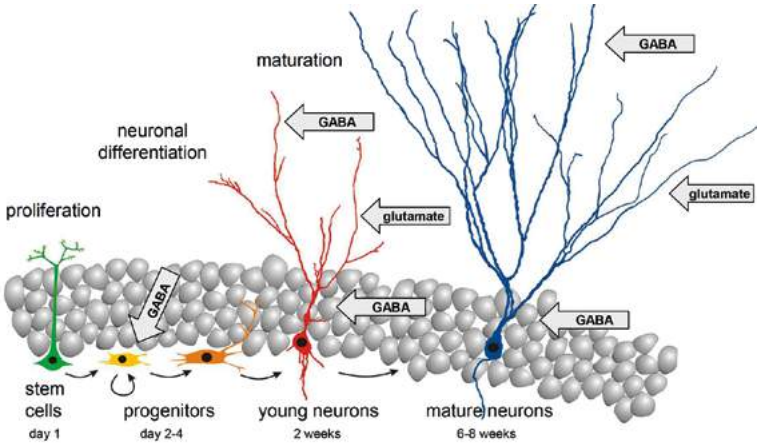

Fig. 1: Adult neurogenesis in the hippocampus. Adult neural stem cells (green) are localized within the subgranular zone of the hippocampus and give rise to transient amplifying cells (yellow). They generate postmitotic neuroblasts which subsequently differentiate into young neurons (red). During the following ~6 weeks, they form new dendrites and several thousand new synaptic connections with glutamatergic neurons as well as with various types of soma- and dendrite-targeting GABAergic interneurons.

GABAergic interneurons. We further studied the function of soma- and dendrite-targeting GABAergic interneurons, identified by parvalbumin (PV) or somatostatin (SOM) expression, respectively (Schulz *et al.* 2018, 2019). Synapses onto young and mature GCs as well as CA1 pyramidal cells were investigated. Remarkably, in young GCs both, PV and SOM interneurons activated α5-subunit containing GABAA receptors (α5-GABAR), showing a pronounced voltage- dependent outward rectification. As a consequence, the conductance was 4-fold larger at depolarized potentials close to AP threshold (40 mV) as compared to the resting potential. By contrast, in fully mature hippocampal neurons (GCs and CA1 pyramidal cells) α5-GABARs are only involved in dendritic inhibition and fully excluded from PV interneuron synapses (Schulz *et al.* 2018, Lodge *et al.* BioRxiv, 2020).

Although GABA is considered to be the major inhibitory transmitter in the adult brain, it depolarizes newly generated young neurons, due to a depolarized GABAA reversal potential (-35 mV). Nevertheless, we could show, that GABA can still act as an inhibitory transmitter in young GCs, due to shunting inhibition (Lodge and Bischofberger, 2019). Although activation of a low number of synaptic α5-GABAARs facilitates depolarization, strong activation of synaptic α5- GABAARs can nevertheless inhibit AP firing in young neurons, similar to mature GCs, because of the voltage-dependent conductance profile of α5-GABAARs, generating shunting inhibition.

In conclusion, our studies explain how sparse glutamatergic connectivity and fine-tuned excitation-inhibition balance via specific GABAA receptors enable distinct activation of different young neurons. This will not only help to avoid hyperexcitability, but also supports sparse activity in the hippocampus to improve hippocampal pattern separation.

Selected Publications

Lodge M, Bischofberger J (2019) Synaptic properties of newly generated granule cells support sparse coding in the adult hippocampus. Behav Brain Res. 372:112036

Schulz JM, Knoflach F, Hernandez MC, Bischofberger J (2019) Enhanced Dendritic Inhibition and Impaired NMDAR Activation in a Mouse Model of Down Syndrome. J Neurosci. 39:5210–5221.

Schulz JM, Knoflach F, Hernandez MC, Bischofberger J (2018) Dendrite-targeting interneurons control synaptic NMDA-receptor activation via nonlinear α5-GABAA receptors. Nat Commun. 9:3576. doi:10.1038/s41467-018-06004-8.

Normann C, Frase S, Haug V, von Wolff G, Clark K, Münzer P, Dorner A, Scholliers J, Horn M, Vo Van T, Seifert G, Serchov T, Biber K, Nissen C, Klugbauer N, Bischofberger J (2018) Antidepressants Rescue Stress-Induced Disruption of Synaptic Plasticity via Serotonin Transporter-Independent Inhibition of L-Type Calcium Channels. Biol Psychiatry. 84:55–64.

Li L, Sultan S, Heigele S, Schmidt-Salzmann C, Toni N, Bischofberger J (2017) Silent synapses generate sparse and orthogonal action potential firing in adult- born hippocampal granule cells. Elife. 6:e23612. doi:10.7554/eLife.23612.

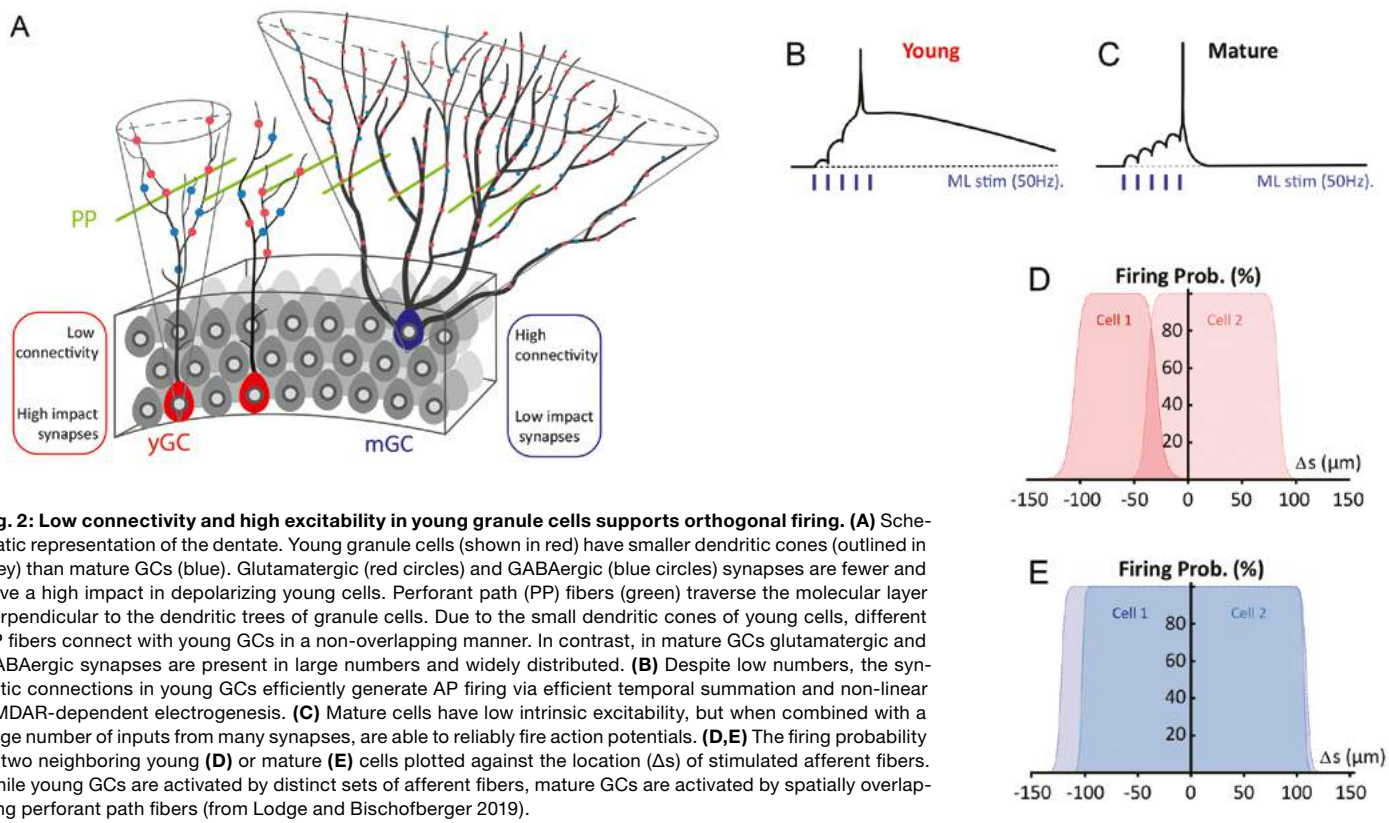

Fig. 2: Low connectivity and high excitability in young granule cells supports orthogonal firing. (A) Schematic representation of the dentate. Young granule cells (shown in red) have smaller dendritic cones (outlined in grey) than mature GCs (blue). Glutamatergic (red circles) and GABAergic (blue circles) synapses are fewer and have a high impact in depolarizing young cells. Perforant path (PP) fibers (green) traverse the molecular layer perpendicular to the dendritic trees of granule cells. Due to the small dendritic cones of young cells, different PP fibers connect with young GCs in a non-overlapping manner. In contrast, in mature GCs glutamatergic and GABAergic synapses are present in large numbers and widely distributed. **(B)** Despite low numbers, the synaptic connections in young GCs efficiently generate AP firing via efficient temporal summation and non-linear NMDAR-dependent electrogenesis. **(C)** Mature cells have low intrinsic excitability, but when combined with a large number of inputs from many synapses, are able to reliably fire action potentials. **(D,E)** The firing probability of two neighboring young **(D)** or mature **(E)** cells plotted against the location (Δs) of stimulated afferent fibers. While young GCs are activated by distinct sets of afferent fibers, mature GCs are activated by spatially overlapping perforant path fibers (from Lodge and Bischofberger 2019).

Human Genomics

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Human Genomics: investigating the molecular basis of human genetic disesases

The research group "Human Genomics" aims to identify the molecular (genetic) basis of human diseases and the underlying molecular mechanisms and pathomechanisms by combining human genetics knowledge with new genomics technologies (project leader: Per Hoffmann), bioinformatics and biostatistical approaches and in-depth phenotyping. We focus on genetically complex neuropsychiatric disorders (project leader: Sven Cichon, DMB's Focal Area Neurobiology), congenital developmental disorders (project leader: Isabel Filges), and hereditary cancer syndromes (project leader: Karl Heinimann, DBM's Focal Area Oncology). We closely interact with the research group Skin Biology and have a strong interest in the molecular basis of genodermatoses (project leader: Bettina Burger) and hereditary angioedema (project leader: Sven Cichon).

Neuropsychiatric disorders

One strong focus of the research group is the genetic analysis of neuropsychiatric disorders, in particular bipolar disorder. In the context of the Psychiatric Genomics Consortium (PGC), we performed the so far largest genome-wide association study (GWAS) including 20,352 cases and 31,358 controls of European descent (Stahl *et al.,* 2019). 30 loci were genome-wide significant, including 20 newly identified loci (Fig. 1). The significant loci contain genes encoding ion channels, neurotransmitter transporters and synaptic components. Pathway analysis revealed nine significantly enriched gene sets, including regulation of insulin secretion and endocannabinoid signaling. The study also showed that the clinical subgroup Bipolar I disorder is strongly genetically correlated with schizophrenia, driven by psychosis, whereas bipolar II disorder is more strongly correlated with major depressive disorder. These findings address key clinical questions and provide potential biological mechanisms for bipolar disorder.
In parallel we performed exome sequencing studies in large and multiply affected bipolar disorder families (e. g. Maaser *et al.,* 2018). Current and future projects aim at a mechanistic understanding of common and rare genetic risk variants for bipolar disorder. This will include sequencing in further large families with bipolar disorder as well as the study of sets of common risk variants in induced pluripotent stem cell (iPSC) models.

Congenital developmental disorders

Our specific interest relates to birth defects and multiple congenital anomaly syndromes which present early during pregnancy, since the monogenic aetiology of most severe fetal anomalies is poorly understood. In addition, the clinical description of most genetic conditions relates to paediatric and adult patients, and we are trying to understand how those same conditions may present in the prenatal period.
We systematically investigate families with one or more fetuses presenting with distinctive anomaly patterns and identified novel disease genes, new fetal phenotypes and phenotypes as a variable of developmental timing (Meier *et al.,* 2017; Meier *et al.,* 2019; Meier *et al.,* 2020). We further characterized the function of KIF14 in humans and zebrafish (Reilly *et al.,* 2019) and reviewed the emerging role of kinesin family member genes in birth defects, which we proposed to term "kinesinopathies" as a recognizable entity (Kalantari&Filges, 2020; Fig. 2).
Our group also studies Arthrogryposis multiplex congenita (AMC), a heterogeneous group of conditions with multiple contractures (Filges *et al.,* 2019). In an international consortium we work towards a standardized interdisciplinary approach to diagnose and care for patients with AMC.

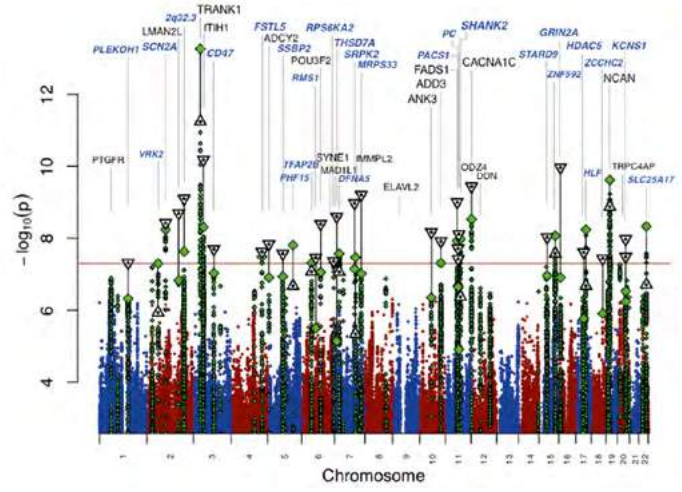

Fig. 1: Results of a large GWAS of bipolar disorder (Stahl *et al.,* 2019, Nat. Genet.): Manhattan plot for our primary genomewide association analysis of 20,352 cases and 31,358 controls. GWAS -log^{10}P-values are plotted for all SNPs across chromosomes 1-22 (diamonds, green for loci with lead SNP GWAS $P < 10^{-6}$). Combined GWAS+followup -log^{10}Pvalues for lead SNPs reaching genome-wide significance in either GWAS or combined analysis (triangles, inverted if GWAS+followup -log^{10}P > GWAS -log^{10}P). Labels correspond to gene symbols previously reported for published loci for bipolar disorder (black) and the nearest genes for novel loci (blue), at top if GWAS+followup $P < 5x10^{-8}$.

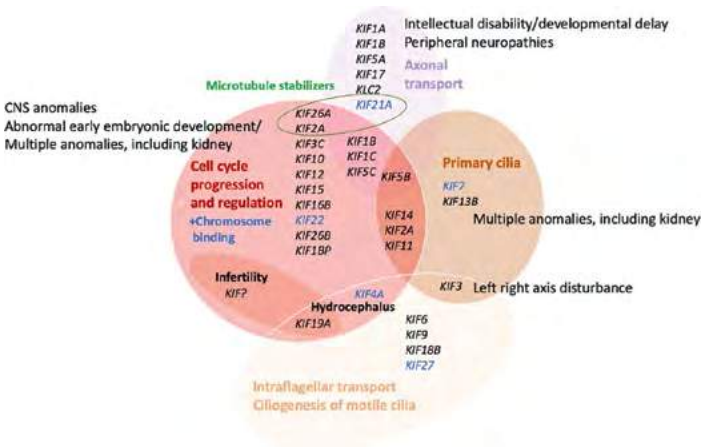

Fig. 2: Congenital developmental disorders: Assignment and clustering of *KIF* genes to various functions and relation to birth defect or monogenic phenotype groups. Detailed phenotypes are shown in tables 1 and 3. Cancer and multifactorial conditions are not included. CNS, central nervous system (from Kalantari, S. & Filges, I. (2020) J. Med. Genetics).

Hereditary cancer syndromes

In a collaborative study on autosomal dominant Juvenile Polyposis Syndrome (JPS), we analysed data on almost 700 JPS patients. Compared with BMPR1A carriers, SMAD4 carriers displayed anaemia twice as often, exclusively showed overlap symptoms with haemorrhagic telangiectasia and an increased prevalence of gastric juvenile polyps. Cancer, reported in 15 % of JPS patients, mainly occurred in the colorectum and the stomach. Our results facilitate recommendations for clinical management, and contribute to SMAD4 and BMPR1A databases (Blatter *et al.,* 2020).

In addition, we collated prospective clinical data on 80 Lynch syndrome patients harbouring pathogenic DNA mismatch repair (MMR) gene variants. Integration into the Prospective Lynch Syndrome Database (PLSD) resulted in studies assessing cancer incidence, prognosis, gene-specific cancer risks and the effect of current surveillance measures on mortality (Seppala *et al.,* 2019; Dominguez-Valentin *et al.,* 2020). Research collaborations on RET germline alterations in osteosarcoma patients and on colorectal carcinogenesis, particularly MMR deficient cancers, were successfully published (Kovac *et al.,* 2020; Cross *et al.,* 2018).

Selected Publications

Stahl EA, Breen G, Forstner JF, Cichon S, Ophoff RA, Scott LJ, Andreassen OA, Kelsoe J, Sklar P. Bipolar Disorder Working Group of the Psychiatric Genomics Consortium (2019) Genome-wide association study indentifies 30 loci associated with bipolar disorder. Nat Genet 51, 793–803.

Maaser A, Forstner AJ, Strohmaier J, Cichon S, Marcheco-Teruel B, Mors O, Rietschel M, Nöthen MM (2018) Exome Sequencing in large, multiplex bipolar disorder families from Cuba. PLoS One 13, e0205895.

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Sensory Processing and Behaviour

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Imaging deep: Sensory and state coding in subcortical circuits

Encoding of behavioural states in amygdala circuits

Internal states define sensory perception and actions. For example, we are more alert after a loud bang or lose focus during states of hunger. Brain states are associated with neuronal circuits in cortex. However, the behaviors that are affected by internal states are complex and result in diverse actions including changes in autonomic and hormonal responses. We studied how the amygdala – a center for the regulation of emotional states, associative learning as wells as complex behavior like social interactions – encodes internal states. We hypothesized that states are most likely not encoded on the level of individual neurons but by orchestrated changes in large neuronal populations. To measure activity of large populations of amygdala neurons we used novel miniaturized microscopes in freely moving mice (Fig. 1). This allowed us to longitudinally image neural activity across a series of behavioral paradigms in different contexts across multiple days. We found that two large ensembles of amygdala neurons signaled antagonistic information about an animal's behaviour in an open field context. This signature of neuronal population activity was slow and occurred across consecutive days and paradigms and predicted transitions between exploratory and defensive states in a moment-to- moment fashion (Fig. 2). During fear conditioning, an aversive associative learning paradigm, amygdala population activity to sensory stimuli was orthogonal to state coding. This shows that fast sensory representations in the amygdala and slow state dynamics are separately represented. These state signals are sent to a wider brain network, including cortical and subcortical areas and might be crucial for normal brain function. Future studies can now use this population signature and investigate if amygdala state coding is affected in animal models of neuropsychiatric diseases (Gründemann *et al.,* 2019).

Auditory thalamus plasticity upon associative learning

Cortical as well as limbic brain areas like the amygdala are classically regarded as centers for associative learning. In a recent study, we investigated how thalamic sensory neurons, which are upstream of the amygdala, shape plasticity upon associative fear learning. Using our miniature microscope approach, we recorded activity patterns of large numbers of auditory thalamus neurons in freely moving animals during fear conditioning. On the single cell level, we find that individual neurons exhibit mixed selectivity and respond to tone and foot shock. Furthermore, single cells exhibit heterogeneous plasticity patterns to auditory and aversive stimuli upon learning (Fig. 3). This plastic change in activity is particularly intriguing given that auditory thalamus is supposed to be a reliable relay of sensory information. However, contrasting individual cells, we find that the encoding of auditory stimuli remained stable across days on the level of the total neural population. These findings suggest that auditory thalamus is more than a sole sensory relay and balances experience-dependent, diverse single cell plasticity with stable ensemble level encoding of the sensory environment to support perception (Taylor *et al.,* 2020).

Integration of multiple sensory modalities in thalamus

Malfunctions of sensory integration like false (or "phantom") representations can result in detrimental behavioural outcomes. Higher brain areas are involved in computation, storage and retrieval of these sensory representations. However, how multisensory information flow to these areas is integrated, preprocessed and routed in subcortical circuits remains elusive. In our ongoing work, we are interested in how the brain, and particularly early thalamic relays, integrate sensory inputs from different sensory modalities, e.g. vision and audition to generate be-

havioural gains. To address this question, we combine state of the art circuit neuroscience tools like opto- and pharmacogenetics with single and two-photon imaging techniques to reveal computational frameworks of multisensory integration in deep brain areas and their effects on behaviour and learning.

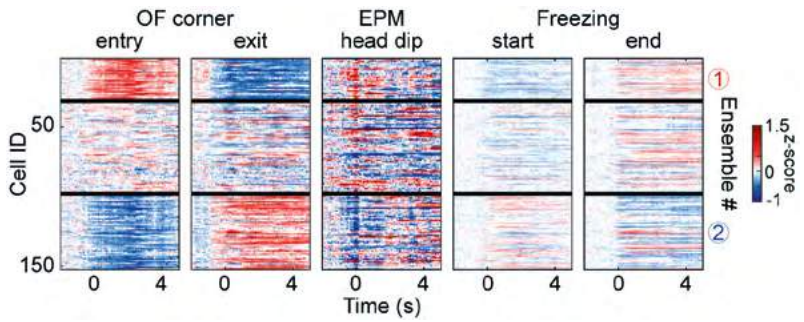

Fig. 2: Neuronal activity of amygdala neurons across behavioral paradigms.
Tracking of neuronal activity in amygdala neurons across behavioural paradigms. The heatmap represents the relative changes in neuronal activity (zScore) of 152 amygdala neurons from one mouse that were tracked across an open field (OF), elevated plus maze (EPM) and fear conditioning (Freezing) paradigm. Three clusters emerge. Two that exhibit antagonistic activity across behaviors and one neutral cluster.

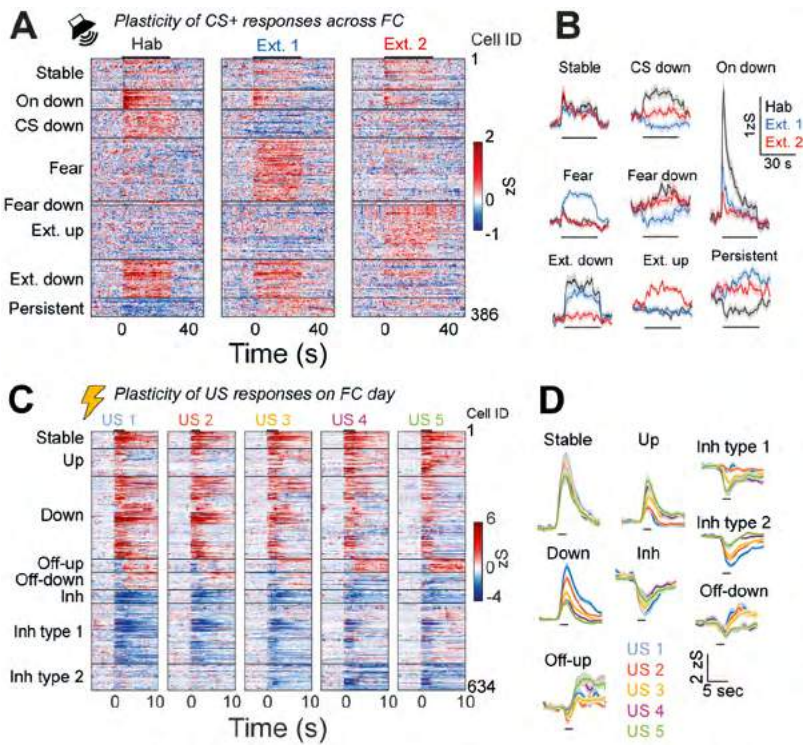

Fig. 3: Plasticity of auditory thalamus neurons upon associative fear learning.
A) Heatmap of activity patterns of 386 tracked auditory thalamus neurons to conditioned tones before fear conditioning (Hab), after fear conditioning (Ext. 1) and after fear extinction (Ext. 2). **B)** Mean response patterns of the neural clusters in A reveal neurons with distinct, diverse plasticity types in auditory thalamus upon fear conditioning. **C)** Heatmap of activity patterns of 634 auditory thalamus neurons to the five unconditioned foot shocks (US1-5) during fear conditioning. **D)** Mean response patterns of the neural clusters in C reveal neurons with distinct, diverse foot shock short term plasticity types in auditory thalamus upon fear conditioning.

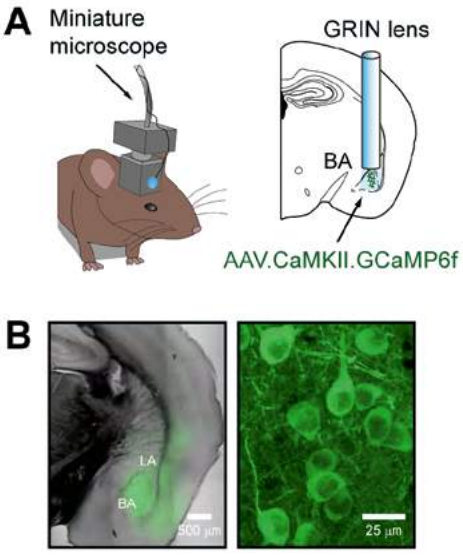

Fig. 1:
Miniature microscope imaging of amygdala neurons.
A) Schematic of the miniature microscope (left). A gradient-refractive index lens is used to relay light to the amygdala (right). **B)** Expression of the GCaMP neural activity sensor in the amygdala (left, overview). GCaMP is a [Ca^{2+}]-sensitive fluorescent protein which allows the measurement of neuronal activity. High magnification confocal image of GCaMP-expressing amygdala principal neurons. Modified after Gründemann *et al.,* 2019.

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Developmental Neurobiology and Regeneration

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Purkinje cell dendrites, Protein kinase Cγ and spinocerebellar ataxia

The cerebellum is a part of the brain which is involved in many neural functions, in particular when precision in time and space is required. This is of course the case for movements and a functional deficit of the cerebellum becomes usually evident in the form of unprecise movements, called an ataxia. Purkinje cells are the principal cells of the cerebellar cortex and have a large and highly branched dendritic tree (Fig. 1). A large and heterogeneous group of hereditary diseases called spinocerebellar ataxias is caused by dysfunction and death of Purkinje cells.
Our laboratory has a long-standing interest in the molecules and mechanisms regulating growth and development of Purkinje cell dendrites. We have identified Protein Kinase C (PKC) activity as a major regulator of Purkinje cell dendritic growth and have shown that PKC activity via the intracellular calcium concentration regulates the shape and size of the Purkinje cell dendritic tree. The predominant subtype of PKC in Purkinje cells, PKCγ, is also linked to one form of the spinocerebellar ataxias, SCA-14, which is caused by point mutations or deletions in the PKCγ gene. The mechanisms by which the mutations in the PKCγ gene lead to Purkinje cell dysfunction and death in SCA-14 are still not known. This is an important question because SCA14 can be viewed as a model for neurodegenerative diseases and understanding the mechanisms in SCA14 may also help understanding neurodegeneration in general. Our group is studying in which ways PKCγ may contribute to the pathogenesis of SCA and how this may be related to its effects on dendritic growth. We have generated a transgenic mouse model with a point mutation found in some SCA-14 patients which is located in the catalytic domain of PKCγ (PKCγ-S361G). We could show that the presence of the mutated protein in mouse Purkinje cells induces a striking reduction of Purkinje cell dendritic outgrowth. A similar effect is seen when PKC is stimulated with pharmacological agonists indicating that the mutated protein has increased kinase activity and is biologically active in Purkinje cells (Fig. 2). The finding of a strongly reduced dendritic growth caused by a mutation from spinocerebellar ataxia has also linked the disturbance of dendritic

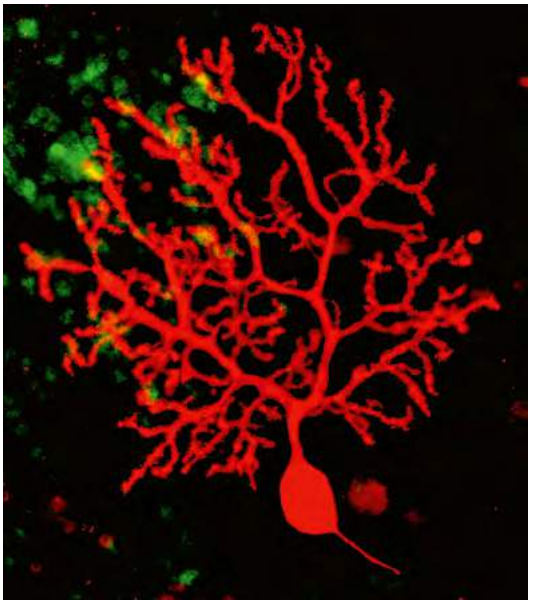

Fig. 1: View of a Purkinje cell in an organotypic slice culture after 12d *in vitro*. Anti-calbindin staining for Purkinje cells is shown in red. The elaborate dendritic tree of this cell has developed almost entirely during the culture period.

development of Purkinje cells to the pathogenesis of spinocerebellar ataxias. In a new mouse model, we have introduced a point mutation which keeps PKCγ in an open active conformation with increased activity also causing dendritic reduction of Purkinje cells (Fig. 2). This mouse model will allow us to better study the contribution of PKC activity to the pathogenesis of SCAs.

The Purkinje cell-specific expression of the S361G mutation has allowed us to use this this mouse model for identifying molecules which are transcriptionally regulated in Purkinje cells carrying this mutation and which might be involved in the signaling mechanisms eventually resulting in the reduction of dendritic growth. As a first candidate molecule, we have identified Car8 as a potential mediator of PKC signaling. Further work in our group has now identified more potential candidate molecules which have an altered expression in S361G Purkinje cells, and which might interact directly or indirectly with PKCγ. These molecules are linked to PKCγ signaling and include the IP3 receptor 1 (IP3R1), the Collapsin response mediator protein 2 (CRMP2), the Regulator of G-Protein Signaling 8 (RGS8) and the serine/threonine kinase 17b (STK17b, also known as DRAK2). We know for all of the mentioned candidate molecules that they are expressed in Purkinje cells and that their expression is changed in the S361G mouse model.

A major goal of our group is to better define the interaction of these molecules with PKCγ and better characterize their role for PKC signaling, Purkinje cell dendritic development and Purkinje cell dysfunction in spinocerebellar ataxia. Our studies aim at a better understanding of the role of PKCγ signaling for Purkinje cell dendritic development and for dysfunction in spinocerebellar ataxia as the basis for developing novel therapeutic strategies for cerebellar diseases.

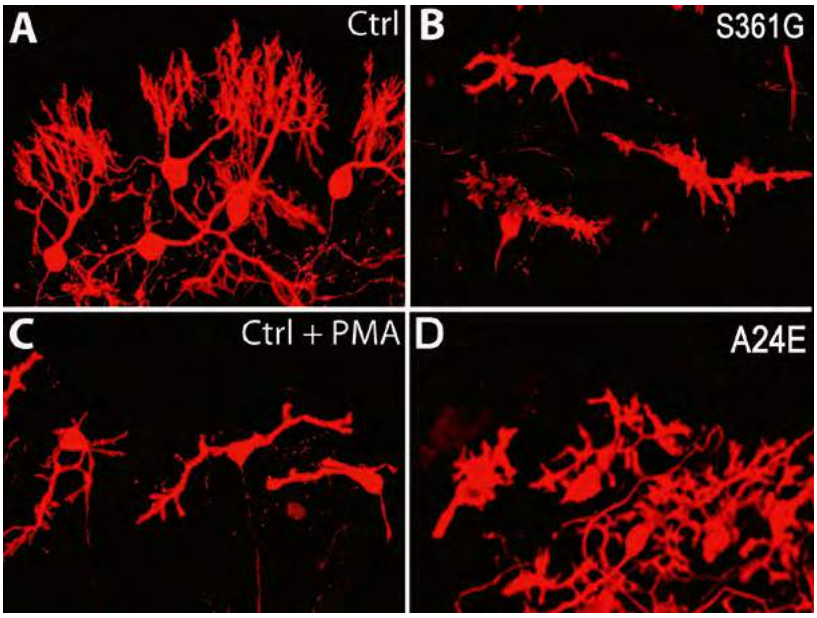

Fig. 2: The Purkinje cell dendritic tree in slice cultures derived from mice with transgenic expression of a mutated PKCγ-S361G from SCA14 **(B)** is severely compromised compared to control **(A)** and resembles strongly that of Purkinje cell with pharmacological activation of PKCγ **(C)**. The morphology of Purkinje cells from slice cultures of a new mouse model with a mutation in the pseudosubstrate domain PKCγ-A24E keeping PKCγ in the open active conformation again resembles that of activated PKCγ **(D)**.

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Psycho-pharmacology

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Pharmacology of psychoactive substances

Our research is focused on the pharmacology of psychoactive substances. This may include the designing and synthesis of novel compounds in collaboration with medicinal chemists. Many compounds studied in our laboratory are also misused recreationally as classic or novel psychoactive substances. We then study the mechanism of action of these substances in comparison with classic drugs of abuse or well-known psychoactive substances using *in vitro* pharmacological approaches. This includes the study of the receptor and transporter interaction profiles using receptor binding assays and tests of function such as transporter inhibition *in vitro* in human cells expressing different human target as well as receptor activation assays. Toxicology studies may also be performed mainly in collaboration with other groups. We perform studies of the metabolism *in vitro*. Then many substances are further investigated *in vivo* in humans. For example, we have extensively investigated the clinical pharmacology of MDMA including many phase 1 studies in healthy subjects to examine the pharmacokinetics, tolerability, acute effects, pharmacogenetics, metabolism, and safety pharmacology. The group has also conducted a series of clinical studies on the acute effects of the classic psychedelic substance LSD in humans. This includes studies of the acute subjective, emotional, autonomic, and endocrine effects of LSD, safety studies, pharmacokinetics, and pharmacokinetic- pharmacodynamic modeling. Then, different psychoactive substances are compared with each other. This includes comparative studies of MDMA, LSD, d-amphetamine or of LSD and psilocybin. Furthermore, LSD is currently being investigated as a medication in patients with anxiety disorder, major depression, and cluster headache in collaboration with the respective clinical experts.

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Selected Publications

Holze F, Vizeli P, Muller F, Ley L, Duerig R, Varghese N, Eckert A, Borgwardt S, and Liechti ME (2020). Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. Neuropsychopharmacology 45, 462–471.

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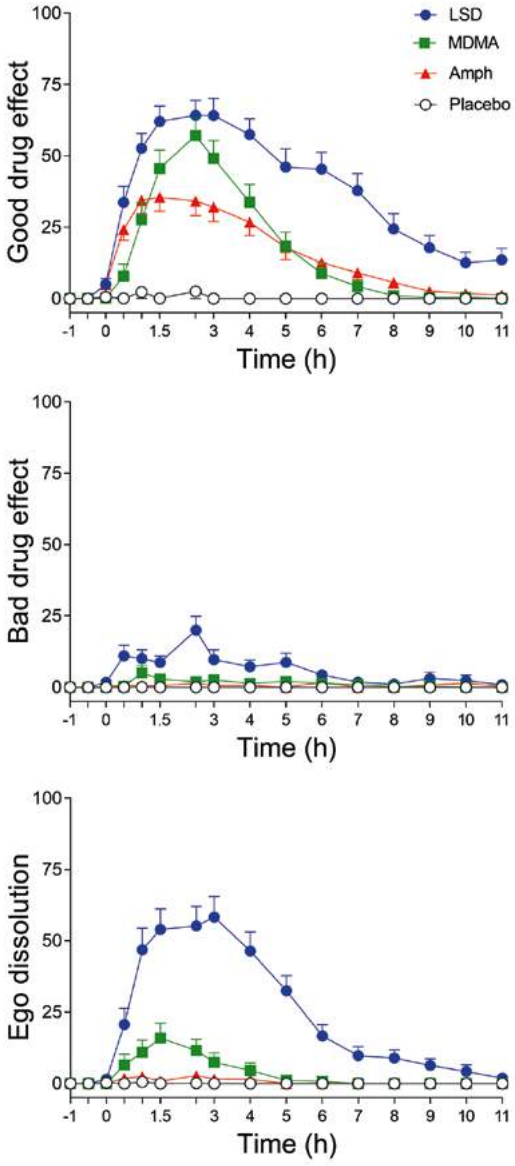

Fig. 1: Acute subjective effects of the classic psychoactive substances LSD (0.1 mg), MDMA (125 mg), and D-amphetamine (40 mg) in healthy human subjects. The data are expressed as mean ± SEM. LSD produced significantly greater ratings of "good drug effect," "bad drug effect," and "ego dissolution" compared with MDMA and D-amphetamine. In contrast, LSD reduced ratings of "talkative," "concentration," "sense of time," and "speed of thinking" compared with MDMA and D-amphetamine (data not shown) (Holze *et al.,* 2020).

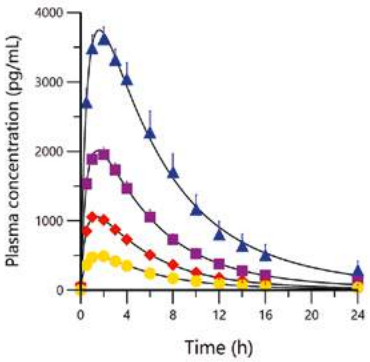

Fig. 2: Plasma LSD concentration-time curves for 25, 50, 100, and 200 µg doses of LSD. LSD administration resulted in dose-proportional increases in plasma concentrations of LSD. The data are expressed as the mean ± SEM in 16 subjects. LSD was administered at t = 0 h. The lines represent the means of individual predictions using compartmental modeling (one-compartment).

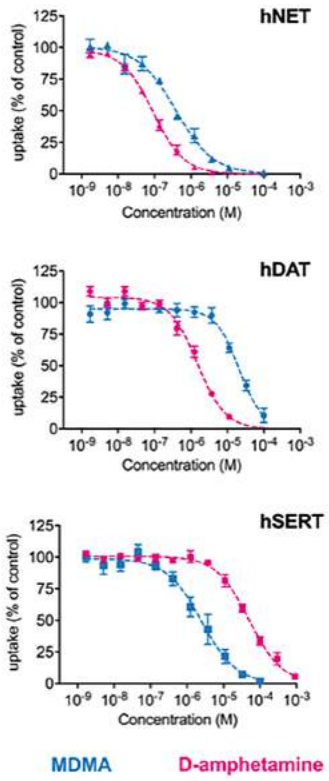

Fig. 3: Inhibition of the human monoamine transporters by MDMA and d-amphetamine to illustrate the different pharmacological profiles that do then translate into differential effects in humans. Both MDMA and d-amphetamine inhibit the human norepinephrine transporter (hNET). D-amphetamine more potently inhibits the human dopamine transporter (hDAT) whereas MDMA inhibits more potently the human serotonin transporter (hSERT). LSD has no activity at these transporters but highly potently stimulates to the serotonin 5-HT2A receptor directly. Transporter inhibition is shown as uptake of the respective monoamine into human cells expressing the respective transporter.

Ocular Pharmacology and Physiology

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*left during report period

Translational research to treat blinding diseases

Visual impairment and the associated socio-economic impact affects an estimated 290 million people worldwide. Our research is aimed at understanding the causes of vision loss and to develop novel therapies to prevent or treat blinding diseases.

Treating autosomal dominant optic atrophy

The optic nerve formed by the axons of retinal ganglion cells (RGCs) relays visual information form the light-sensing retina to the vision centers in the brain. Thus, loss of RGCs results in visual impairment and ultimately blindness.
Autosomal dominant optic atrophy (ADOA) is the most common inherited form of optic nerve degeneration. Mainly caused by mutations in the OPA1 gene, visual impairment develops in the first decade of life and can progress to complete blindness. The OPA1 gene codes for a mitochondrial protein involved in maintaining mitochondrial morphology by modulating mitochondrial fusion. In addition, OPA1 is essential for mitochondrial cristae organization and, thus, electron transport chain function. Loss of OPA1 is known to diminish mitochondrial fidelity and to increase sensitivity to apoptotic stimuli. Critically, OPA1 mRNA is subject to extensive alternative splicing giving rise to at least eight different OPA1 isoforms with a balanced isoform expression important for OPA1 function.
About 70 % of ADOA cases are caused by OPA1 haploinsufficiency. Using artificial transcription factors (ATFs) capable of upregulating OPA1 expression, we aim to alleviate OPA1 haploinsufficiency while maintaining OPA1 isoform balance, thus providing a functional cure for ADOA. Based on TAL effectors, we generated ATFs capable of upregulating mouse or human OPA1 (Fig. 1). To test efficacy of such ATFs, we generated a novel *in vivo* model of pharmacologically accelerated RGC degeneration in ADOA mice. This allowed us to synchronize RGC death and shortened the time it takes to detect treatment efficacy from 12-15 months to 14 days. Currently, we are in the process of optimizing viral delivery to allow for efficient delivery of OPA1-upregulating ATFs to RGCs by simple intravitreal injection.

Towards a treatment for Fuchs' dystrophy

Vision starts with light entering the eye through a transparent cornea. The cornea is a five-layered tissue with the outermost corneal epithelium together with Bowman's layer and the innermost corneal endothelium with Descemet's membrane sandwiching the almost cell-free corneal stroma. To keep the corneal stroma transparent, corneal endothelial cells (CECs) actively remove water from this tissue. During Fuchs' dystrophy and due to CEC loss, water accumulates inside the stroma causing a disorganization of the carefully arranged stromal matrix leading to severe visual impairment. Interestingly, about 4 % of the population over 40 years of age suffers from Fuchs' dystrophy to a varying degree. Severe Fuchs' dystrophy is treated by replacing the damaged CEC layer with human donor material in a procedure called Descemet Membrane Endothelial Keratoplasty (DMEK). However, the demand for corneal transplants outweighs availability about 70:1.
By combining additive manufacturing and stem-cell technology, we want to address this unmet medical need by generating a drop-in replacement for human donor material for DMEK. We employ melt electrowriting to fabricate a suitable scaffold for culturing human CECs (Fig. 2). Furthermore, a differentiation protocol for CECs from induced pluripotent stem cells (iPSCs) was developed and adapted to be compatible for culturing these cells on such scaffolds. To assess whether these implants are compatible with the established transplantation procedure, cell-free scaffolds were implanted into porcine eyes *ex vivo*. Imaging revealed that the fabricated structural support is well suited as drop-in replacement during DMEK. Taken together, with developing a donor tissue replacement for DMEK we hope to address the unmet medical need of patients suffering from Fuchs' dystrophy.

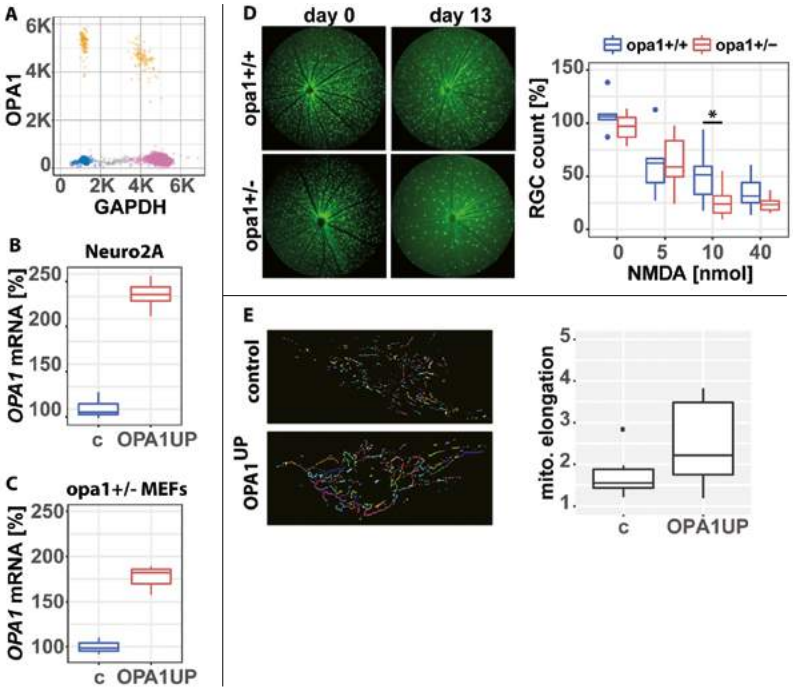

Fig. 1: *Xanthomonas* transcriptional activator like (TAL)-based artificial transcription factors ($OPA1^{UP}$) capable of upregulating *OPA1* in mouse or human cells was generated. **(A)** To accurately measure *OPA1* mRNA levels, a digital droplet PCR (ddPCR) assay was established. Following expression of $OPA1^{UP}$ fused to T2A-GFP, GPF^{+} cells were sorted and multiplexed measurement of *OPA1* and *GAPDH* mRNA levels was possible in as little as 100 cells. **(B)** Mouse neuron-like Neuro2A and **(C)** $opa1^{+/-}$ mouse embryonic fibroblasts (MEFs) were transfected with expression plasmid for $OPA1^{UP}$-T2A-GFP, GFP^{+} cells were isolated by fluorescence activated cell sorting and *OPA1* mRNA levels were quantified relative to *GAPDH*. Please note, $opa1^{+/-}$ MEFs are haploinsufficient for *OPA1*. **(D)** $OPA1^{+/-}$ mice with GFP-expressing retinal ganglion cells (RGCs) and their wildtype littermates were treated with increasing amounts of NMDA by intravitreal injection. Fluorescent fundoscopy was performed before and 13 days after NMDA application. Please note the significantly lower amount of surviving RGCs in $opa1^{+/-}$ animal compared to wildtype controls following application of 10 nmol of NMDA (n>15 animal/condition). (E) Patient-derived, primary human fibroblasts transfected with $OPA1^{UP}$ or inactive control were stained for the mitochondrial marker cytochrome c and mitochondrial morphology was analyzed. Please note the increase in mitochondrial length following $OPA1^{UP}$ expression compared to controls indicative for restored OPA1 function.

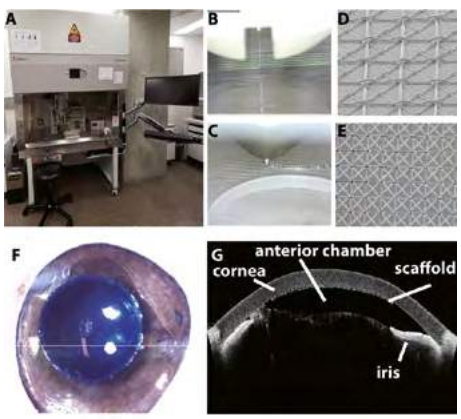

Fig. 2: (A) Precision 3D printer (regenHU, 3D Discovery) equipped with four printheads including a melt electrowriting head capable of depositing molten polymer with a lower diameter of 600 nm in a highly reproducible fashion. **(B)** Microscopic image of molten polycaprolactone (PCL) deposited onto a glass collector plate in a 6000 KV electric field to form 10 µm fibers. **(C)** Deposition of PCL support structures onto melt electrowritten scaffold using a fused deposition printhead. **(D+E)** Electron microscopic images of melt electrowritten PCL fibers. **(F)** A PCL scaffold embedded into artificial extracellular matrix (stained blue for better visualization) was implanted *ex vivo* into a porcine eye using the standard surgical procedure to perform Descemet Membrane Endothelial Keratoplasty (DMEK). **(G)** Anterior chamber optical coherence tomography was used to assess placement and attachment of the implanted scaffold.

Connection to Clinical Practice

Prof. Hendrik Scholl
Prof. Dr. Zisis Gkatzioufas
University Eye Hospital

Visual impairment greatly affects a patient's quality of life. Thus, the focus is on halting or even reversing loss of vision. Understanding degenerative mechanisms affecting ocular tissues such as the optic nerve, the retina or the cornea is of great importance to develop novel treatment modalities. Such modalities include gene therapeutic approaches as well as stem cell-based treatments for retinitis pigmentosa, Stargardt disease, age-related macular degeneration, diabetic retinopathy, autosomal dominant optic atrophy, but also corneal dysfunction as encountered in Fuchs' dystrophy. The clinical research center of the Institute of Molecular and Clinical Ophthalmology (IOB) in collaboration with the University Eye Hospital offers the opportunity for clinical research into causes of vision loss as well as the natural history of ocular diseases. Together with the evaluation of clinical outcome measures and the possibility to conduct clinical trials, the clinical research center provides an integrated environment for successful transition from bench-to-bedsite by bridging the "valley of death" often encountered by translational research. Only careful studies into the natural history of diseases as well as thoughtful selection of outcome parameters - especially in the case of slowly progressing eye diseases – minimize the inherent risk of translational research projects and development of new therapies. The close connection between the ocular pharmacology and physiology lab and the IOB clinical research center, both headed by Prof. Hendrik Scholl, is instrumental to leverage our translational research for the benefit of the patients.

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Neuronal Development and Degeneration

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Pathogenic Protein Spreading and Neurodegeneration

The aim of our research is to reveal the role and mechanism of cell-to-cell spreading of potential toxic proteins in neurodegenerative disorders.
In neurodegenerative diseases the nervous system gets progressively altered. Impaired structure and function, due to degeneration of neural cells, results in severe behavioural disabilities and often death of the patient.
Understanding pathogenic mechanisms underlying the severe clinical progression of neurodegenerative disorders (NDs), like Alzheimer's (AD), Parkinson's (PD), and Huntington's disease (HD) is critical for developing novel therapeutic strategies. Patients display a progressive accumulation of pathological changes ranging from epigenetic and transcriptional abnormalities to degeneration of neural circuits. These lesions arise in a typical spatiotemporal pattern in the brain. This might be explained by a potential novel disease pathway, which is termed: misfolded protein spreading. A process in which disease-linked, misfolded proteins propagate from cell to cell and function as seeds which convert healthy, like-proteins into toxic species by a procedure called templated misfolding. This phenomenon was first identified in Prion disorders in which it underlies the progressive spatiotemporal spreading of neuronal lesions through the brain. A series of exciting new studies have provided strong experimental evidence that a 'prion-like' self-propagating mechanism is applicable to a variety of proteins related to dissimilar neurodegenerative protein misfolding diseases (PMDs). These include Aβ and tau in AD, α-synuclein in PD, SOD1 in amyotrophic lateral sclerosis (ALS), TDP-43 in ALS and frontotemporal lobar dementia (FTLD), and mutant huntingtin (mHTT) in HD. Recent work suggests that pathogenic protein spreading matches the spatiotemporal progression pattern of neuronal lesions through the brain and that it propagates along neural networks in a pattern that matches the architecture of functional synaptic connectivity in the healthy human brain. The spreading of misfolded proteins might therefore be an important contributor to neuronal damage in PMDs.

We use HD as a model disease to address the following questions:

- Is mHTT cell-to-cell spreading causally linked to neurodegeneration?
- Does mHTT transneuronal spreading depend on functional synaptic connectivity?
- Does mHTT spreading from spinal motor neurons to skeletal muscles contribute to muscle pathology?

These questions we address with a multidisciplinary experimental approach, including a wide array of tools, spanning from morphological and molecular cell biology to systemic physiology and behavioural analyses, applied to both HD mouse- and human induced pluripotent cell models.
With this approach we aim to disclose novel mechanisms of mHTT trans-neuronal spreading and consequences thereof for HD progression. The results likely are of high relevance to other neurodegenerative PMDs.

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Hörnberg H, Perez-Garci E, Schreiner D, Hattstatt-Burkle L, Magara F, Baudouin S, Matter A, Nacro K, Pecho-Vrieseling E and Scheiffele P (2020). Restoration of oxytocin receptor signaling and social recognition in a mouse model of autism. Nature 584(7820):252–6.

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Brain and Sound Lab

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Development and function of neuronal circuits in the central auditory system

Sounds and hearing play a pivotal role in human communication. People who suffer from central auditory processing abnormalities are affected in their daily lives and might not be able to appreciate even the most basic verbal communication. Tinnitus, in which phantom sounds are experienced in the absence of acoustic stimulation, is an example of pathology of the central auditory system. More than 10% of the population suffers from it. Despite the importance of hearing in human communication, we still understand very little of how sounds are perceived and how they are processed in the central auditory system. The aim of our lab is to understand the role of specific neuronal circuits in making sense of sounds, and to lead to new ways of reinstating normal connectivity in cases of abnormal auditory processing. We combine *in vivo* physiology, optogenetics, rabies virus tracing, immunohistochemistry, behavioral assays, cochlear implants and computer modeling to explore the functions of neuronal circuits in the mouse auditory cortex.

Adaptability of the auditory system in health and disease

We use several approaches to reach our lab's aim (Fig. 1). First, we study auditory circuits during postnatal development. We identified a new form of developmental plasticity linked to a specific sound feature and to the maturation of a cortical interneuron subtype (Bhumika *et al.,* 2019). We also demonstrated that the development and plasticity of the processing of different sound features is asynchronous, and follows a temporally precise developmental program (Nakamura *et al.,* 2020). Then, we study how neuronal responses change with context, whether it is related to the auditory environment, to the internal state of the animal or to learning. We showed how a white noise background can improve tone discrimination performance and, more generally, how manipulating the cortical neural code leads to perceptual improvements (Christensen *et al.,* 2019). We also demonstrated that the modulations in neuronal activity arising when switching from actively listening to passively hearing are diverse and widespread in the auditory system (De Franceschi and Barkat, 2020). We also study the specific roles of spatially distinct cortical neural circuits in sound processing and perception. We identified some cortical regions specialized in coding sound termination, whereas others are better for spectral integration (Solyga and Barkat, 2019). Finally, we established a mouse model of cochlear implants (Navntoft *et al.,* 2019) providing us with the tool to link basic to translational research. Our findings put forward the central role of adaptive plasticity in central auditory circuits. We will pursue this line of research to explore the different forms of adaptability that the brain uses to make sense of sounds. Not only will this new knowledge advance our understanding of auditory functions, but it will also set the ground for new approaches in translational research to help reinstating normal neuronal processing in central auditory dysfunctions.

From basic to translational research with a mouse model of cochlear implant

Cochlear implants (CIs) are neuroprosthetic devices that can provide a sense of hearing to deaf people. However, a CI cannot restore all aspects of hearing. Improvements are needed if CI users are to appreciate music or more complex environments, such as hearing out a voice in a noisy crowd. Such improvements include the necessity of experimental animals to better understand the mechanisms of electric stimulation in the cochlea and its response in the whole auditory system. We developed a mouse model providing a powerful opportunity to study genetic and neurobiological mechanisms that would be of relevance for CI users (Fig.

2A, B). In collaboration with the Danish Technical University, we then asked whether the classical electrical stimulation paradigm used in humans could be improved. We used our mouse model to investigate the potential of a novel stimulation paradigm and found a more charge-efficient stimulation paradigm, with the potential to produce more battery-efficient cochlear implants (Fig. 2C, D; Navntoft *et al.,* 2020).

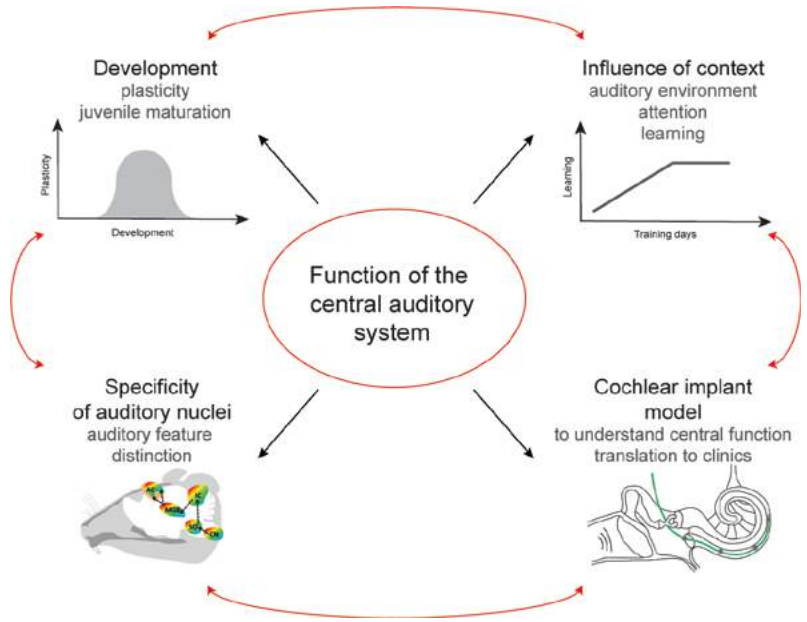

Fig. 1: Research topics in the Brain and Sound Lab

Selected Publications

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Solyga M, Barkat, TR (2019). Distinct processing of tone offset in two primary auditory cortices. Scientific Reports 9:9581.

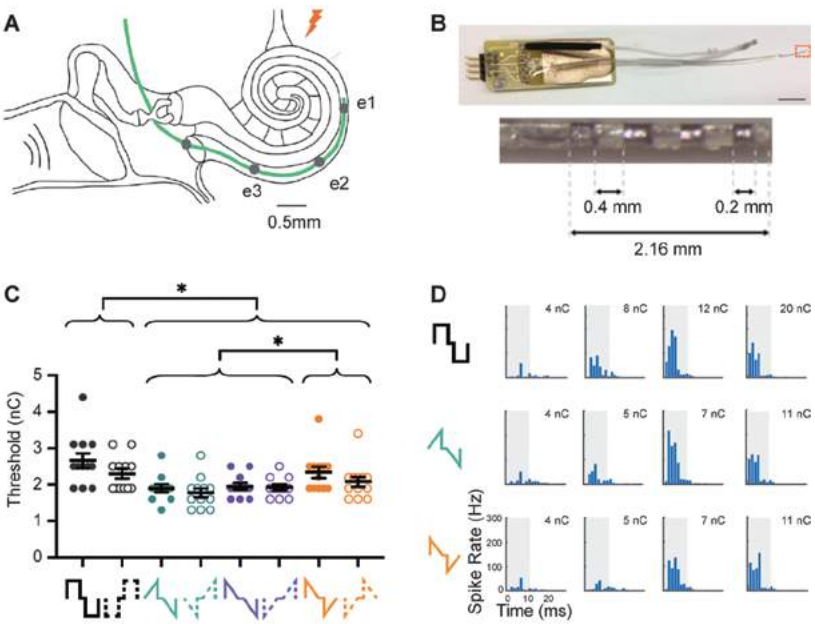

Fig. 2: The mouse model of cochlear implant

A. Schematic of a mouse cochlear implant.

B. The mouse cochlear implants are made of 4 stimulating electrodes that can be controlled independently by an external stimulation device.

C. Response threshold of auditory brainstem responses with a cochlear implant stimulation using different pulse shapes (schematized on the x-axis). The ramped pulse shapes (green, violet and orange) show lower thresholds than the classically used square pulse shape (black).

D. *In vivo* electrophysiological recording of neurons in the mouse inferior colliculus as a response to cochlear stimulation of different pulse shapes (rows) and stimulation amplitude (columns).

Neurobiology

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Molecular Mechanisms of Myelin Formation and Maintenance in Health and Disease

Chronic Cortical Pathology in Multiple Sclerosis

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system and leads to long-term disability already in young adults. Its etiology is still unclear, but the interpretation of recent genome-wide association studies in MS, which identified almost exclusively immune system-related genes, has been that MS develops from the outside, i.e. the peripheral immune system, which then attacks the central nervous system. In the search of identifying factors preceding demyelination, we investigated the molecular pathomechanisms in the so-called normal appearing cortical grey matter, where there is no sign of inflammation and demyelination. We performed the to-date largest whole-genome gene expression study conducted with normal-appearing human brain cortical grey matter tissue of multiple sclerosis cases (Fig. 1). There we detected an upregulation of HLA-DRB1 gene expression in multiple sclerosis brain tissue compared to control cases. We were further able to link the high HLA- DRB1 gene expression to a higher frequency of HLA-DRB1*15:01 allele carriers amongst the multiple sclerosis cases. The HLA-DRB1*15:01 allele is known to be the strongest risk factor for developing multiple sclerosis. We were further able to link the elevated HLA-DRB1 gene expression to higher protein expression, mainly by brain-resident microglia cells, and notably to increased size of cortical grey matter lesions. The fact that HLA-DRB1*15:01 is expressed at higher levels in the brain parenchyma challenges the outside-in hypothesis of multiple sclerosis and demonstrates the possibility of relevant immunological mechanisms taking place within the brain itself, i.e. from the inside (Enz *et al.,* 2020).

Combinatory multifactor treatment effects on primary nanofiber oligodendrocyte cultures

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system. Neurological deficits are attributed to inflammatory demyelination, which compromises axonal function and survival. These are mitigated in experimental models by rapid and often complete remyelination of affected axons, but in MS this endogenous repair mechanism frequently fails, leaving axons increasingly vulnerable to the detrimental effects of inflammatory and metabolic stress. Understanding the molecular basis of remyelination and remyelination failure is essential to develop improved therapies for this devastating disease. However, recent studies suggest that this is not due to a single dominant mechanism, but rather represents the biological outcome of multiple changes in the lesion microenvironment that combine to disrupt oligodendrocyte differentiation. This identifies a pressing need to develop technical platforms to investigate combinatory and/or synergistic effects of factors differentially expressed in MS lesions on oligodendrocyte proliferation and differentiation. We developed a protocol using primary oligodendrocyte cultures from Bl6 mice on 384-well nanofiber plates to model changes affecting oligodendrogenesis and differentiation in the complex signaling environment associated with multiple sclerosis lesions (Fig. 2). Using platelet-derived growth factor (PDGF–AA), fibroblast growth factor 2 (FGF2), bone morphogenetic protein 2 (BMP2) and bone morphogenetic protein 4 (BMP4) as representative targets, we demonstrate that we can assess their combinatory effects across a wide range of concentrations in a single experiment. This *in vitro* model is ideal for assessing the combinatory effects of changes in availability of multiple factors, thus more closely modelling the situation *in vivo* and furthering high-throughput screening possibilities (Enz *et al.,* 2019).

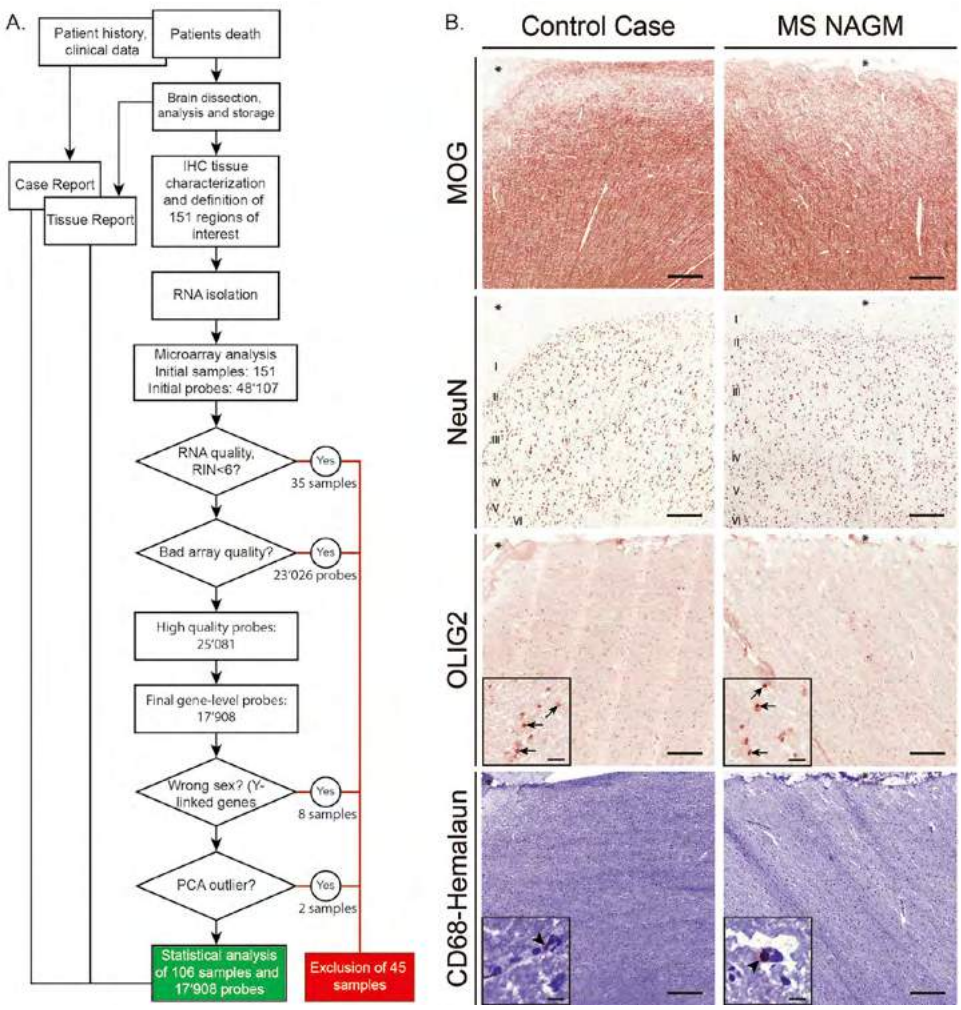

Fig. 1: Tissue processing for microarray and tissue characterization
(A) Flowchart to illustrate the process from the patient's death to statistical analysis of the gene expression microarray. After dissection of the brain and exclusion of confounding pathologies, the tissue blocks were sent from the UK MS Tissue Bank to Basel, Switzerland. There, an immunohistochemical characterization was performed, any tissue with bad preservation was excluded, and regions of interest were selected. After RNA isolation, the RIN was measured, and samples with RIN smaller than 6 were excluded. Sample mix up was checked by wrong sex and by principal component analysis. **(B)** Representative images of control cortical gray matter (case C30) and MS NAGM (case MS08, asterisk delineates the meninges, I–VI indicate the 6 neuronal layers). NAGM was defined as no loss of MOG, NeuN, or OLIG2 (inset, arrows) staining compared with control cases and no increase in CD68 compared with controls; i. e., occasional CD68+ staining intra- or perivascular (inset, arrowheads) and nearly no CD68+ staining in the tissue. Scale bars: 250 µm; inset Olig2: 20 µm, inset CD68: 10 µm. IHC = immunohistochemistry; MOG = myelin oligodendrocyte glycoprotein; NAGM = normal-appea-ring cortical gray matter; NeuN = neuronal nuclei; OLIG2 = oligodendrocyte transcription factor 2; PCA = principal component analysis; RIN = RNA integrity index. Image was copied from Enz *et al.,* 2020.

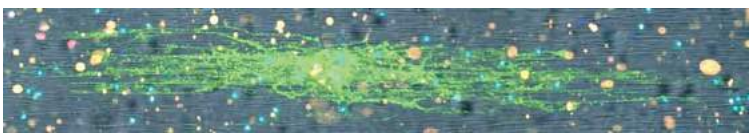

Fig. 2: MOG positive oligodendrocyte enwrapping nanofibers
Oligodendrocytes were cultured on nanofiber plates with 20ng/ml PDGF and 20ng/ml FGF2 for 3 weeks.

Selected Publications

Jäckle K, Zeis T, Schaeren-Wiemers N, Junker A, van der Meer F, Kramann N, Stadelmann C, Brück W. Molecular signature of slowly expanding lesions in progressive multiple sclerosis. Brain. 2020 Jun 24:awaa158. doi: 10.1093/brain/awaa158. Epub ahead of print. PMID: 32577755.

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Neuromuscular Research

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Translational Research in Neuromuscular Diseases

Our Neuromuscular Research Laboratory is part of the Clinic of Neurology and the Department of Biomedicine and focuses on the elucidation of pathophysiological mechanisms involved in neuromuscular diseases and on the development of therapeutic strategies.

Myotonic dystrophy type I (DM1) is a disabling neuromuscular disease with no causal treatment available. It is the most prevalent muscular dystrophy in adults, affecting about 1 in 10'000 individuals. This disease is caused by expanded CTG trinucleotide repeats in the 3' UTR of the dystrophia myotonica-protein kinase gene (DMPK). On the RNA level, expanded (CUG)n repeats form hairpin structures that sequester splicing-factors, such as muscleblind-like 1 (MBNL1). Lack of available MBNL1 leads to mis-regulated alternative splicing of many target pre-mRNAs, causing multisystemic involvement in DM1. In an effort to identify small molecules that liberate sequestered MBNL1 from (CUG)n RNA, we developed a pathomechanism-based screening cascade including biochemical, cellular and animal model assays which allow for high throughput screening of small molecular weight compounds. Identified hits may provide pharmacophores for further medicinal chemistry optimization.

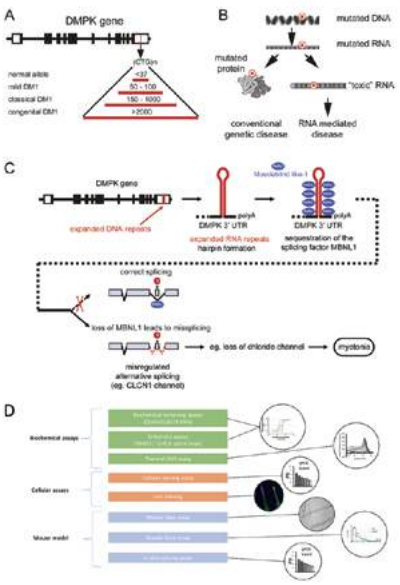

Fig. 1: Pathophysiology of DM1 and screening cascade to identify small molecular weight compounds. A) The molecular basis of DM1 is an expansion of an unstable repeat sequence in the noncoding part of the DMPK gene. Severity of disease is correlated with the size of the repeat expansion. **B)** In DM1, the mutation is located in a noncoding region and does not alter the protein sequence, but leads to toxic RNA. **C)** The sequestration of the alternative splicing factor MBNL1 by toxic RNA leads to altered splicing of target pre-mRNAs like CLCN1, encoding muscle-specific chloride channel (ClC-1). This mis-splicing leads to *ClC-1* deficiency and to myotonia. **D)** We established a pathophysiology based screening cascade including biochemical, cellular and animal model assays to identify small molecular weight compounds able to disrupt the interaction between MBNL1 and the toxic RNA, and to restore splicing and function.

Facio-scapulo-humeral muscular dystrophy (FSHD) is the second most common muscular dystrophy in adults, affecting about 1:20'000 persons. An epigenetic aberration leads to the ectopic expression of the transcription factor Double Homeobox protein 4 (DUX4) in skeletal muscle and other tissues, which leads to muscle cell degeneration and muscular dystrophy, sensorineural hearing loss and retinal teleangiectasias. Expression of DUX4 variants are also involved in certain cancers including acute lymphoblastic leukemia. An attractive therapeutic approach would be the interference with aberrantly expressed DUX4.
By applying Systematic Evolution of Ligands by Exponential Enrichment (SELEX) and fluorescence-based biochemical assays we were able to generate a DNA aptamer with high affinity towards DUX4. In a collaborative effort we co-crystallized DUX4 together with the identified oligonucleotide enabling us to explain the affin-

ity boost caused by certain bulge loops. We plan to use this oligonucleotide as a tool to further study DUX4-DNA interactions and to develop treatment strategies for FSHD and other DUX4-mediated diseases.

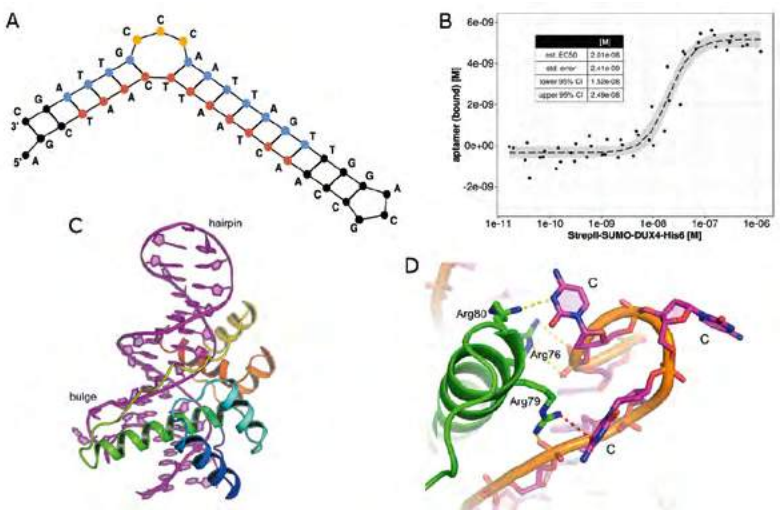

Fig. 2: Generation of a high affinity aptamer against DUX4. A) Predicted secondary structure of the high affinity oligonucleotide. DUX4 binding motif is highlighted in red (forward motif) and blue (reverse motif). Affinity bulge loop is highlighted in yellow. **B)** KD value for DUX4–oligonucleotide binding, determined by fluorescence polarization assay. Data are shown with 95 % confidence band in gray. Fitting results are displayed in the table at the upper left corner. **C)** Crystal structure of DUX4 double homeodomain bound to the DNA oligonucleotide containing a trinucleotide (-CCC-) bulge and a GCA hairpin loop. DNA is shown in magenta. DUX4 is colored in a gradient of blue to red from the N- to C-terminus, respectively. **D)** A close-up view showing the DUX4 interactions with the CCC bulge loop. The guanidinium group of Arg79 stacks onto the first C base of the bulge (the van der Waals or cation-π-contact is indicated by a red dotted line). Arg80 forms a salt bridge with the third C base and Arg76 is hydrogen-bonded to a DNA backbone phosphate at the 3'-end of the bulge (yellow dotted lines)

An additional line of research in our laboratory is dedicated to the identification of mechanisms underlying disruption of proteostasis as a cause for muscle diseases. To this end, we initiated experimental strategies to identify molecular networks that specifically control protein synthesis and degradation in human myofibers under physiological conditions and upon atrophic stress. Our strategy integrates the genome-wide measurements of a.) transcript levels (RNA-Seq), b.) translation levels (sequencing of ribosome foot prints) and c.) protein levels (proteomics) from genetically (Crispr/Cas9) modified human immortalized myoblasts. The ribosome foot-printing method, which we developed together with the laboratory of Prof. M. Zavolan, provides us with estimates of protein synthesis rates of individual RNA molecules, thus allowing us to further uncover the regulatory factors of translation for each gene under normal and diseased conditions. In parallel, we developed in situ proximity-dependent labelling assays (BioID) to map the direct and indirect interactome of the two main proteins we have already identified in skeletal muscle atrophy, MAFbx and EIF3F (Fig. 3).

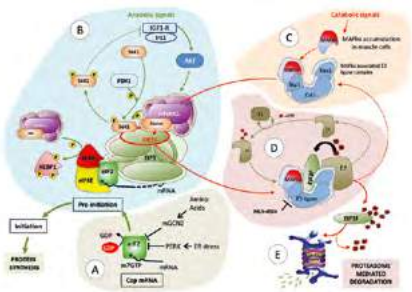

Fig. 3: Proposed model for modulation of protein synthesis in skeletal muscle. A) Assembly of capped mRNA and integration of stress signaling. **B)** EIF3F dual function: protein initiation complex (PIC) recruitment at the mRNA cap and scaffolding platform for mTORC1 and S6K1. mTORC1 affects protein synthesis via phosphorylation of 4EBP1, which thereby dissociates from eIF4E; and phosphorylation of S6K1, which facilitates the release of S6K1 from EIF3F and its activation by PDK1. **C)** Atrophy dependent induction of MAFbx leads to the formation of MAFbx E3ligase complex together with Cul1, Skp1 and Rbx1. **D)** MAFbx dependent EIF3F ubiquitination followed by **E)** proteasome mediated degradation.

Connection to Clinical Practice

Michael Sinnreich
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Interdisciplinary Neuromuscular Clinic

At our interdisciplinary Neuromuscular Clinic we care for patients affected by a broad range of neuromuscular diseases. In collaboration with our colleagues from pathology, genetics, plastic surgery, pulmonary medicine, rehabilitation, ergo-, physio- and speech therapy as well as social services, we provide clinical and electrophysiological evaluation, perform muscle and nerve biopsies with histopathological and biochemical workup, genetic workup and counseling, rehabilitation, ergo-/physio- and speech therapy as well as assistance in social matters. Novel clinical observations are being worked up scientifically and form the basis for translational research projects.

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Ham DJ, Börsch A, Lin S, Thürkauf M, Weihrauch M, Reinhard JR, Delezie J, Battilana F, Wang X, Kaiser MS, Guridi M, Sinnreich M, Rich MM, Mittal N, Tintignac LA, Handschin C, Zavolan M, Rüegg MA. The neuromuscular junction is a focal point of mTORC1 signaling in sarcopenia. Nat Commun. 2020 Sep 9;11(1).

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Skeletal Muscle Disorders

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Functional effects of ryanodine receptor mutations linked to congenital muscle diseases

In skeletal muscle calcium is a key second messenger regulating contraction and the sarcoplasmic reticulum (SR) is the intracellular organelle involved in its regulation. The ryanodine receptor Ca2+ channel (RyR1) present on the terminal cisternae of the SR, is closely apposed to and is directly activated by, the dihydropyridine receptor an L-type Ca2+ channel functioning as voltage sensor. Upon depolarization, the voltage sensor undergoes a conformational change promoting the opening of the RyR1, leading to Ca2+ release from the SR; this elevation of the myoplasmic [Ca2+] is necessary for, and leads to, muscle contraction and this process is called excitation-contraction coupling (Fig. 1).

More than 700 RYR1 variants have been identified in patients worldwide, making this gene the primary target of neuromuscular disorders and accounting for over 30 % of mutations found in patients with congenital myopathies. Both dominant and recessive RYR1 mutations occur and usually associate with different phenotypes. Dominant mutations are causative of malignant hyperthermia/rhabdomyolysis/exertional heat intolerance and central core disease and functionally impact the channel's biophysical properties. Patients bearing recessive mutations are generally more severely affected, characteristically also display involvement of extraocular muscles and are diagnosed as having multi-minicore disease/centronuclear myopathy. The latter mutations have no major effect on the channel properties, but their presence is accompanied by profound biochemical changes in patients' muscles, including a significant reduction of the RyR1 protein content and high levels of expression of class II histone de-acetylases. The reduced RyR1 levels in the SR membrane cause a decrease of calcium release during excitation contraction coupling, leading to weak muscles.

Our laboratory focuses on determining the functional effect of RYR1 mutations with the long-term goal of developing a pharmacological strategy to improve muscle function in patients. To do so we use two main experimental models: patient-derived biological material and transgenic mouse models knocked in for mutations identified in patients. Muscle biopsies are evaluated biochemically and physiologically. Our results have demonstrated that muscle biopsies from patients carrying recessive RYR1 mutations show abnormally low RyR1 protein content, alteration of gene methylation and an increase in the content of chromatin modifying enzymes including class II histone de-acetylases and DNA methyl transferases. A mouse model we knocked in for a mis-sense mutation in one allele and a frameshift mutation in the other allele (DKI mouse, Fig. 2) exhibits severe muscle impairment, reduced levels of calcium release and disorganization of the muscle ultrastructure. Additionally, extraocular muscles from the transgenic mice have impaired excitation contraction coupling, as well as almost no EO-MyHC, the eye-muscle specific myosin heavy chain isoform. These results are consistent with the weak eye muscles of patients carrying recessive RYR1 mutations.

We are also interested in other aspects of skeletal muscle and in particular in identifying and validating the function of newly identified SR proteins. We have characterized a number of novel proteins including JP-45, junctate, SRP-27 and SRP-35; the latter is a membrane bound retinol-dehydrogenase converting retinol (Vitamin A) to all trans-retinaldehyde. Our results show that SRP-35 is involved in glucose metabolism, facilitating glucose uptake into skeletal muscle. We are currently investigating directly the role of Vitamin A in skeletal muscle physiology.

Taken together the results of our studies will have important implications especially since they will promote the development of pharmacological therapies to improve the quality of life of patients with disorders leading to a decreased levels of RyR1 and may shed new information regarding the link between metabolic disorders and skeletal muscle glucose metabolism.

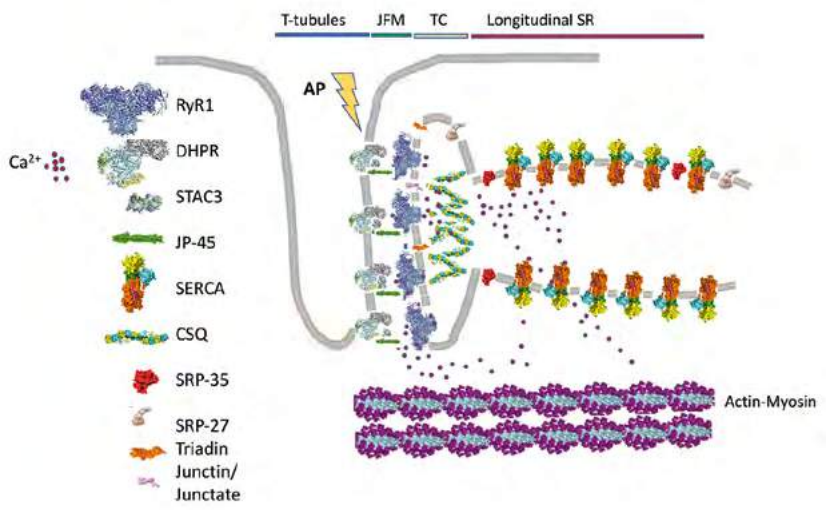

Fig. 1: Schematic representation of skeletal muscle proteins involved in excitation-contraction coupling. The figure shows the main components and subcellular localization of the proteins involved in skeletal muscle excitation–contraction coupling (ECC). The transverse (T-) tubules containing are invaginations of the plasma membrane where the voltage sensing dihydropyridine receptor (DHPR) is located. STCA3 binds to the DHPR. The T- tubules face the sarcoplasmic reticulum junctional0 face membrane (JFM) containing the ryanodine receptor 1 (RyR1) Ca^{2+} release channel, as well as JP-45, triadin and junctin/junctate/asparty β-hydroxylase. Calsequestrin bind Ca^{2+} and forms a mesh within the lumen of the sarcoplasmic reticulum. Opening of the RyR1 leads to Ca^{2+} release into the myoplasm which then binds to the contractile proteins resulting in sarcomeric shortening (muscle contraction). ECC is terminated when Ca^{2+} is actively pumped back into the sarcoplasmic reticulum by the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) Ca^{2+} pumps. SRP-35 is a retinol dehydrogenase converting retinol to *all* trans-retinaldehyde, SRP-27 (TRIC-A) oligomerizes on the terminal cisternae (TC) and longitudinal sarcoplasmic reticulum membrane where it is thought to be involved in the transport of K+ ions during Ca2+ release to maintain a neutral electrochemical gradient across the sarcoplasmic reticulum membrane.

Selected Publications

Eckhardt J, Bachmann C, Benucci S, Elbaz M, Ruiz A, Zorzato F and Treves S (2020). Molecular basis of impaired extraocular muscle function in a mouse model of congenital myopathy due to compound heterozygous Ryr1 mutations. Hum Mol. Genet. 29,1330–1339.

Elbaz M, Ruiz A, Nicolay S, Tupini C, Bachmann C, Eckhardt J, Benucci S, Pelczar P, Treves S and Zorzato F (2020). Bi-allelic expression of the RyR1 p.A4329D mutation decreases muscle strength in slow-twitch muscles in mice. J. Biol. Chem. 295, 10331–10339.

Elbaz M, Ruiz A, Bachmann C, Eckhardt J, Pelczar P, Venturi E, Lindsay C, Wilson AD, Alhussni A, Humberstone T, *et al.* (2019). Quantitative RyR1 reduction and loss of calcium sensitivity of RyR1Q1970fsX16+A4329D cause cores and loss of muscle strength. Hum. Mol. Genet. 28, 2987–2999.

Bachmann C, Noreen F, Voermans NC, Schär PL, Vissing J, Fock JM, Bulk S, Kusters B, Moore SA, Beggs AH, *et al.* (2019). Aberrant regulation of epigenetic modifiers contributes to the pathogenesis in patients with selenoprotein N-related myopathies. Hum. Mutat. 40, 962-974

Ruiz A, Dror E., Handschin C, Furrer R, Perez-Schindler J, Bachmann C, Treves S and Zorzato F (2018). Over-expression of a retinol dehydrogenase (SRP35/DHRS7C) in skeletal muscle activates mTORC2, enhances glucose metabolism and muscle performance. Sci. Rep. 8, 636 doi: 10.1038/s41598-017-18844-3.

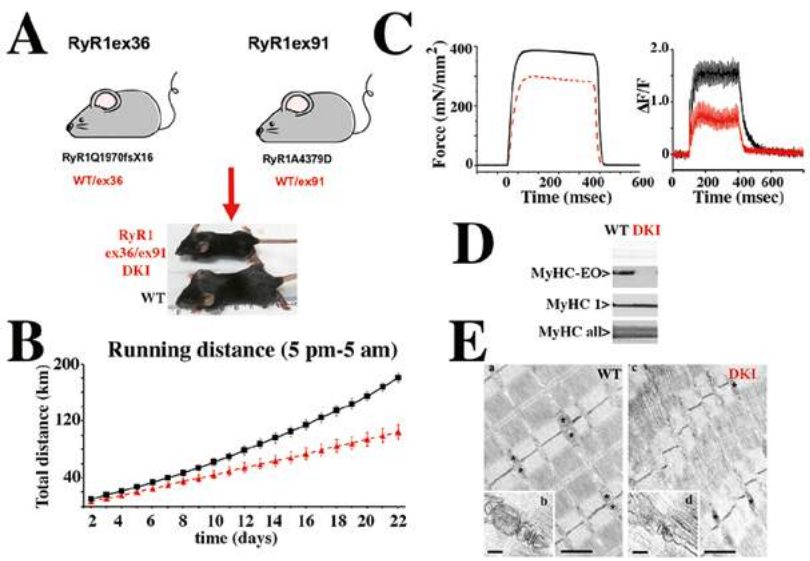

Fig. 2: Characterization of the DKI mouse model, knocked in for recessive RYR1 mutations. A. Double Knock In (DKI) mice were obtained by crossing heterozygous mice carrying a WT allele plus the frameshift mutation RyR1Q1970fsX16 with heterozygous mice carrying a WT allele plus the missense mutation RyR1A4329D. DKI mice (red) were on average 20% smaller than WT littermates (black). **B.** Muscle force assessed using the voluntary running wheel shows that DKI mice (red) run on average 50% less than their WT littermates (black). **C.** *Ex vivo* tetanic force stimulation of *externsor digitorum* longus muscles shows that muscles isolated from DKI mice (red) develop significantly less force than muscles from WT littermates (black)(left panel); the calcium transients elicited by electrical field stimulation at 150 Hz is also significantly reduced in EDL fibers from the DKI mice (right panel). **D.** EOMs from DKI mice show altered expression and content of the extra-ocular (EO) myosin heavy chain (MyHC) isoform. Top panel, membrane stained with Ponceau Red; central panel, blots stained with a monoclonal Ab specific for MyHC-EOM (top lanes) and a monoclonal Ab specific for MyHC1 (bottom lanes); bottom panel, blot stained with a monoclonal Ab recognizing all MyHC. **E.** Ultrastructure of EDL from WT and DKI mice. (a) In adult WT EDL fibers mitochondria are usually placed at the I band in proximity of Z lines (asterisks), next to CRUs. CRUs are mostly in the form of triads: two SR vesicles closely opposed to a central T-tubule (b). (c) In EDL fibers from DKI mice, mitochondria are less abundant and CRUs are often found in the form of dyads (d). Scale bars: a and c, 1 µm b and d, 0.1 µm.

Stem Cells and Regenerative Medicine

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Stem cell research and regenerative medicine are major pillars within the Department of Biomedicine (DBM) and the life science strategy of the University of Basel. The last two decades has seen massive progress in identifying and isolating multipotent progenitor and stem cells from adult and embryonic origin, which can be induced to differentiate into various specific cell-types relevant to regenerative medicine. While the groups that are part of this focal area have rather heterogenous research interests, several are actively studying how stem cells of the blood are maintained in the bone marrow, differentiate into the various different cell-types of the hematopoietic system, and how their differentiation potential is altered in malignant states that are caused by aberrant stem cell-based cancers (e.g. leukemia or lymphomas). The close interactions of clinical with basic researchers allow bridging the gap between fundamental and translational research. For example, attempts to grow and differentiate mesenchymal stem cells from human and mouse bone marrow *in vitro* into different cell- and tissue types, aim at developing cartilage and bone replacement therapies that can be translated to the clinic. The knowledge gained from these studies forms the basis for designing and developing clinically applicable tissue engineering strategies and in moving toward re- generative medicine.

One of the major aims of regenerative medicine is to reactivate and support the regenerative potential of the body in a controlled manner. To this aim, understanding the normal regulation of organogenesis and tissue homeostasis is crucial. While first attempts have given encouraging results, it is important to gain a much better knowledge of how stem cells interact with their niche to maintain their multipotency and give rise to daughter cells that undergo transient amplification upon leaving the niche. These populations of transient amplifying cells will then initiate their specification and differentiation in a controlled manner. Major advances in this direction include the establishment of organoids multipotent progenitors and stem cells under controlled culture conditions. This can now be done for an ever increasing number of organs and tissues including e.g. liver, gut, lung, bones and last but not least brain from both mouse and human stem cells. With respect to the later, patient derived organoids provide an excellent test system to study the etiology of disease and test potential therapeutic avenues *in vitro*. However, organoids have their limitations as they are not able to fully recapitulate the complex pattering and interactions of cells that originate from different lineage and differentiate into fully functional tissues. Any functional organ and tissue will consist of well-organized and functionally interacting cells with different identities, which at this stage can only be studied in its full extent in model organisms. Therefore, it is important to e.g. understand the control of tissue patterning & organization and cell-type specification & differentiation by molecular and genetic analysis signaling and gene regulatory interactions during embryonic development.

The knowledge gained the molecular analysis of cell-type and tissue specification during organogenesis in embryos and/or using organoids is highly relevant to directed engineering of tissues from multipotent progenitor and stem cells. Another important approach includes the use of so-called induced pluripotent stem (iPS) cells, which are adult cells (e. g. skin cells) reprogrammed into stem-like cells. iPS cells are increasingly used as they can be obtained from patients for cell differen-

tiation and tissue engineering studies. The generation and analysis of iPS cells fits the strategy of the DBM to promote collaborative efforts between basic research groups and clinicians with the aim to significantly reduce the gap between bench and bedside. In addition to interactions within the DBM, there are numerous collaborations with groups at the Biozentrum, FMI and the D-BSSE. Finally, several of the research groups in this focal area in this are actively participating in the Basel Stem Cell Network (BSCN), which is one of the life science research networks of the University of Basel. The BSCN is a scientific platform bridging the interdisciplinary stem cell community in Basel, representing 50 research groups from the academic institutions and pharmaceutical industry. Within the BSCN, stem cell researchers have the opportunity to closely interact and collaborate with developmental biologists, geneticists and clinicians with the objective to foster interdisciplinary and innovative basic and clinically-oriented research.

Cell and Gene Therapy

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Therapeutic angiogenesis from vascular biology to regenerative medicine

Therapeutic angiogenesis aims at restoring blood flow to ischemic tissues by growing new vessels. Our research focuses on the basic mechanisms governing vascular growth and their translation into rational approaches to: 1) treat ischemic diseases and 2) improve the vascularization of tissue-engineered grafts.
Vascular endothelial growth factor (VEGF) is the master regulator of vascular growth. However, uncontrolled expression causes vascular tumors (angiomas). By the close interaction of basic scientists and clinical surgeons, we are developing novel methods to deliver VEGF alone or in combination with modulating factors to increase its safety and efficacy *in vivo*. Key approaches include: 1) transduced progenitors, combining the specific advantages of cell and gene therapy; 2) gene therapy vectors; and 3) engineered recombinant proteins to decorate smart biomaterials or endogenous tissue matrix (Fig. 1). Research is funded by Swiss agencies (SNF, Swiss Nanoscience Institute and Swiss Diabetes Foundation) and the European Union (FP7 and H2020).

Cellular and molecular mechanisms of VEGF-induced angiogenesis

Our understanding of angiogenic mechanisms is mostly based on developmental models, in which new vessels sprout to vascularize tissues. However, we found that VEGF delivery to skeletal muscle, at the doses needed for functional benefit, induces angiogenesis without sprouting, but by circumferential enlargement of vessels, followed by longitudinal splitting ("intussusception", Gianni-Barrera 2020). The mechanisms regulating intussusceptive angiogenesis are essentially unknown and likely to differ from those of sprouting.
For example, the transition between normal and aberrant vascular growth during intussusceptive angiogenesis is not an intrinsic property of VEGF dose, but depends on the balance between VEGF-induced endothelial stimulation and vascular maturation mediated by pericyte recruitment by PDGF-BB (Gianni-Barrera 2018). The underlying molecular mechanism involves the activation of ephrinB2/EphB4 signaling between endothelium and pericytes, which finely tunes the degree of ERK1/2 activation downstream of VEGF-Receptor 2 and can be targeted pharmacologically (Groppa 2018).
Taking advantage of the highly controlled cell-based gene delivery platform we developed, we are currently pursuing a systematic investigation of the mechanisms that regulate intussusceptive angiogenesis *in vivo* through single-cell transcriptomics and non-invasive live imaging, to identify novel and more specific molecular targets for therapeutic angiogenesis.

Controlled factor delivery for therapeutic vascularization

We previously found that the transition between normal and aberrant angiogenesis depends on the VEGF amount in the microenvironment around each producing cell rather than on the total dose, since VEGF remains tightly localized in the extracellular matrix (Ozawa & Banfi 2004). In order to translate this biological concept into a clinically applicable approach, we developed a high-throughput FACS-based technology to rapidly purify transduced progenitors expressing specific VEGF levels (Misteli 2010). Controlled VEGF expression by FACS-purified progenitor populations could induce effective vascularization both inside and outside of thick, engineered cardiac patches (Marsano 2013; Boccardo & Gaudiello 2016), therapeutic angiogenesis in ischemic myocardium (Melly 2018) and increased *in vivo* vascularization of osteogenic grafts (Largo & Di Maggio 2020).
To avoid the need for genetic modification and improve clinical applicability, in collaboration with Jeffrey Hubbell (University of Chicago, USA) we developed a state-

of-the-art biomaterial platform based on fibrin hydrogels that enables independent control of the dose and duration of release of matrix-bound growth factors, by which we could identify a 500-fold range of VEGF concentrations inducing only physiological capillary networks, which were long-term stable and therapeutically effective in ischemic wounds and osteogenic grafts (Sacchi 2014; D'Amico manuscript submitted; Burger & Grosso manuscript submitted).

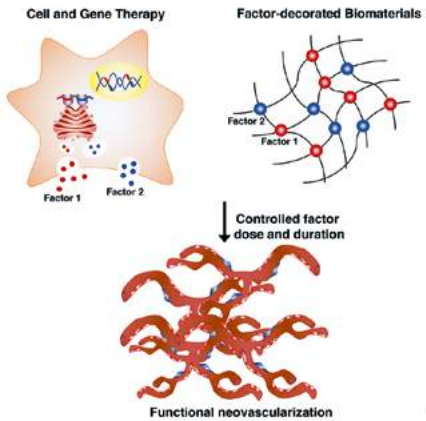

Fig. 1: Therapeutic angiogenesis is the generation of new blood vessels by delivery of specific factors, e.g. by genetic modification of progenitors or recombinant factor-decorated biomaterials.

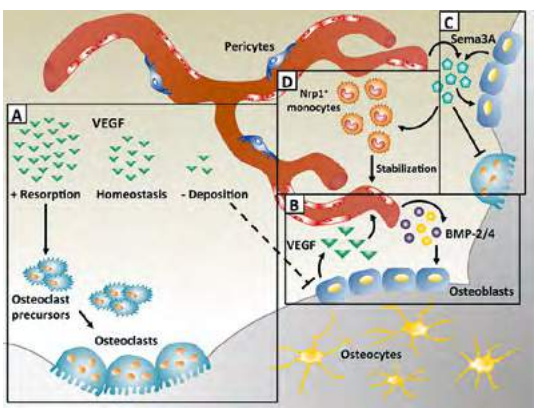

Fig. 2: The complex cross-talk between blood vessels and bone-forming cells provides molecular targets to couple angiogenesis and osteogenesis for bone regeneration.

Selected Publications

Gianni-Barrera R, Di Maggio N, Melly L, Burger MG, Mujagic E, Gürke L, Schaefer DJ and Banfi A (2020). Therapeutic Vascularization in Regenerative Medicine. Stem Cells Transl. Med. 9: 433–444.

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Groppa E, Brkic S, Uccelli A, Wirth G, Korpisalo-Pirinen P, Filippova M, Dasen B, Sacchi V, Muraro MG, Trani M, Reginato S, Gianni-Barrera R, Ylä-Herttuala S and Banfi A (2018). EphrinB2/EphB4 signaling regulates non-sprouting angiogenesis by VEGF. EMBO Rep. 19: e45054.

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Connection to Clinical Practice

Prof. Dr. Dirk J. Schäfer[1]
Prof. Dr. Lorenz Gürke[2]
Prof. Dr. Friedrich Eckstein[3]

1 Plastic and Reconstructive Surgery, University Hospital Basel
2 Vascular Surgery, University Hospital Basel
3 Cardiac Surgery, University Hospital Basel

Therapeutic angiogenesis and tissue regeneration

We aim at translating the basic biological principles of functional vascular network formation into rational strategies to induce therapeutic growth of new blood vessels. We pursue this concept in 3 main areas of clinical interest:

1) Rapid and pervasive vascularization of the inner core of clinical-size osteogenic grafts, coupled with robust osteogenic differentiation of progenitors, for improved bone formation. We investigate the molecular cross-talk between angiogenesis and osteogenesis (Fig. 2) to generate bio-active microenvironments (Dr. M. Burger and Prof. D. J. Schäfer, Plastic and Reconstructive Surgery USB). Funding by the SNF Marie-Heim Vögtlin (to Dr. N. Di Maggio) and by the EU H2020 program (cmRNAbone and B2B).

2) Therapeutic angiogenesis in chronically ischemic muscle and non-healing wounds, especially in diabetic patients. Controlled delivery of recombinant angiogenic factors is achieved by smart biomaterials or by protein engineering for matrix super-affinity (PD Dr. E. Mujagic, PD Dr. T. Wolff and Prof. L. Gürke, Vascular Surgery USB). Funding by the EU FP7 Marie Curie program (AngioMatTrain) and Swiss Diabetes Foundation (Dr. R. Gianni-Barrera).

3) Therapeutic angiogenesis in the myocardium by controlled delivery of recombinant factors through decorated fibrin hydrogels, to treat cardiac ischemia (Dr. L. Melly PhD, Catholic University of Louvain and Prof. F. Eckstein, Cardiac Surgery USB). Funding by Swiss Nanoscience Institute (KOKORO).

Inner Ear Research

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Unravelling molecular mechanisms of auditory hair cell loss to find new therapeutic possibilities to treat hearing loss

Hearing impairment has a significant impact on people's live affecting their social life, access to education and career opportunities. According to WHO estimation, 466 million people worldwide are currently affected by hearing loss, including 34 million children. Approximately one third of the people over 65 live with disabling hearing loss and more than 1 billion young people are at risk of developing gradual hearing loss due to regularly and prolonged exposure to loud sound. As reported by the non-profit organization Hear-it, disabling hearing loss costs 260 billion per year in Europe.

Hearing loss may result from a variety of factors such as genetic factors, infectious diseases, noise overexposure, ototoxic drugs and natural aging process. The main functions of the outer and the middle ear are transducing and amplification of sound, while the cochlea in the inner ear is the auditory sensory organ. The outer hair cells of the organ of Corti are mechanically active, while the inner hair cells of the same organ convert the stimulus into neuronal impulses via afferent synapses to the dendrites of primary auditory neurons. Loss of sensorineural elements of the inner ear, hair cells and auditory nerve, lead to sensorineural hearing loss. Since sensory cells of mammals do not regenerate, hearing loss is often progressive and irreversible. Although the causes of hearing loss are known, the molecular mechanisms underlying cochlear degeneration and auditory function remain incompletely understood. Understanding the molecular mechanisms of the sensory cell damage will provide the basis to develop new prophylactic and therapeutic approaches.

Our research group has conducted investigations on mechanisms that maintain the hearing function and survival of sensory cells. We have tested several candidates as otoprotective agents that could attenuate inner ear damage and hearing disabilities. We observed that the use of simvastatin, a statin commonly used for the treatment of hyperlipidemia, resulted in a dose dependent risk of neurotoxicity suggesting cautions about using it as otoprotective drug. Further drugs used for the treatment of diabetes and dyslipidemia were tested. Pioglitazone, tesaglitazar and fenofibric acid, that are peroxisome proliferator-activated receptor (PPAR) agonists, have shown protection against the ototoxic drug gentamicin via regulation of production of reactive oxygen species. Similarly, telmisartan, a partial agonist of PPAR , protected hair cells from gentamicin-induced damage. Furthermore, protection of hair cell against gentamicin has been successfully achieved by using brimonidine, an alpha-2 adrenergic receptor agonist. In addition, we examined the effect of pasierotide, an analog of the neuropeptide somatostatin. In-vitro, pasierotide antagonized gentamicin-induced hair cell death via nuclear factor of activated T cells. In-vivo, pretreatment with pasierotide decreased hearing thresholds in gentamicin-exposed mice.

In response to noise, ototoxic drugs and aging process; sensory cells activate various anti- stress signaling pathways. A number of those signaling pathways of cochlear degeneration are known, however other pathways still need to discover. We were the first research group reporting the involvement of Sestrin-2, stress-responsive protein, in the protection of hair cell against gentamicin exposure. We have found that Sestrin-2 exerted its protective effect via AMPK/mTOR pathway. Recently, we have reported that sodium-hydrogen exchange 6 (NHE6) was important for hearing function, as NHE6 knockout mice showed significant hearing impairment compared to wild type. Further studies to unravel the ototoxicity mechanism included the examination of mitophagy. We found that gentamicin had no

impact in the activation of mitophagy in auditory hair cells. Our investigations on insulin receptors in the mammalian cochlea suggested that insulin increased glucose uptake into hair cells via glucose transporter 3.
The findings obtained from our research studies will contribute to attenuate inner ear damage and to understand restoration of hearing that will provide valuable information for translational medicine.

Connection to Clinical Practice

Daniel Bodmer and Alexander Bausch
USB and Strekin AG

Clinical trial of STR001 in Sudden Sensorineural Hearing loss

STR001 contains the antidiabetic drug pioglitazone as active substance. Our investigations have shown that pioglitazone protected hair cells against the ototoxic drug gentamicin. In addition, the research group of Dr. Anna Fetoni reported that pioglitazone promoted hearing restoration in noise-exposed mice. These findings suggested that STR001 could be a potential therapeutic candidate for sensorineural hearing loss and should be examined for further clinical development. Our clinic are participating in the international placebo-controlled phase 3 clinical trial of STR001 on patients suffering from a sudden sensorineural hearing loss.

Selected Publications

Kucharava K, Brand Y, Albano G, Sekulic-Jablanovic M, Glutz A, Xian X, Herz J, Bodmer D, Fuster DG and Petkovic V (2020). Sodium-hydrogen exchanger 6 (NHE6) deficiency leads to hearing loss, via reduced endosomal signalling through the BDNF/Trk pathway. Sci Rep 10, 3609.

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Sekulic-Jablanovic M, Petkovic V, Wright MB, Kucharava K, Huerzeler N, Levano S, Brand Y, Leitmeyer K, Glutz A, Bausch A *et al.* (2017). Effects of peroxisome proliferator activated receptors (PPAR)-gamma and -alpha agonists on cochlear protection from oxidative stress. PloS one 12, e0188596.

Cardiobiology

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Regulation of cardiac cell growth – implications for heart disease

Our group investigates mechanisms whereby receptor tyrosine kinases regulate hypertrophic and hyperplastic cell growth in the heart. To this end we use primary neonatal rat heart cultures and several *in vivo* mouse models of cardiac disease. During the past reporting period we have investigated models of high-fat diet-induced cardiomyopathy and aortic-constriction-induced cardiac hypertrophy to mimic the pathophysiology associated with obesity and valve disease, respectively. In addition, we are establishing a model of anthracycline-induced cardiomyopathy, relevant to the interdisciplinary field of oncology and cardiology. Our focus at the cellular level is on protein turnover mechanisms, which to a large extent depend on available energy resources together with hormone and cytokine levels. We have recently directed our attention to the ErbB family of receptor tyrosine kinases activated by neuregulin-1β (NRG-1), while also extending our earlier work on the insulin/IGF-I/Akt/mTOR pathway.

Neuregulin-1β

NRG-1 regulates cell growth and differentiation in various tissues including the heart. After myocardial infarct or anthracycline therapy, NRG-1 is released by the endothelium and activates multiple signaling pathways leading to distinct biological effects depending on the expression levels and dimerization of its receptors ErbB2, ErbB3 or ErbB4 on neighboring cells in the heart. NRG-1 is cardioprotective in a range of animal models of cardiac disease. While its therapeutic use is being tested in heart failure, the hormone risks to enhance tumor growth. A better understanding of the mechanisms whereby NRG-1 acts in cardiac versus cancer cells is important.
We reported that NRG-1 causes glucose uptake in neonatal cardiomyocytes by triggering translocation of GLUT4 to the plasma membrane via ErbB2/ErbB4 (Fig. 1). Using Seahorse, we showed that NRG-1 also enhances glycolysis. Like for insulin and IGF-I, the mechanism involves PI3Kα, Akt and AS160 (Pentassuglia *et al.,* 2016; Heim *et al.,* 2020). Under stress conditions cardiomyocytes switch from fatty acids to glucose as energy source. We hypothesized that the NRG-induced glucose uptake contributes to cardiomyocyte contractility e.g. under ischemic conditions or in insulin-resistant states. However, our experiments demonstrated that NRG-1 does not activate this cardiac glucose uptake pathway in adult models. We are currently testing whether the metabolic effects of NRG-1 provide the means for cell cycle activation and proliferation observed in neonatal cardiomyocytes (Fig. 2). While our studies reveal mechanisms that contribute to normal physiological cardiac growth and differentiation observed in neonatal hearts, they also aim to provide fundamental insights that may contribute to cardiac regenerative approaches.

Function of mTORC2 in the heart

To perform its function as biological pump that provides oxygen and nutrients to our whole body, the heart consumes large amounts of energy. A tight regulation of the available resources, including cellular proteins, becomes critical in disease states where metabolism must increase to maintain cardiac performance, e. g. in hypertensive or valve disease. We previously reported that the metabolic regulator mTOR is essential for cardiac function when part of mTORC1: its cardiomyocyte-specific ablation causes heart failure rapidly followed by death of the mice, a phenotype explained by mTORC1's role in protein synthesis as well as mitochondrial metabolism. We next demonstrated that aortic constriction-induced pressure overload significantly increases rictor (an essential mTORC2-specific protein) and PKCβII and PKCδ phosphorylation in control mice, but not in cardiac rictor knockout mice. Whereas pressure-overload causes hypertrophy with maintained func-

tion in controls, it leads to systolic dysfunction in rictor-deficient hearts without having any effects on cardiac weight or fibrosis. These data suggest that mTORC2 regulates metabolism and contractility of the heart via PKCβII and PKCδ and is not implicated in its hypertrophic growth (Shende *et al.,* 2016; Xu *et al.,* 2016).

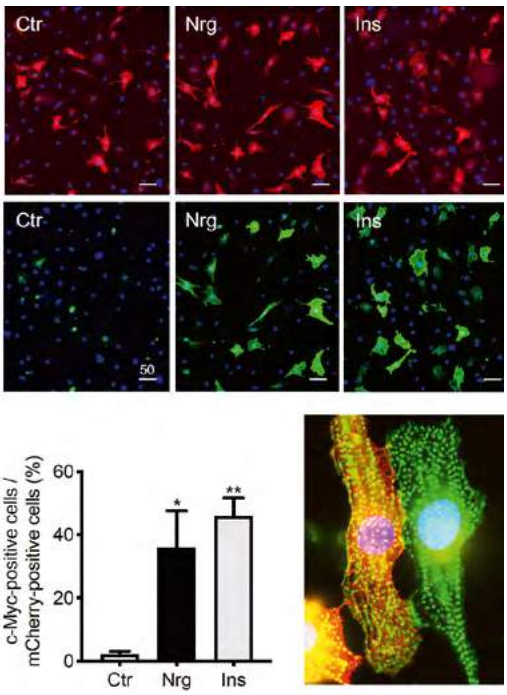

Fig. 1: NRG-1 causes translocation of GLUT4 to the plasma membrane. pLenti-myc-GLUT4-mCherry transfected cardiomyocytes from neonatal rats were stimulated with NRG-1 (Nrg, 10 ng/mL), insulin (Ins, 13 nM) or vehicle (Ctr) and fixed with 4 % paraformaldehyde after 30 min. The GLUT4-transfected cells are revealed based on the mCherry label (red, top pictures). Translocated GLUT4 was detected on the surface of the fixed non-permeabilized cells using a c-Myc-specific antibody followed by an Alexa 633-labeled secondary antibody (green). The bottom picture identifies the the left mCherry-positive cells (red) as cardiomyocytes after staining with antibodies specific for sarcomeric actinin (green), The nuclei were stained with DAPI (blue).

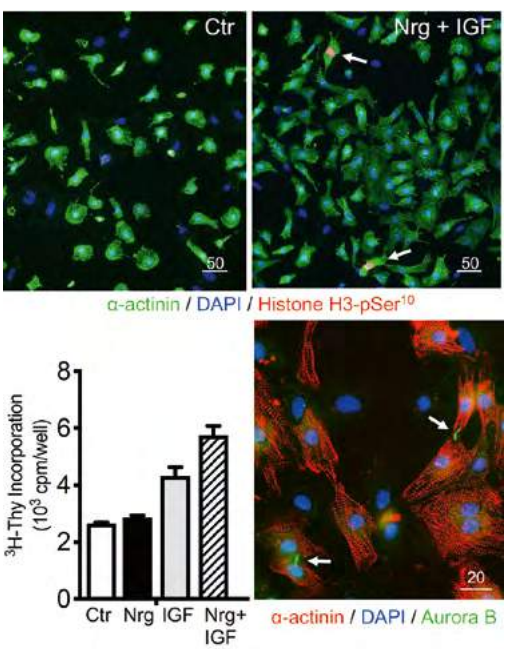

Fig. 2: Effects of IGF-I and NRG-1 on cardiomyocyte cell cycle activation. Cardiomyocyte cultures prepared from neonatal rats were stimulated with NRG-1, IGF-I or both factors together for 24 h. Cell cycle activation was evaluated by measuring ^{3}H-thymidine incorporation and by immunofluorescent labeling with antibodies to phosphorylated Histone H3 (top). To confirm cytokinesis in cardiomyocytes, double labelling with antibodies to α-actinin and Aurora B was performed (Bottom micrograph). Bar size indicated in µm.

Connection to Clinical Practice

ErbB4 agonists

For the translational side of our work on NRG-1, we collaborate with teams of the University of Antwerpen (Profs Gilles de Keulenaer and Vincent Segers) and Moscow (Profs Anastasia Shchendrygina and Yuri Belenkov), funded by a European ERA.Net RUS Plus grant.

Multiple lines of evidence demonstrate that the cardiac NRG-1/ErbB4 system is activated in chronic heart failure, exerting disease mitigating and regenerative effects. NRG-1 is developed as a drug for heart failure and clinical trials have progressed to stage III. In addition, there is solid evidence from animal studies that the NRG-1/ErbB4 pathway is involved in other chronic diseases, such as diabetic nephropathy, pulmonary hypertension, atherosclerosis and fibrotic disorders. All of these are common chronic disorders, and potential therapeutic targets for NRG-1. In the project together with Antwerpen and Moscow, a multi-disciplinary approach is taken to identify novel potent and selective agonists of the ErbB4 receptor, to test these in validated rodent models of heart failure, and to define specific patient populations in the heterogeneous field of cardiovascular diseases that could benefit from ErbB4 agonists.

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Gynecological Endocrinology

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Ovarian and reproductive disease modelling

We are interested in unraveling the signaling pathways in ovarian physiology. For that reason, we focused much of our research on E3 ubiquitin ligase for inhibin B receptor, EULIR, which was originally identified in our lab as a putative mediator of inhibin signaling in the ovary. Later EULIR was renaimed HECTD1. In a transgenic mouse model with the HECT domain deletion mutant mice homozygous for *Hectd1*-mutant showed early embryonic lethality with abnormal placental development and defective of neural tube closure resulting in exencephaly. The thickness of the placenta of both *Hectd1*-mutant homozygous and heterozygous mice was distinctly thinner than that of wildtype mice, the difference being most pronounced in the labyrinth layer of the placenta (Fig. 1). Moreover, as an E3 ubiquitin ligase, many aspects of the functional role of HECTD1 still remain to be elucidated. By Y2H and MS assays, the HECTD1 interactome network was generated. HECTD1 regulates the protein level of IQGAP1 through ubiquitination and therefore mediates cell spreading and directionality of migration by regulating the dynamics of the focal complexes, especially determining paxillin and zyxin localizations. HECTD1 also regulates the expression of SNAIL and epithelial mesenchymal transition (EMT). The knockdown of HECTD1 in HeLa cells increased cell migration and induced a mesenchymal phenotype, in addition to demonstrating sustained EGF/R signaling, which was observed through increased phosphorylated ERK expression levels. We found that the sustained signaling of EGFR is accompanied by co-localization of Rab4 together with APPL1, another HECTD1 effector. We identified APPL1 as a critical player during fast recycling endosome biogenesis, in which APPL1 is not only a marker of the very early endosome but plays a crucial role in early endosome sorting. Mechanistically, we demonstrated that APPL1 is essential for the recruitment of KXD1 to the Rab5-Rab4 endosomes. BLOC-1 is required for RAB4 fast recycling. APPL1 establishes a network of interactions with RAB5, BORC/BLOC1 and RAB4 for fast endosome recycling (Fig. 2). Regulation of membrane transports by HECTD1 has other samples. Hax1 is an effector of HECTD1. Centrosomal recruitments of Mob1 and Nek2 are required by Hax1 to regulate the function of Mst1/Mob1-NDR and Mst1/Nek2 at the centrosome. Hax1-Sav1–Mst1–Mob1/HDR1 and PLK4 cooperate in centrosome amplification.

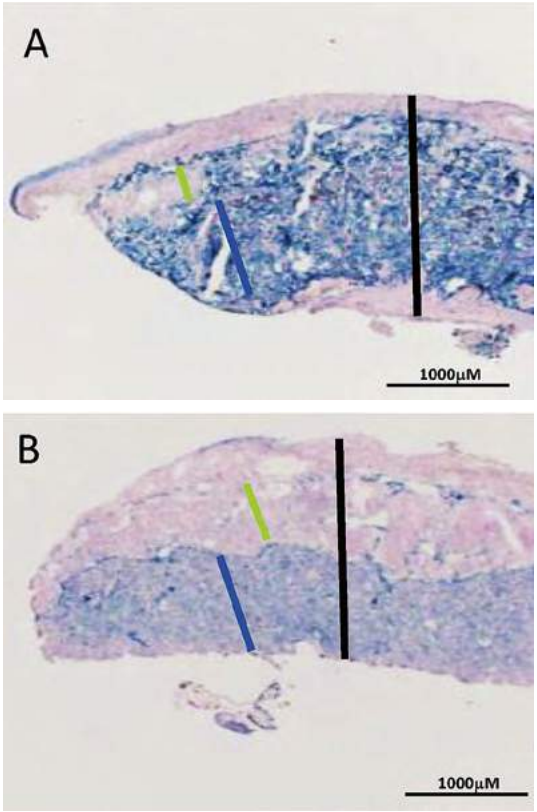

Fig. 1: Developmental defects in homozygous (Hectd1R/R) mutant mice. **A.** represents the thickness of a homozygous Hectd1R/R mouse placenta; **B.** represents the thickness of the placenta of a Hectd1+/R mouse.

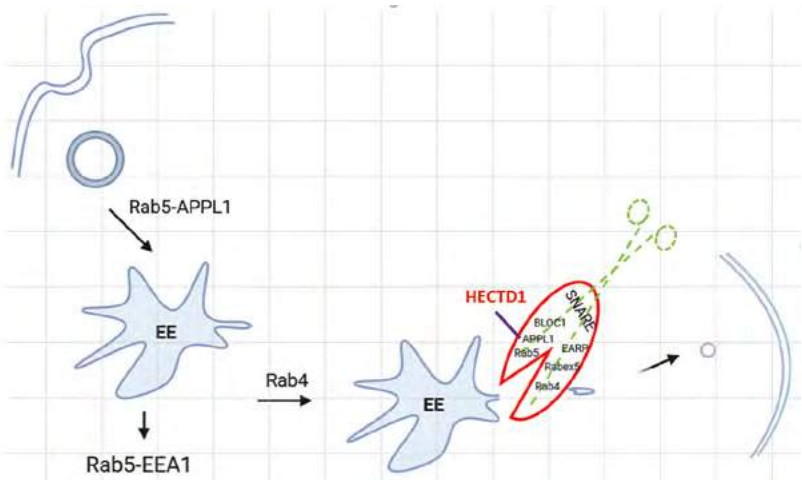

Fig. 2: Identification of molecular machinery of Rab4-mediated fast recycling pathway of the epidermal growth factor receptor (EGFR).

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Brain Ischemia and Regeneration

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Neuroimmune interactions and CNS regeneration

Our laboratory conducts basic and translational research aiming at testing and developing protective and regenerative strategies to repair the central nervous system (CNS) after injury.

Neonatal hypoxic-ischemic encephalopathy (HIE)

HIE is a brain injury resulting from an impaired delivery of oxygen (hypoxia) and blood (ischemia) to the brain of a newborn. It causes significant mortality, and up to 25 % of surviving infants endure lifelong neurological deficits, collectively referred to as cerebral palsy (CP). Currently, therapeutic hypothermia is the only approved therapy, nevertheless the rates of death and severe disabilities in treated children remain high. Thus, there is an urgent need for alternative therapies. Preclinical and clinical data indicate that stem cell (SC) transplantation improves the functional outcome of HIE, but the underlying mechanisms remain unclear.
A major research goal of our laboratory is to study the cellular and molecular determinants of repair in the developing brain. Our focus is on neurogenesis and oligodendrogenesis, two complex endogenous processes that generate mature neurons and oligodendrocytes respectively from neural stem/progenitor cells (NSCPs). Data in rodent models of neonatal HIE suggest that these repair processes are induced by HI (Brégère *et al.,* 2017)-albeit insufficiently –, and can be potentiated by SC therapy. Postnatally, these processes are mainly retained in two restricted and specialized areas of the brain, the neurogenic niches, namely the subventricular zone (SVZ) and the hippocampal dentate gyrus (DG). Using *in vivo* and *in vitro* rodent models, our previous data showed that microglia, the main immune cells in the CNS, are more densely populated in the neurogenic niches than in non-neurogenic areas of the brain. We and others also demonstrated that a reciprocal NSPCs/microglia crosstalk contributes to the regulation of neurogenesis. This aspect is being further investigated in the context of neonatal HI brain injuries (Fig. 1).

Neuroimmune interactions during brain ischemia

Using a rat model of neonatal hypoxia-ischemia (HI), we recently showed that microglia in the SVZ have a very distinct response to injury when compared to microglia in the adjacent cortex or corpus callosum (Fisch *et al.,* 2020). Specifically, we found that 3 and up until 33 days after HI, SVZ microglia (i) accumulate, (ii) are activated and phagocytic, and (iii) upregulate immunomodulatory and neurotrophic genes, features not or less observed in non-neurogenic areas (Fig. 2). *In vitro*, microglia isolated from the SVZ supported neurosphere generation in a concentration-dependent manner. Altogether these data suggested a functional impact of SVZ microglia on neurogenesis after a developmental brain injury.

The effect of glucose deprivation on the microglial phenotype

We are also investigating the impact of ischemia on brain cells through subjecting primary rodent mixed glial cultures to glucose deprivation (GD). Mixed glial cells comprise predominantly astrocytes, and to a lesser extent microglia and oligodendrocyte progenitor cells (OPCs). We observe that after GD, microglia are the main survivors among glial cells. Microglia under GD conditions display an 'activated', phagocytic like phenotype, as indicated by an increased cell size, and higher co-expression of IBA1 (microglia/macrophage marker) and CD68 (lysosomal marker). The concentration of PDGF-AA, -an important chemokine for the proliferation of OPCs-, in the conditioned medium from GD mixed glial cultures is 247 times higher than that from non-GD cultures. These data highlight microglia as very flexible cells for energy substrate, and point to a role of microglia in oligodendrogenesis during ischemia.

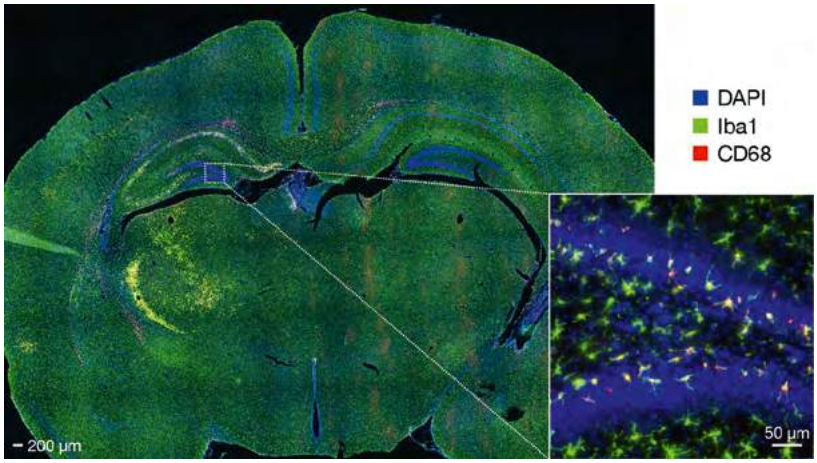

Fig. 1: 10X confocal micrograph showing a coronal overview of a postnatal day 15 (P15) rat brain exposed to HI at P7. The HI surgery consists of right common artery ligation followed by 40 minutes exposure to hypoxia (8 % oxygen). HI produces an injury on the same side of carotid ligation (or ipsilateral) while leaving the contralateral hemisphere intact. The rat brain slice is stained at the level of the dorsal hippocampus with Iba1 (green) and CD68 (red). Activated microglia (double positive cells in yellow) can be observed in the ipsilateral side of the brain, especially in the thalamus and hippocampus, while almost none are visible on the contralateral side of the brain, thus demonstrating the neuroinflammation induced by HI. The enlarged image shows the hippocampal dentate gyrus, a neurogenic niche, with the molecular layer containing also more activated microglia than the surrounding tissue (unpublished data).

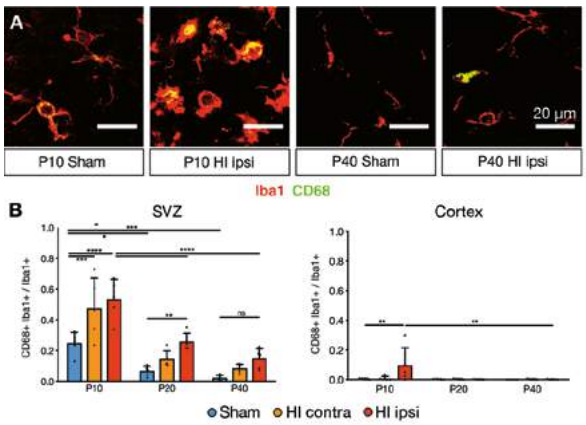

Fig. 2: After neonatal HI in the rat, the microglial density and the number of activated microglia in the SVZ remain significantly higher in the injured (ipsilateral) hemisphere than in the contralateral hemisphere from HI animals and in brains from sham animals. **A.** Representative confocal 40X images of CD68+ (green) Iba1+ (red) activated microglia in the SVZ. The images are taken 3 (P10) and 33 (P40) days post-HI. **B.** Corresponding quantification of the proportion of activated microglia in the SVZ (neurogenic niche) and cortex (non-neurogenic area). Individual data shown as dots, bars as mean with SD (error bar). Adapted from Fisch *et al.,* 2020.

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Connection to Clinical Practice

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Neuroprotective mechanisms of hypothermia-role of RBM3, a cold-inducible protein

Therapeutic Hypothermia (TH) is the only approved treatment for term born infants diagnosed with HIE. Even tough it is not fully effective, it reduces mortality and disabilities up to 24 months of age if applied within 6 hours of birth. TH appears also neuroprotective in patients undergoing cerebrovascular surgery, but randomized controlled trials have yielded conflicting results. Yet, subgroups of patients may still benefit from this intervention. Research has established that the benefit of TH lays in the modulation of several injury pathways, but the molecular mechanisms are not fully elucidated. In collaboration with Prof. Dr. Sven Wellmann (SNF grant 31003A_163305), we examined the role of RNA-binding motif protein 3 (RBM3), a cold-inducible stress protein, in brain repair. Hypothermia up-regulates RBM3, which is neuroprotective under stressful conditions. We demonstrated that, after an HI injury, RBM3 stimulates neuronal differentiation and inhibits HI-induced apoptosis in the two neurogenic niches, i.e. the SVZ and the DG, while promoting NSPCs proliferation only in the DG. The severity of HI-induced neuronal injury was greater in RBM3 knockout mice than in wildtype mice. We unraveled a novel RBM3- IMP2-IGF2 signaling pathway in the hippocampus that explains the niche-dependent regulation of neurogenesis after adult HI (Zhu *et al.,* 2019 and Fig. 3). In a second report, we showed that RBM3 contributed to the regulation of the cell cycle of NSPCs and their viability under hypoxic conditions (Yan *et al.,* 2019). Altogether, the data indicate that RBM3 may be an important clinical target in neuroprotection.

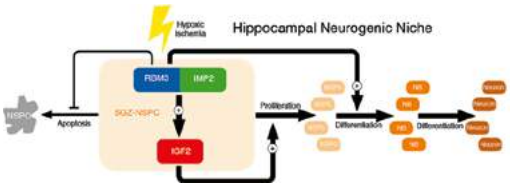

Fig. 3: Proposed scheme showing how RBM3 may regulate IGF2 release in the hippocampal dentate gyrus. After an HI injury, RBM3 interacts with IMP2. This interaction inhibits the apoptosis of NSPCs, and favors the release of IGF2, eventually leading to the proliferation of NSPCs and their differentiation. Adapted from Zhu *et al.,* 2019.

Cardiovascular Molecular Imaging

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Ultrasound molecular imaging in cardiovascular disease

Ultrasound molecular imaging

Developments in hardware, computing power and image processing have contributed to impressive improvements in medical imaging over the last decades with depiction of the human body with ever increasing resolution. However, early disease processes are often characterized by changes in cellular phenotype and will remain out of range for conventional imaging. To overcome this limitation, molecular imaging that uses contrast media to image biological processes at a cellular level has been developed for all major medical imaging modalities, and it is thought that molecular imaging will in the future allow to detect diseases earlier, lead to better understanding of pathophysiology and will be an integral part of personalized medicine. In our laboratory, we are developing targeted contrast agents for ultrasound molecular imaging. Microbubble ultrasound contrast agents have been in use in the clinical field for some years for blood pool and perfusion imaging. With a size range of 1–4µm, microbubbles circulate freely throughout the microcirculation. Being composed of a gas core and a monolayer lipid shell, microbubbles re-radiate sound waves efficiently and can be depicted using clinical ultrasound equipment. For ultrasound molecular imaging, microbubbles have been functionalized for molecular imaging by anchoring antibodies or other ligands to the microbubble surface (Fig. 1). Upon injection, these functionalized microbubbles accumulate on the vascular endothelium expressing a particular marker in diseased tissue, and can be imaged non-invasively with ultrasound.

Ultrasound molecular imaging in atherosclerosis

Risk assessment for atherosclerotic cardiovascular events currently relies on clinical risk factors. This approach places a large proportion of individuals in an intermediate risk category, where the value of interventions to reduce the risk for events is uncertain. Therefore, tools to better assess the risk in these patients are needed. Noninvasive imaging of molecular events associated with atherosclerotic disease may serve this purpose. Previous studies have shown that contrast enhanced ultrasound molecular imaging using microbubble contrast agents directed against vascular cell adhesion molecule 1 (VCAM-1), which is involved in inflammatory processes in atherosclerosis, is feasible in murine disease models. However, the ultrasound contrast agents used in these studies are not suitable for clinical translation and there is a need for the development of microbubbles employing clinically translatable strategies for conjugation of targeting moieties, and targeting ligands that can readily be used in the clinical field. Therefore, recent work in our laboratory has concentrated on the development of contrast agents that will allow translation of this non-invasive imaging technique into the clinical field. Nanobodies are small antibody fragments (10–15kDa) derived from heavy-chain-only antibodies. They are attractive for applications in molecular imaging, as they are highly specific, non-immunogenic and thus offer the potential for clinical translation. We have shown that MBs bearing nanobodies with cross reactivity for murine and human VCAM-1 can be not only used to image various stages of murine atherosclerosis, but that imaging of VCAM-1 expression on human carotid thrombendarterectomy specimens is also possible using an in-vitro flow chamber setup (Fig. 2). Likewise, Designed Ankyrin Repeat Proteins (DARPins) are potential candidates for clinical ultrasound molecular imaging given their easy production and selection, high affinity and low immunogenicity, and we have examined their use as ligands for targeting of VCAM-1. For this purpose, ribosome display was used to select >400 DARPin binders targeted against murine VCAM-1. Subsequently, flow cytometry and flow chamber assays were used to select 5 top candidate binders that were assessed in-vivo. Using these top candidates, assessment of murine hindlimb inflammation was possible using ultrasound molecular imaging.

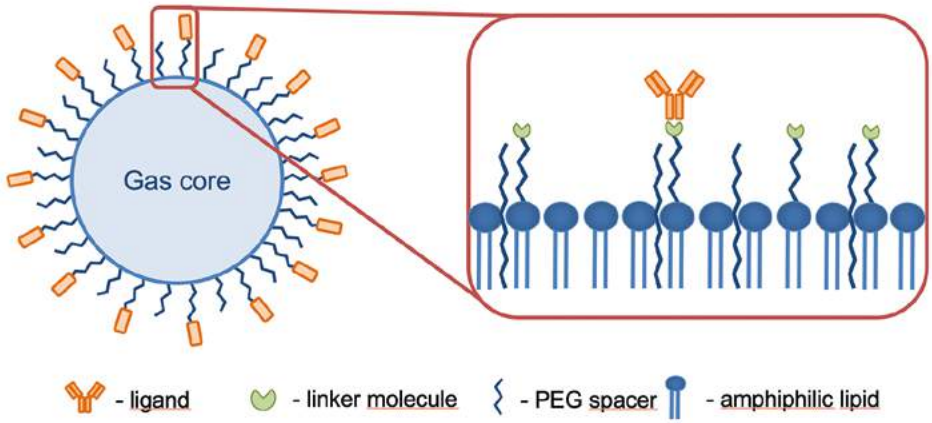

Fig. 1: Microbubble contrast agent used for ultrasound molecular imaging. Microbubbles consist of a lipid monolayer shell and a heavy weight gas core. The shell is functionalized with a specific ligand bound to the surface through linker molecules.

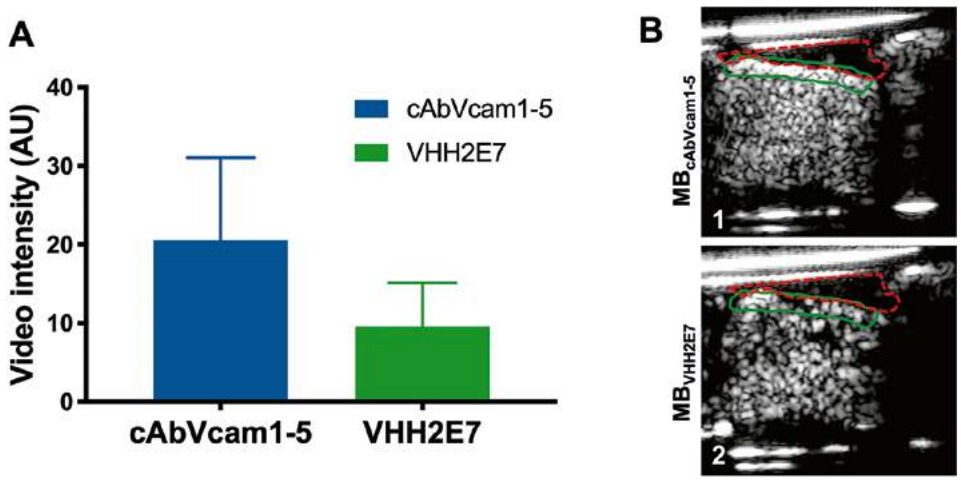

Fig. 2: (A) Background-subtracted ultrasound molecular imaging signal intensity on the luminal endothelial surface of human endarterectomy specimens (n=7) for microbubbles targeted to VCAM-1 ($MB_{cAbVcam1-5}$) or control microbubbles (MB_{VHH2E7}). Data is mean ± SD, $MB_{cAbVcam1-5}$ showed increased retention (*p=0.0156) as compared to MB_{VHH2E7}. **(B)** Example of ultrasound molecular imaging showing high signal on the plaque surface for $MB_{cAbVcam1-5}$ (panel 1) and low signal for MB_{VHH2E7} (panel 2). The red color outline shows the human thromboendarterectomy specimen, the green color outline attached microbubbles at the tissue-fluid interface.

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Toxicological mechanisms of drugs

Valproic acid (valproate) is a branched medium-chain fatty acid (Fig. 1) that is used as an antiepileptic. Valproate frequently causes hepatocellular triglyceride accumulation, clinically manifesting as non- alcoholic fatty liver disease (NAFLD). We investigated the effect of valproate on lipid metabolism in HepaRG cells, a human hepatoma cell line. For that, we first established methods to assess fatty acid import, activation, mitochondrial degradation, triglyceride formation and VLDL export. The study showed that several mechanisms are responsible for valproate-associated triglyceride accumulation. The main mechanisms identified were increased fatty acid transport into hepatocytes, impaired mitochondrial fatty acid metabolism and impaired export of VLDL. With the same techniques, we assessed triglyceride accumulation associated with the COMT inhibitor tolcapone in HepG2 cells. Here, mainly impaired mitochondrial metabolism of fatty acids and reduced export of VLDL were the mechanisms. The studies show that the techniques developed deliver valuable results regarding mechanisms of hepatocellular triglyceride accumulation by xenobiotics.

Statins are drugs used widely to lower LDL-cholesterol in patients with dyslipidemia but can lead to myotoxicity and impaired insulin sensitivity. Regarding myotoxicity, we have shown previously that statins impair insulin and IgF-1 signaling by inhibiting the activation of AKT. Impaired activation of AKT leads to a reduced function of mTORC1, which favors protein breakdown and diminishes protein synthesis. In C2C12 cells and in mice we could show that impaired activation of AKT is due to a reduced function of mTORC2, a kinase which phosphorylates AKT ser473. We explain reduced function of mTORC2 by impaired prenylation of certain G proteins essential for formation and function of mTORC2. In addition, treatment with statins can lead to glucose intolerance and diabetes type II. In one of our recent studies, we showed that treatment of mice with simvastatin leads to higher blood glucose concentrations as compared to untreated control mice whereas the plasma insulin concentrations were not affected (Fig. 2). These findings were compatible with impaired insulin sensitivity of skeletal muscle. Indeed, simvastatin impaired skeletal muscle glucose uptake *in vivo* in mice and *in vitro* into C2C12 cells. Reduced activation of AKT impaired downstream phosphorylation of GSK3β, leading to diminished translocation of GLUT4 into plasma membranes of C2C12 myotubes. In addition, simvastatin was associated with ER stress, which caused accumulation of Glut4 in the ER.

We also investigated the effect of simvastatin on C2C12 myoblasts and satellite cells in mice. Simvastatin was more toxic on C2C12 myoblasts, a surrogate of satellite cells, than on myotubes. Simvastatin inhibited the proliferation and maturation of satellite cells in mice and of C2C12 myoblasts, suggesting that simvastatin impairs skeletal muscle regeneration. This effect could be prevented by mevalonate but not by insulin, indicating that impaired prenylation of proteins is an important mechanism.

Metamizole is an analgesic and antipyretic drug used widely in some countries but is associated with neutropenia and agranulocytosis. To explore potential toxic mechanisms, we used HL60 cells, a human promyelocytic cell line. In a first study, we showed that metamizole reacts with Fe^{3+} in hemin (Fig. 3), yielding reactive metabolites, which can cause myelotoxicity. Using an *in vitro* system, we could propose a potential structure of the reactive metabolite. Since HL60 cells can be differentiated to granulocytes, we were interested up to which cell type metamizole is toxic. Toxicity was predominantly seen for promyelocytes, but not for metamyelocytes or granulocytes, corresponding to the clinical findings in affected patients. The toxicity correlated inversely with the development of the antioxidative defense

system in granulocyte differentiation (not developed in promyelocytes, well developed in granulocytes). This supports the notion that reactive metabolites play a role and matches well with a recent genome- wide association study.

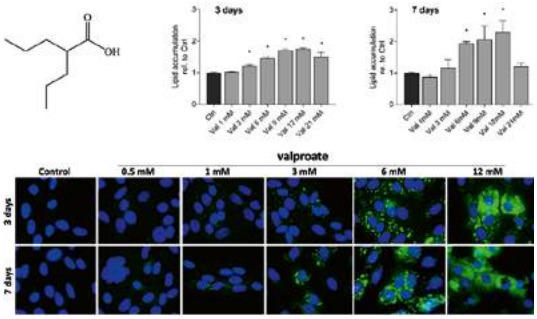

Fig. 1: Valproate causes triglyceride accumulation in HepaRG cells. The lower panel shows triglyceride accumulation in HepaRG cells exposed to fatty acids and treated with valproate for 3 or 7 days. The quantification is shown in the upper panel. Results were normalized to the values of control cells and are expressed as mean ± SEM of 3 independent experiments. *p < 0.05 vs. control values.

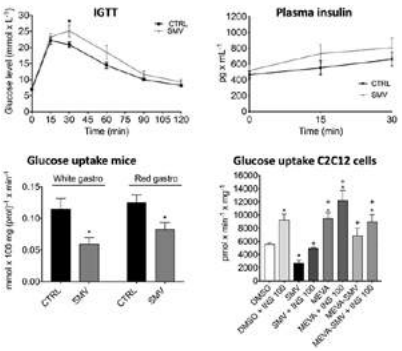

Fig. 2: Simvastatin enhances glycemia during the IGTT and impairs muscle deoxyglucose uptake. Male C57BL/6 mice were treated daily with 5 mg/kg simvastatin for 21 days. For the intraperitoneal glucose tolerance test (IGTT), mice received an i.p. glucose challenge (2 g/kg) followed by serial blood glucose determinations. Plasma insulin was determined by an ELISA. Glucose uptake by the white and red gastrocnemius was determined using ^{3}H-deoxyglucose. C2C12 myotubes were treated for 24 hours with 10 µM simvastatin, and/or 10 or 100 ng/mL insulin, and/or 100 µM mevalonate (MEVA) with 0.1 % DMSO serving as a control before determination of the ^{14}C-deoxyglucose uptake. Data are presented as the mean ± SEM. *P < 0.05 versus 0.1 % DMSO; +p < 0.05 versus 10 µM simvastatin.

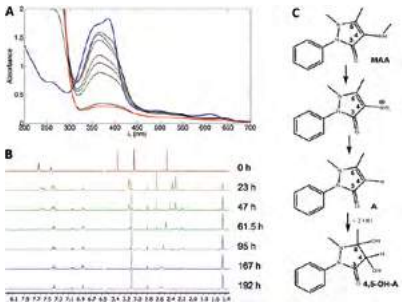

Fig. 3: Reaction of MAA with hemin and formation of MAA reaction products. (A) Hemin was dissolved in D2O and an absorption spectrum was recorded in the range of 200 to 700 nm. MAA was added to the solution in steps of 0.5 equivalents up to 4 equivalents. The blue line represents the spectrum of MAA alone and the red line hemin in the presence of 4 equivalents MAA. **(B)** Hemin was dissolved in D2O and 4 equivalents of MSS were added. The solution was kept at 37° C and 1H and 13C NMR spectra were recorded at room temperature at the time points indicated. **(C)** Based on the NMR spectra, a reaction pathway could be proposed. The pathway includes an electrophilic intermediate, which may be trapped by electron donors such as NAC and glutathione and which may be cytotoxic. MAA: N-methyl-4-aminoantipyrine, 4,5-OH-A: 4,5-dihydroxyantipyrine.

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Panajatovic MV, Singh F, Roos NJ, Duthaler U, Handschin C, Krähenbühl S and Bouitbir J (2020). PGC-1α plays a pivotal role in simvastatin-induced exercise impairment in mice. Acta physiologica (Oxford, England) 228, e13402.

Roos NJ, Duthaler U, Bouitbir J and Krähenbühl S (2020). The uricosuric benzbromarone disturbs the mitochondrial redox homeostasis and activates the NRF2 signaling pathway in HepG2 cells. Free radical biology & medicine 152, 216–226.

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Sanvee GM, Panajatovic MV, Bouitbir J and Krähenbühl S. (2019). Mechanisms of insulin resistance by simvastatin in C2C12 myotubes and in mouse skeletal muscle. Biochemical pharmacology 164, 23–33.

Connection to Clinical Practice

Stephan Krähenbühl
Clinical Pharmacology & Toxicology

Toxicological mechanisms of drugs

Adverse drug reactions can broadly be divided into type A and type B reactions. Type A reactions are typically observed when drugs are overdosed and often correspond to an exaggerated pharmacological action. Type B reactions occur at therapeutic doses in patients with susceptibility factors. Metamizole-associated agranulocytosis is a type B reaction. Our studies show that N-methyl- aminoantipyrine (MAA, primary metamizole metabolite) may react with Fe^{3+} in hemin in the bone marrow, which produces a reactive metabolite that damages granulocyte precursors. Susceptibility factors may be a high hemin concentration (hemin is produced by hemoglobin degradation) and/or an insufficient antioxidative system (suggested by our recent genome-wide association study).

Valproate is a type A drug for liver steatosis. Since treatment with valproic acid is not often mentioned as a risk factor for liver steatosis, our publication may help to make this subject more popular. Considering the possible severe consequences, patients treated with valproate may be screened for liver steatosis.

Statin-associated myotoxicity and type II diabetes are dose-dependent and therefore type A reactions. As shown, these adverse reactions can be explained by the pharmacological action of the statins: block of HMG-CoA reductase with impairment of the synthesis of cholesterol intermediates that are important for protein prenylation. Since statins act in the liver, they should not reach the systemic circulation, necessitating excellent hepatic uptake properties. If they reach the systemic circulation, they should not be transported into skeletal muscle. Skeletal muscle transport characteristics are therefore critical.

Stem Cells and Hematopoiesis

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Stem cells in development and oncogenesis

Various tumors have been shown to contain subpopulations of so-called cancer stem cells (CSCs), which are thought to be responsible for disease initiation, maintenance, metastasis and relapse after conventional anti-tumor therapies. We hypothesize that signaling pathways that regulate stem cells during development are reactivated during oncogenesis in CSCs. For example, we showed that enhanced expression of the pluripotency-related embryonic protein SOX2 associates with stemness, disease aggressiveness and therapy resistance in putative ovarian and breast CSCs (e.g. Schaefer *et al.,* 2015). Current research in our lab focuses on novel post-translational mechanisms by which SOX2 regulates stemness in cancer cells and during the reprogramming of somatic cells to induced pluripotent stem cells.

Acute myeloid leukemia is driven by chemotherapy-resistant leukemic stem cells that selectively evade immune surveillance by natural killer cells

Patients treated for leukemia often achieve remission yet subsequently die of relapse. Initiation and relapse of human acute myeloid leukemia (AML) are thought to be mediated by LSCs, defined by their ability to initiate leukemia in immunodeficient mice. Interestingly, we could recently demonstrate that AML LSCs are also immune-privileged and escape recognition and lysis by natural killer (NK) cells. Mechanistically, leukemic stem cells (LSCs) suppress for example the surface expression of ligands for activating NKG2D receptors expressed on such immune cells.
We developed an experimental xenograft model that enables robust engraftment of ~95 % of human AML and can be used as pre-clinical model to investigate new treatment avenues (Paczulla *et al.,* 2016). Here we could show that *in vivo* treatment of human AML cells with PARP inhibition (PARPi) was able to sensitize LSCs to lysis by co-transplanted human allogeneic NK cells (Fig. 1, Paczulla *et al.,* 2019). We currently focus on the detailed investigation of mechanisms underlying suppression of NKG2D ligands in stem cells and the role of PARP1 therein. Compared to healthy hematopoietic stem cells (HSC), LSCs have growth advantages induced by oncogenic mutations, but are in many ways similar to their healthy counterparts. We investigate the complex interactions between LSCs and HSCs, since their similarities makes it difficult to target LSCs without simultaneously eradicating HSCs. Like HSCs, LSCs home to protective bone marrow niches promoting stemness and therapy resistance and modify them to displace HSCs and promote their own expansion. Supported by an ERC Consolidator Grant, we investigate interactions between LSCs, HSCs and niche cells with the goal of identifying strategies that can promote the fitness of HSCs and target LSCs.

The zebrafish as a model organism in health and disease

Zebrafish offer a powerful vertebrate model for studies of development and disease. The major advantages of this model include the possibilities of conducting reverse and forward genetic screens and of observing cellular processes by *in vivo* imaging of single cells (Fig. 2, Konantz *et al.,* 2016). Moreover, pathways regulating blood development are highly conserved between zebrafish and mammals. Whole exome sequencing analyses are increasingly performed on patients presenting with suspected inherited disease but lacking classical mutations linked to the presented phenotype. We use the zebrafish to explore the functional relevance of genes that are identified by this method, such as *SRP54* (Carapito, Konantz *et al.,* 2017) or *NCKAP1L* (Castro *et al.,* 2020). We currently use a novel zebrafish *srp54* mutant to show that the heterogenic phenotypes observed in patients, rang-

ing from mild congenital neutropenia to SDS-like disease, may be due to different dominant negative effects of mutated SRP54 proteins and analyze potential underlying mechanisms. Zebrafish are also used in our laboratory to xenograft human tumor cells and monitor tumor-induced angiogenesis, invasiveness, and response to a range of treatments *in vivo* and in real time (e. g. Jacob, Alam, Konantz *et al.,* 2018).

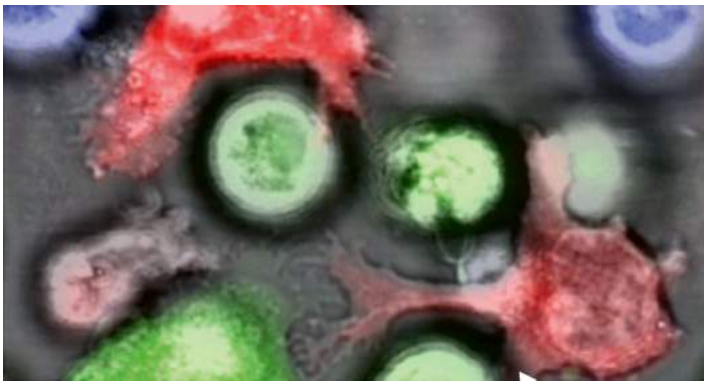

Fig. 1: Absence of NKG2D ligands defines leukemia stem cells and mediates their immune evasion. Natural killer cells (red, CellTracker™ CM-DiI Dye) attack normal leukemia cells (green, CellTrace™ CFSE) but not leukemia stem cells (blue, CellTracker™ Blue CMAC Dye). This is because the latter use stem cell-specific mechanisms to suppress the expression of key recognition proteins (NKG2D ligands) on the cell surface (Paczulla *et al.,* Nature 2019). Image: Christoph Schürch.

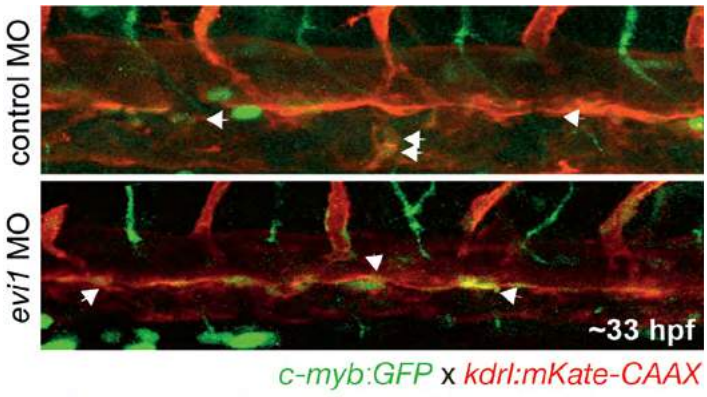

Fig. 1: *evi1* regulates HSC emergence from the ventral dorsal aorta. During embryonic development, definitive hematopoietic stem cells (HSCs) arise from aortic endothelial cells (EC) by a process known as endothelial-to-hematopoietic transition (EHT). *In vivo* live imaging indicates that suppression of the transcription factor *evi1* impairs endothelial cell progression to hematopoietic fate cell autonomously: In control-injected embryos, *c-myb:eGFP*$^{+}$ hematopoietic cells directly arise from *kdrl:mKate*$^{+}$ ECs along the VDA as previously described: ECs, normally flattened in appearance, transform into double-positive *kdrl*$^{+}$*c-myb*$^{+}$ cells of spherical shape before budding into the lumen of the dorsal aorta (DA). However, after knockdown of *evi1* using Morpholino Oligonucleotides (MO), *kdrl*$^{+}$*c-myb*$^{+}$ cells start transitioning to spherical shape but are not able to emerge from the DA. Confocal time-lapse live imaging was performed in *Tg(c-myb:GFP; kdrl:mKate-CAAX)* embryos from 28 to 42 hpf. Shown is one representative time point in which the transformation from hemogenic EC to the hematopoietic fate is visible, indicated by the white arrowheads. Merged images are shown. White arrowheads denote double-positive cells (Konantz *et al.,* EMBO J. 2016). Image: Anna Lenard.

Connection to Clinical Practice

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1) NK cells in AML treatment
2) Next generation sequencing molecular analysis of AML cells
3) Mouse leukemia models
4) Identification of new mutations associated with neutropenia and immune disorders
5) Cancer stem cells, zebrafish xenograft models

Selected Publications

Castro CN, Rosenzwajg M, Carapito R, Shahrooei M, Konantz M, Khan A, Miao Z, Groß M, Tranchant T, Radosavljevic M, *et al.* (2020). NCKAP1L defects lead to a novel syndrome combining immunodeficiency, lymphoproliferation, and hyperinflammation. J Exp Med 217.

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Cardiac Surgery and Engineering

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3D Engineered tissues as angiogenic therapeutic approach and as functional cardiac models

The main goal of our group is to investigate repair therapies based on engineered tissues (patches) to induce safe and efficacious angiogenesis and to rescue hibernating myocardium in a chronic ischemic myocardium. The three-dimensional (3D) bioreactor culture of heterogenous Stromal Vascular Fraction (SVF) cells aims to standardize the production of engineered patches (Fig.1). SVF as a cell population is capable of releasing a broad secretome range comprising angiogenic and pro-survival factors. Further aims are to develop *in vitro* functional cardiac models to investigate processes of myocardial repair and regeneration.
Research is funded by the Swiss National Science Foundation, Swiss Heart Foundation, the University Hospital of Basel (USB), and the University of Basel (Unibas).

Patches engineered by cells with a high angiogenic and repair potential
In this approach, we use human adipose tissue-derived SVF cells as a heterogeneous cell population with a high angiogenic potential thanks to the presence of numerous endothelial and mural progenitors (collaboration with A. Scherberich, Tissue Engineering Group, Department of Biomedicine, Unibas). We demonstrated that perfusion-based bioreactor culture supported the maintenance of endothelial and mural cells as compared to static culture, thereby accelerating whole construct vascularization and support of cell survival upon implantation in a subcutaneous nude rat model (Fig. 1–2). Moreover, medium conditioned during 3D perfusion- based culture of SVF was showed to partially rescue damaged cardiomyocyte function during monolayer culture under sever hypoxic condition (<1% of oxygen) (Mytsyk and Isu, 2018). An ongoing *in vivo* diseased study aims to investigate the repair potential of SVF-perfused patches in nude rat model of cardiac ischemia (in collaboration with the Department of Cardiac Surgery, USB).

3D functional cardiac models
Our angiogenic engineered tissues might also affect cardiac repair and regeneration by influencing cardiomyocyte maturation and functionality while increasing progenitor cell recruitment. Therefore, we aim to generate a 3D functional cardiac models as a tool to investigate the interactions of SVF cells' secretome and cardiomyocytes. We hypothesize that the recapitulation of the proper physiological conditions, mimicking the native tissue environment, enhanced the cardiomyocyte maturation, 3D organization and functionality. Culture medium perfusion systems were employed to mimic the highly dense capillary network present in the myocardium to ensure the cardiomyocyte survival *in vitro* (Marsano, *et al.* 2010; Maidhof, *et al.* 2010; Cerino, *et al.* 2016). Mechanical stimulation (collaboration with the Politecnico of Milano, Italy and Politecnico of Torino, Italy) was employed to greatly promote rat neonatal cardiomyocytes or human induced pluripotent stem cell-derived cardiomyocyte maturation and contractility both at the micro- and macro- scale (Marsano, *et al.* 2016, Massai and Pisani, *et al.* 2020). Microfluidic culture systems harnessing mechanical stimulation was recently generated to recapitulate some of key steps of a scar formation (Occhetta, Isu, *et al.* 2019).
A novel 24-multi-well bioreactor (Patent number: EP19165964) was also developed to culture mm-scale engineered cardiac constructs in a highly controlled environment under multi-physical stimulations (isotonic and auxotonic loads combined with electrical stimulation).

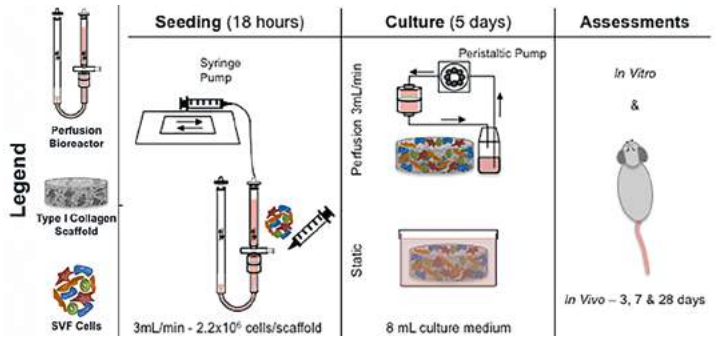

Fig. 1: Scheme of the SVF-based patch study. Summary of the main steps to generate SVF cell-based engineered tissues (patches). SVF cells were seeded on a collagen-based scaffolds under direct alternated perfusion for 18 hours followed by 5 days of culture either under direct uni-directional perfusion or in static condition. The resulted patches were assessed *in vitro* and *in vivo* (in subcutaneous pockets of nude rats).

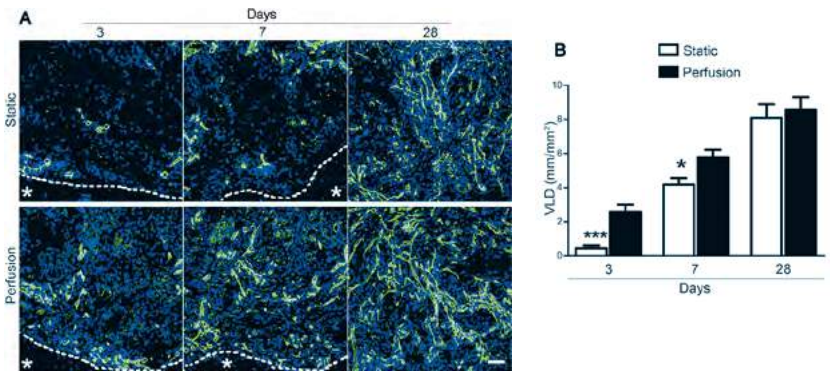

Fig. 2: Perfusion accelerated *in vivo* vascularization of engineered tissues. Engineered patches generated either under perfusion or in static culture were analysed after 3, 7, and 28 days *in vivo*. **(A)** Representative immunofluorescence images stained for endothelial cells (CD31; green). Dashed lines outline the border between the patch and rat tissue (identified by the *). Scale bar = 50 µm. **(B)** VLD quantification normalized over the analysed area.

Selected Publications

Massai D†, Pisani G†, Isu G, Rodriguez Ruiz A, Cerino G, Galluzzi R, Pisanu A, Tonoli A, Bignardi C, Audenino AL, Marsano A† and Morbiducci U† (2020). Bioreactor Platform for Biomimetic Culture and in situ Monitoring of the Mechanical Response of *in vitro* Engineered Models of Cardiac Tissue. Front. Bioeng. Biotechnol. † equally contributing authors.

Isu G, Robles Diaz D, Grussenmeyer T, Gaudiello E, Eckstein F, Brink M, Marsano A. (2020). Fatty acid-based monolayer culture to promote *in vitro* neonatal rat cardiomyocyte maturation. Biochim Biophys Acta Mol Cell Res. 1867(3):118561.

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Connection to Clinical Practice

Prof. Dr. Friedrich S. Eckstein
Dr. David Santer

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In vivo animal models to tackle vascularization issues at the macro- and micro-scale

Cardiovascular diseases and chronic myocardial ischemia cause progressive deterioration of cardiac function and lead to end-stage heart failure. However, the restore of blood flow both at the macro and micro-level and the additional treatment with cardioprotective factors in the hypo-perfused myocardial areas could preserve cardiomyocyte survival and rescue their contraction, therefore improving the overall cardiac function.

Macro-circulation. Revascularization strategies aim to use autologous blood vessels (e. g. saphenous vein) as coronary artery bypass grafts (CABG). However, some patients might need an alternative to the autologous vessels due to recurrent operations or morbidity issues. Nowadays there still lacks a valid alternative to autologous grafts used for CABG. Our research group has developed a vascular graft made of acetobacteria-derived nano cellulose reinforced by a cobalt-chrome mesh. Previous results showed the cellulose vascular graft's patency and its colonization by host vascular cells following a one-month implantation.

The clinical research counterpart has established two long term studies to test the patency of the cellulose vascular grafts used as carotid artery replacement in sheep and as CABG in pigs. Micro-circulation. 3D SVF cell-based patches as an adjuvant angiogenic and repair therapy could provide control over the targeted area, reducing undesired systemic effects, while enhancing implanted cell survival, compared to intramyocardial cellular injections. A nude rat model of chronic cardiac ischemia was recently established to test the angiogenic and repair potential of SVF cell-based patches.

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From 3D culture models to regenerative surgery

The common denominator of the research projects in the group is related to the establishment of 3D cell culture systems, combining interdisciplinary efforts in cell biology, engineering technologies and materials science. These systems are used as models to investigate fundamental aspects of tissue development/pathologic changes, or as grafts to induce tissue regeneration. Our main focus is the development of cartilage and bone/bone marrow tissues, though the developed expertise has also been implemented in collaboration with other groups in different areas, including tumor modelling.

Cartilage tissue engineering and regeneration (Prof. A. Barbero)
Our goal is to repair cartilage defects of traumatic or degenerative nature using grafts engineered from autologous cells. We discovered that nasal chondrocytes (NC) have a larger and more reproducible capacity for cartilage regeneration as compared to other cell types, including articular chondrocytes. Moreover, NC display features of environmental plasticity and can thus genetically and functionally adapt to implantation in a joint. Our concept has been translated into a first-in-man study for the treatment of focal cartilage defects in the knee (Fig. 1). Based on the promising findings, we are now coordinating a multicenter phase II trial (BioChip) for the same indications, funded under the EU-Horizon2020 program. In parallel, with the goal to treat also degenerative cartilage diseases (e. g., osteoarthritis), we are currently investigating the capacity of NC to regulate the main pathological processes activated in a joint by inflammation and abnormal loading. In the framework of an ERC Synergy project (collab. with F. Rijli, FMI), we target understanding the molecular and epigenetic mechanisms endowing NC with their distinct functionalities.

Vascularized bone and bone marrow engineering (Prof. A. Scherberich)
One goal of the program is the controlled development of bone / bone marrow ossicles using human cells, as models for human hematopoiesis and as grafts for bone regeneration. We demonstrated that mesenchymal progenitors from human bone marrow or adipose tissue can recapitulate the developmental process of endochondral ossification. This involves the formation of cartilaginous intermediate tissues which robustly and efficiently remodel into functional ossicles upon implantation. The system was used to investigate interactions between stromal and hematopoietic cell components (collab. with T. Schroeder, D-BSSE) and to generate osteoinductive extracellular matrices (collab. with P. Bourgine, Univ. Lund).
An associated goal is the efficient vascularization of the implanted grafts to support scaled up bone regeneration. We found that axial vascularization of engineered implants with an arterio- venous (AV) bundle leads to a rapid formation of vascular networks (Fig. 2). This principle was used to reconstruct maxillary bone in a patient following carcinoma excision. The bone defect was satisfactorily restored by ectopic prefabrication of a vascularized bone graft using autologous fat-derived cells and an AV bundle, which was transferred into the defect site. Studies are ongoing to adapt and evolve the paradigm for use in the challenging clinical settings of infected bone.

Engineering platforms for 3D cell culture
Dynamic 3D cell culture under perfusion flow (Fig. 3A) has been introduced to model *in vitro* tissue development and physiological homeostatic processes (e. g., bone matrix deposition and resorption, stromal-vascular-hematopoietic cell interactions) as well as pathologic settings (e. g., cartilage degeneration, hematologic malignancies, solid tumor microenvironment) (collab with R. Skoda , C. Lengerke,

M. Bentires, G. Hutter). Generated systems have shown patterns of response to drugs or immunotherapy which cannot be mimicked by 2D cultures or by simple spheroids.

The bioreactor-based culture tools are being further developed (i) to introduce automation/control towards streamlined manufacturing of clinical grafts (Fig. 3B) or (ii) to increase throughput for larger scale tests in miniaturized compartments (Fig. 3C).

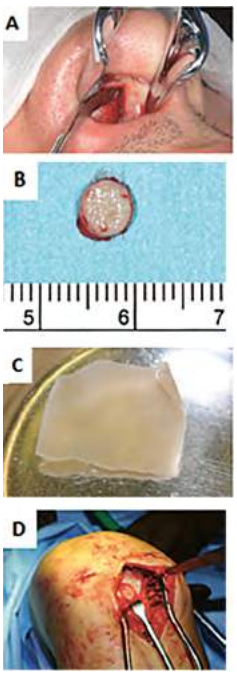

Fig. 1 Engineering of autologous nasal cartilage grafts. **(A)** Collection of a nasal cartilage biopsy from a patient, under local anesthesia and with minimal donor site morbidity. **(B)** Collected specimen of nasal cartilage septum, from which cells are isolated and expanded in culture. **(C)** Tissue engineered cartilage graft (macroscopic appearance) inserted in the knee cartilage defect of the patient following intraoperative shaping **(D)**. (See ref 5 for more details.)

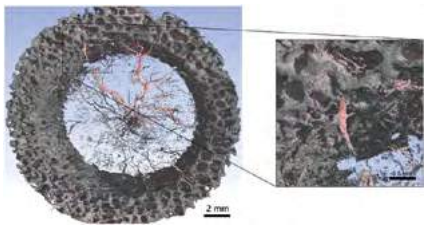

Fig. 2 Phosphotungstic acid-enhanced, three-dimensional micro-computed tomography reconstruction (left picture), showing ramified, radial vascularization (red staining) of an engineered osteogenic implant developing from an arterio-venous (AV) bundle (in the very center of the construct), after 8 weeks *in vivo.* The implant was initially inserted inside a hollow cylinder of devitalized bone (structure in grey) mimicking osteonecrosis. This dead material is also colonized by vascular structures (magnified picture in the right). (See ref 2 for more details)

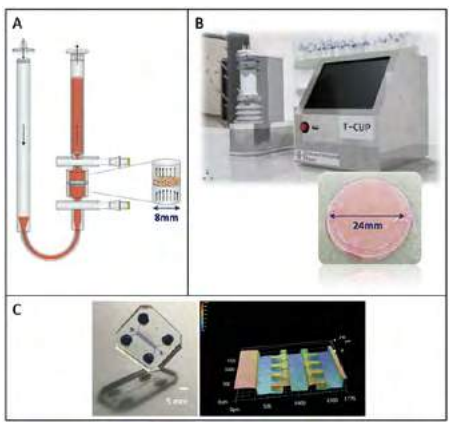

Fig. 2 (A) Direct perfusion system for efficient cell seeding and culture into 3D porous scaffolds to model *in vitro* tissue development and mimic physiological homeostatic processes or pathological settings. **(B)** Bioreactor-based system with automation and monitoring/control features for the clinical manufacturing of cartilage grafts. **(C)** Microfluidic-based system for dynamic loading of chondrocyte cultures, modelling traits of osteoarthritis, and testing possible therapeutic effects of soluble compounds. (See refs 1&3 for more details)

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Epple C, Haumer A, Ismail T, Lunger A, Scherberich A, Schaefer DJ, Martin I (2019). Prefabrication of a large pedicled bone graft by engineering the germ for de novo vascularization and osteoinduction. Biomaterials 192:118–127.

Bourgine PE, Klein T, Paczulla A, Shimizu T, Kunz L, Kokkaliaris K, Coutu D, Lengerke C, Skoda R, Schroeder T, Martin I (2018). *In vitro* biomimetic engineering of a human hematopoietic niche with functional properties. Proc Natl Acad Sci USA 115: E5688–E5695.

Occhetta P, Pigeot S, Rasponi M, Dasen B, Mehrkens A, Ullrich T, Kramerd I, Guth-Gundel S, Barbero A, Martin I (2018). Developmentally inspired programming of adult human mesenchymal stromal cells toward stable chondrogenesis. Proc Natl Acad Sci USA 115:4625–4630.

Mumme M, Barbero A, Miot S, Wixmerten A, Feliciano S, Wolf F, Asnaghi MA, Baumhoer D, Bieri O, Kretzschmar M, Pagenstert G, Haug M, Schaefer DJ, Martin I, Jakob M (2016). Nasal chondrocyte-based engineered autologous cartilage tissue for the repair of articular cartilage defects: an observational first-in-human trial. Lancet 388: 1985–1994.

Connection to Clinical Practice

Prof. C. Kunz, PD Dr. M. Mumme & Prof. A. M. Müller, Prof. D. J. Schaefer, Prof. S. Schaeren

Maxillofacial Surgery / Orthopaedics and Traumatology / Plastic, Reconstructive, Aesthetic and Hand Surgery / Spinal Surgery

Engineered cellular grafts for regenerative surgery

Facial and tracheal cartilage reconstruction

Engineered nasal cartilage grafts, previously successfully used for reconstruction of the alar lobule of the nose, are being investigated for the reconstruction of the nasal cartilage septum after perforation (M. Haug, B. G. Kaiser). Studies are ongoing to explore the use of epithelialized cartilage grafts for the management of empty nose syndromes (S. Negoias) and/or tracheal defects (D. Lardinois)

Articular cartilage and intervertebral disc repair.

Following the demonstration of feasibility and safety of nasal chondrocyte-based engineered cartilage for the treatment of knee cartilage injuries, a phase II study (total of 108 patients in 5 international centers) is ongoing to investigate efficacy (M. Mumme). Work is in progress to obtain regulatory approval (temporary authorization) and funding for the treatment of an extended set of orthopaedic indications using engineered nasal cartilage (M. Mumme). Pre-clinical studies are also exploring the use of nasal chondrocytes to engraft in intervertebral discs and block their degeneration (A. Mehrkens).

Bone repair

Treatment of humerus fractures in elderly individuals previously indicated the safety and biological functionality of stromal vascular fraction (SVF) cells intraoperatively derived from autologous adipose tissue. Grafts based on SVF cells are currently being investigated for axially-vascularized bone graft prefabrication in the reconstruction of the maxilla (C. Jaquiery, T. Ismail, A. Haumer, F. Thieringer), for congenital digit defects (A. Kämpfen) and for infected long bone defects (R. Osinga, M. Clauss, M. Morgenstern).

Musculoskeletal Research

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Form-Function-Relationship in the locomotor apparatus and application in the living as diagnostic tools or for monitoring the outcome of joint surgery.

CT-Osteoabsorptiometry (CT-OAM) – a new investigation technique in the field of mummy research

The objective of the current study was to investigate the applicability of CT-OAM on mummies for the load analysis of joints. In order to clarify whether apparent malpositions of the spinal column existed during lifetime or occurred post-mortem, we evaluated the long-term loading patterns within the endplates of 8 mummies. The implementation of CT-OAM on mummies for load analysis of joints was feasible. The mineral density distribution within the endplates was not homogenous but followed distinct distribution patterns. The vertebra columns without malposition showed an almost even circular allocation of the density maxima within thoracic endplates, the spines with kyphosis displayed a concentration of the density maxima in the ventral area, and the spines with scoliosis exhibited a predominant localization of the density maxima on the concave side. The examined endplates showed characteristic reproducible density patterns consistent with the long-term loading conditions. Pathological load distributions can be visualized with help of CT-OAM before macroscopical changes appear and can therefore help to solve paleopathological and paleoarchaeological questions.

CT-calculometry (CT-CM): advanced NCCT post-processing to investigate urinary calculi

This study aimed at evaluating the potential of CT-calculometry (CT-CM) as a novel method to determine mineralisation, composition, homogeneity and volume of urinary calculi based on preoperative non-contrast-enhanced computed tomography (NCCT) scans. CT-CM was performed in preoperative NCCTs of 25 patients treated for upper tract urinary calculi by ureterorenoscopy or percutaneous nephrolithotomy. Absolute mineralisation values were achieved by use of quantitative CT-osteoabsorptiometry and compared to Fourier infrared spectroscopy as a reference for stone composition. Homogeneity was assessed by advanced software-based NCCT post-processing and visualised by using a maximum intensity projection algorithm. Volumetric measurement was performed by software-based threedimensional reconstruction. CT-CM was feasible in all of the 25 NCCTs. Absolute mineralisation values calculated by quantitative CT-OAM might be used to identify the most frequent stone types. High levels of inhomogeneity could be detected even in pure component stones. Volumetric measurement could be performed with minimal efort. CT-CM is based on advanced NCCT postprocessing software and represents a novel and promising approach to determine mineralisation, composition, homogeneity, and volume of urinary calculi based on preoperative NCCT. CT-CM could provide valuable information to predict outcome of different stone treatment methods.

Adaption of the bony-microstructure of the human glenoid cavity due to long-term biomechanical loading

Structural arrangements of the bony microstructure of a joint through adaptational processes are thought to be determined by the biomechanical demands. Pursuing this theory of “form follows the biomechanical function”, the load distribution of the glenoid cavity, as it is mirrored in its mineralization pattern, should also have an impact on the trabecular network below. To prove this hypothesis, we analyzed the mineral distribution and the distribution of the architectural parameters of the trabecular network below. Our findings clearly show an inhomogeneous but regular and reproducible mineral distribution. Regarding the trabecular network below,

the distribution of the analyzed parameters also revealed an inhomogeneous distribution with a regular pattern in correlation with the biomechanical impact. With increasing depth, the trabecular network administers the expression of each structural parameter given that the strain energy becomes increasingly evenly distributed and changes from a high degree of differentiation just beneath the subchondral bone plate to a more equal distribution within the deeper areas. Thus, the biomechanical situation of a joint directly influences the bony formation of the subchondral bone plate and trabecular network below.

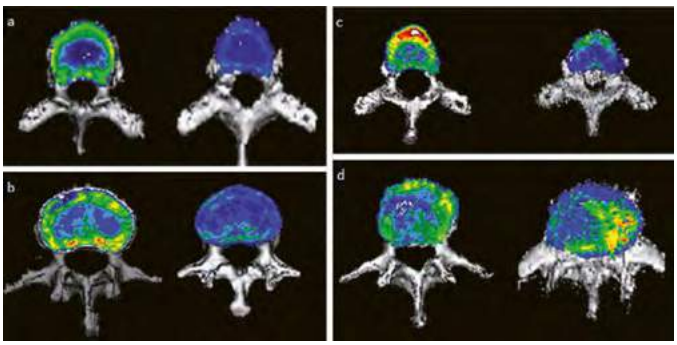

Fig. 1: Examples of the mineralization distribution, **a** densitograms of thoracic endplates in vertebral columns without malposition, on the left: Mummy Lausanne 2, on the right: L-25–14, **b** densitograms of lumbar endplates in vertebral columns without malposition, on the left: Mummy Lausanne 2, on the right: L-25–14 , **c** densitograms of thoracic end-plates in vertebral columns with kyphosis, on the left: Mummy Barfuesser, on the right: L-32–13 **d** densitograms of lumbar endplates in vertebral columns with scoliosis, on the left: Mummy Baroness von Kniestaett, on the right: L-05–15.

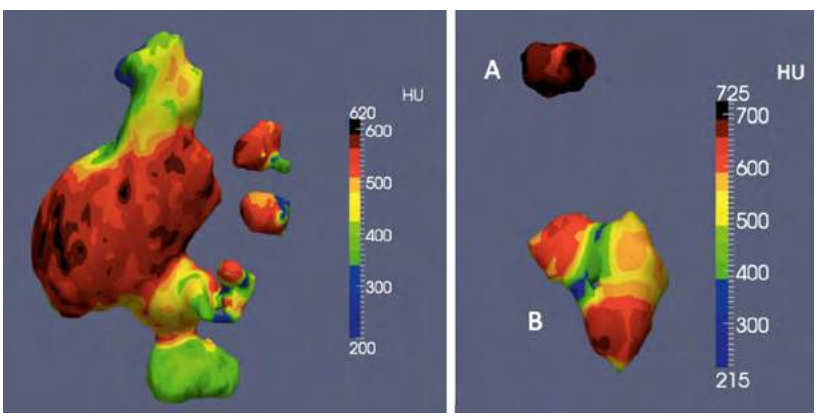

Fig. 3: Homogeneity illustration in a renal staghorn-stone consisting of pure urinary acid (left image). Homogeneity distribution in two stones consisting of urinary acid. Calculus **(a)** appears more homogenous compared to stone **(b)** (right image)

Selected Publications

Hoechel S, Deyhle H, Toranelli M, Müller-Gerbl M. Osteoarthritis alters the patellar bones subchondral trabecular architecture. J Orthop Res 2017 Sep;35(9):1982–1989

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Khimchenko A, Bikis C, Pacureanu A, Hieber S, Thalmann P, Deyhle H, Schweighauser G, Hench J, Frank S, Müller-Gerbl M, Schulz G, Cloetens P, Müller B. Volumetric Nanoscale Imaging: Hard X-Ray Nanoholotomography: Large-Scale, Label-Free, 3D Neuroimaging beyond Optical Limit (Adv. Sci. 6/2018). Adv Sci (Weinh) 2018 Jun; 5(6): 1870036.

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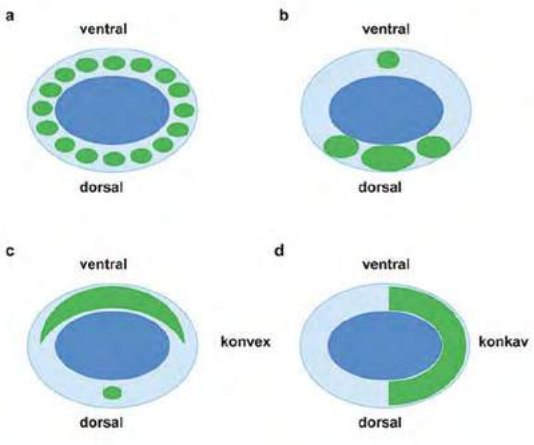

Fig. 2: Schematic illustration of the found mineralization patterns, dark-blue presents the little mineralized center, light-blue the higher mineralized marginal zone and green the localization of the density maxima **a** normal thoracic endplate, **b** normal lumbar endplate, **c** kyphotic endplate, **d** scoliotic endplate.

Pulmonary Cell Research

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Causes and control of tissue remodelling in chronic inflammatory lung diseases

Chronic inflammatory lung diseases (CILD) include asthma, chronic obstructive pulmonary disease (smokers lung), and fibrotic disorders of the lung. The prevalence of all CILD is increasing worldwide since several decades. All CILD have an increase susceptibility to bacterial or viral infections, which cause exacerbations of the disease. Together, they incurred the fourth highest health care costs and significantly reduced education and productivity of the patients. None of the CILD can be cured with available therapies, only the symptoms can be controlled. The American Thoracic Society suggested in 2017 that a cure for CILD would only be found when we understand the cause and role of tissue remodelling, which occurs in all such diseases. Recent studies implied that the pathogenesis of CILD results from a disturbed response of the lung to environmental factors such as allergens, dust, ashes, or microorganisms, as well as humidity, temperature, exercise or stress. Each of these factors alone, or together, trigger epigenetic events that become persistent. Today, it is assumed that the first epigenetic event has to occur during late embryogenesis and early childhood, followed by a second event later in life. However, the nature of these epigenetic events seem to be disease specific and remain largely unknown.

Asthma affects 300 million people worldwide and is characterised by chronic airway inflammation and airway wall remodelling. Today, none of the available drugs can reverse airway wall remodelling, while inflammation can be well controlled. This supports the idea that both pathologies are largely independent. The only therapy that has been shown to reduce airway wall remodelling is bronchial thermoplasty, but the mechanism is largely unknown. In our latest studies, we have proven that the expression of an important epigenetic regulator, protein methyl arginine transferase 1(PRMT1), is constitutively expressed in mesenchymal cells of asthma patients. This is due to the over-expression of C/EBP-β, which suppresses miR-19a, and thereby stimulates the expression of a proliferative signalling pathway. PRMT1 is a major methyl donor for histones, which control the accessibility of pro-inflammatory genes and mitochondria regulating factors. Our research revealed that many well-known asthma triggers, such as TGF-β, PDGF-BB, IL-4, and IL-1β, stimulate the expression of PRMT1 by upregulating C/EBP-β. Thus, we found a mechanism that merges the action of different asthma stimulating factors. Furthermore, bronchial epithelial cells from asthma patients secrete heat shock protein-60 (HSP60), which stimulates the expression of PRMT1 in sub-epithelial mesenchymal cells. Thereby, HSP60 drives remodelling and mitochondria activity in asthma. Bronchial thermoplasty reduced the secretion of HSP60 in asthma patients, and thereby interrupted the remodelling driving signalling cascade of PRMT1. Independent from PRMT1, we showed that non-immune IgE stimulates an autologous signalling loop through inhibition of PTEN by increased synthesis of miR-21. This study indicates that the increased IgE found in many asthma patients contributes to remodelling, even in the absence of an allergen.

Connection to Clinical Practice

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Translational medicine studies in chronic inflammatory lung diseases

Our studies are focused on chronic inflammatory lung diseases. We link basic and clinical research to find novel bio-markers and therapeutic targets for asthma, COPD, ACOS, and idiopathic fibrosis. None of these diseases is easy to diagnose, and despite symptom control, curative therapies are not available. All studies are based on large patient cohorts, diagnosed according to international guidelines. We preform risk factor analysis and validate new biomarkers, as predictors for exacerbation and survival of patients.

The clinical studies are enabled by a close collaboration of pulmonologists, thoracic surgeons, haematologists, pathologists, and basic researchers. This translational approach benefits from the close co-location of the Clinic of Pneumology and the research laboratory (DBM). Using human lung samples of patients we are able to isolate primary diseased human epithelial cells, fibroblasts and bronchial smooth muscle cells and provide them to our collaborators in other countries. The cells are analysed for disease specific expression and regulation patterns of biomarkers and inflammatory mediators. This also allows us to identify novel disease specific pathophysiological pathways and test new medications on the cellular level. Components of tissue remodelling are studied under the influence of allergic and non-allergic stimuli. In addition to this translational research projects numerous investigator driven non-commercial randomised studies are performed to optimise patient's safety during bronchoscopy in COPD patients. Our clinic leads collaborative studies with groups in Germany, Italy, Spain, France, the Netherlands, Belgium, UK, Serbia and Greece.

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Benmerzoug S, Rose S, Bounab B, Gosset D, Duneau L, Chenuet P, Mollet L, Le Bert M, Lambers C, Geleff S, Roth M, Fauconnier L, Sedda D, Carvalho C, Perche O, Laurenceau D, Ryffel B, Apetoh L, Kiziltunc A, Uslu H, Albez FS, Akgun M, Togbe D and Quesniaux VFJ (2018). STING-dependent sensing of self-DNA drives silica-induced lung inflammation. Nat Commun. 9 5226.

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Sun Q, Fang L, Roth M, Tang X, Papakonstantinou E, Zhai W, Louis R, Heinen V, Schleich FN, Lu S, Savic S, Tamm M and Stolz D (2019). Bronchial thermoplasty decreases airway remodelling by blocking epithelium-derived heat shock protein-60 secretion and protein arginine methyltransferase-1 in fibroblasts. Eur Respir J. 54 1900300.

Cell Adhesion

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*left during report period

Cell adhesion in health and disease

All multicellular organisms depend on adhesion between cells and of cells to the surrounding matrix. Our long-standing aim is to identify how cells sense and adapt adhesion on molecular, cellular and tissue levels and to apply this knowledge for identification of novel treatment approaches. We primarily focus on desmosomes, a supramolecular complex required for stable interactions of all epithelial and some non-epithelial cells (Fig. 1). The relevance of this junction is evident by a number of severe diseases caused by desmosome dysfunction, e. g. as a result of mutations in desmosomal proteins (resulting in arrhythmogenic cardiomyopathies, ACM) or of autoantibodies (causing pemphigus, a blistering skin disease).

Plasticity and regulation of desmosomes

While the molecular composition of desmosomes is well defined, much less is known if and how the adhesive function is modulated in response to external and internal stimuli. We showed that desmosomal adhesion, until now considered to be rather static, can rapidly adapt to external or internal stimuli such as mechanical load on junctions or cAMP-dependent signaling. We identified the cytoskeleton as essential player to maintain desmosomal adhesion homeostasis (Fig. 2). Using biophysical techniques such as single molecule force spectroscopy, we demonstrated that intermediate filaments, which are anchored at desmosomes, modulate the adhesive properties of adhesion molecules and their stability in the membrane. This regulatory function is compromised in pemphigus, in which autoantibody binding to desmosomal molecules causes uncoupling of intermediate filaments from the desmosome, subsequent destabilization of cell-cell adhesion and blister formation in the skin and mucous membranes. In contrast, the actin cytoskeleton and associated proteins such as α-adducin indirectly modulate desmosomal turnover by shaping clusters of adhesion molecules which is required during desmosome assembly. Accordingly, adducin-deficient skin fails to adapt to increased mechanical load.

To test the relevance of desmosomal adhesive function in a whole animal model, we generated a mouse line in which a putative binding mechanism of desmosomal adhesion molecules is mutated (Fig. 3). The exchange of a single tryptophane of the adhesion molecule Dsg2 (Dsg2-W2A) results in a severe cardiac phenotype which reproduces the major criteria of ACM on the pathological and clinical level. This not only demonstrates that loss of adhesion is a major trigger of ACM but also gives us an excellent tool to study the impact of adhesion loss on cellular and tissue functions.

Beyond adhesion? Non-canonical functions of desmosomal molecules

Although desmosomes are primarily described as cell adhesion complexes, they also contribute to cellular functions beyond mere adhesion. As example, we showed that desmosomal adhesion molecules are downregulated at the invasion front of pancreatic ductal adenocarcinomas and a loss increases Slug-dependent invasion and malignant behavior in knockout models.

To our surprise, we also detected the expression of distinct desmosomal adhesion molecules in non-adherent cells such as CD4+ T cells. Moreover, tissue-specific loss of Dsg2 in several mouse models led to reduced numbers of regulatory T cells. Application of these knockout lines in distinct disease models will outline the functional relevance of this expression.

Together, these results fuel the conceptual switch from desmosomes being “sticky glue” to representing active modulators of cellular behavior and tissue functions.

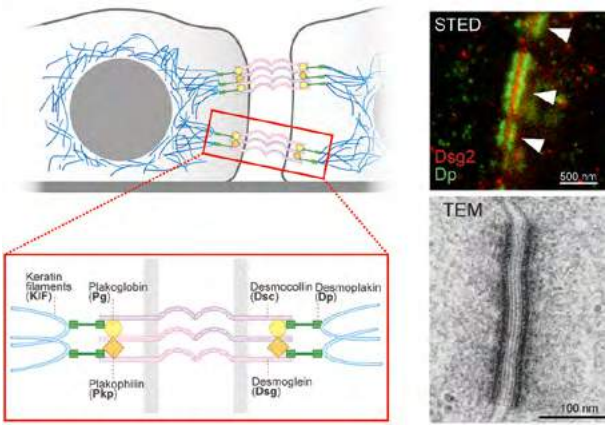

Fig. 1:
Structure of the desmosome
Outlined as schematic and visualized by superresolution (STED) or transmission electron microscopy (TEM).

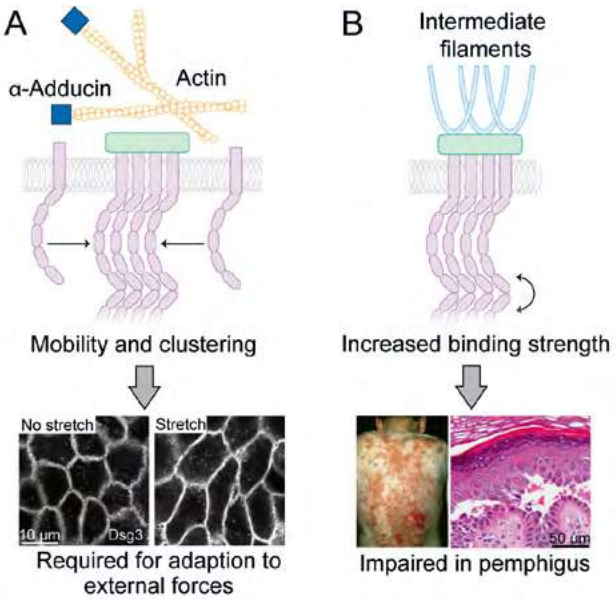

Fig. 2:
Cytoskeletal control of desmosome plasticity and function
(A) Adaption of cell-cell adhesion to mechanical load requires the actin cy-toskeleton and associated proteins such as α-adducin.
(B) Keratin-dependent modulation of desmosomal adhesive forces is impaired in the bliste-ring skin disease pemphigus.

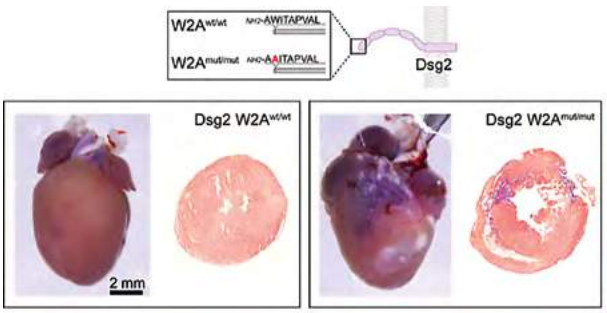

Fig. 3: Loss of cell adhesion causes an arrhythmogenic cardiomyopathy phenotype
Exchange of a N-terminal tryptophane to an alanin (W2A) in the desmosomal adhesion molecule Dsg2 results in cardiac dilation, calcification and fibrosis.

Selected Publications

Hiermaier M, Kliewe F, Schinner C, Stüdle C, Maly PI, Wanuske M-T, Rötzer V, Endlich N, Vielmuth F, Waschke J, Spindler V (2020). The actin binding protein α-adducin modulates desmosomal turnover and plasticity. J Invest Dermatol.,Epub:doi:10.1016/j.jid.2020.09.022.

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Vielmuth F, Wanuske M-T, Radeva MY, Hiermaier M, Kugelmann D, Walter E, Buechau F, Magin TM, Waschke J, Spindler V (2018). Keratins Regulate the Adhesive Properties of Desmosomal Cadherins through Signaling. J Invest Dermatol. 138(1):121–131.

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Embryology and Stem Cell Biology

Verdon Taylor

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Understanding brain development, maintenance and disease

Control of brain development from mice to human
How the billions of neurons and glial cells of the mammalian brain are generated from a pool of multipotent stem cells in a precise and orderly fashion is unclear. Using mouse genetics and human pluripotent stem cells (iPSCs) we are examining the molecular mechanisms controlling neural stem cell (NSC) maintenance, differentiation and fate choices. We perform proteomic and transcriptomic analysis of NSCs, progenitors and newly generated neurons at different stages of mouse development and from human iPSC cultures at the population and single cell levels and obtain unprecedented insight into the transcriptional dynamics and heterogeneity in stem and progenitor cells during neurogenesis.

Regulation of neurogenesis at the signaling and transcriptional levels
Neurogenesis continues in the adult mouse forebrain and hippocampus from NSCs, most of which are quiescent and only a few enter the cell cycle at any point in time. Notch signaling is critical for NSC maintenance. Of the four Notch proteins in mammals, we showed that Notch2 conveys quiescence to adult NSCs by regulating cell cycle-controlling genes and inducing expression of Id4, which prevents cell cycle entry. We found that Notch1 and Notch2 regulate different aspects of neurogenesis, therefore, we are comparing the regulome and interactome of Notch1 and Notch2 in the developing nervous system. In addition, we address the functions of other signaling pathways in the control of neurogenesis including Hippo signaling during cerebral cortex development. We analyze how different Tead transcription factors, the Hippo effectors, control different aspects of neurogenesis.

Regulating NSC fate at the post-transcriptional levels
The composition of a cell's proteome determines its phenotype and function. Protein expression can be regulated at the mRNA level. We showed how the RNAse-III Drosha is an intrinsic regulator of adult NSC maintenance and differentiation though a novel mechanism of direct mRNA cleavage. Drosha represses expression of key transcription factors in NSCs by cleaving hairpins in their mRNAs. Intrigued by how a ubiquitous enzyme, Drosha, can cleave mRNAs in what we found to be a cell-type and stage-specific fashion, we use quantitative proteomics combined with co-immunoprecipitation and affinity pull-down assays to determine the Drosha interactome in NSCs. We identify novel protein complexes and examine how components of these complexes regulate Drosha function and cell fate.

Stem and progenitor cells and the origin of brain tumors
Gliomas are the most common primary brain tumors in adults and the prognosis in many cases is very poor. NSC-like cells exist in brain tumors leading to the question of whether they require the same molecular signals as normal NSCs. We are elucidating molecular mechanisms underlying transformation of neural stem and progenitor cells into tumor cells. Notch signaling has often been implicated as an oncogenic pathway in glioma. Contrary to predictions, we have uncovered a tumor suppressive function for the Notch pathway in brain tumor subtypes. We are currently addressing the differences and similarities between glioma stem cells and NSCs on the molecular level.

Modelling human disease with iPSCs
Human iPSCs can be generated from normal or diseased individuals and retain the ability to generate all cell-types of the adult organism. We are developing differen-

tiation protocols to drive iPSCs into specific neural lineages. We are able to isolate and purify brain region-specific progenitors, neurons and astrocytes from iPSC-derived cultures over >100 days of differentiation. Recently, we established high-density micro-electrode arrays to monitor neuronal circuit formation and monitor disease phenotypes in human iPSC-derived neurons. We have generated iPSC from patients suffering from neurodevelopmental and neurodegenerative disorders including Parkinson's disease, FTLD, and MYCOPS12. Using iPSCs as a model system and the directed differentiation to neurons and glia, we are studying the effects of genetic mutations on neuronal cell biology, gene expression and neuronal function.

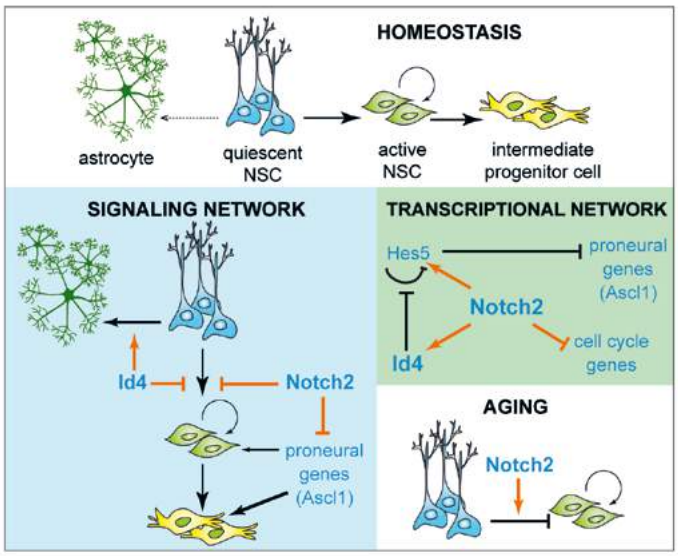

Fig. 1: NSCs of the adult hippocampus are multipotent but mitotically inactive. They must enter cell cycle to generate neurons during homeostatic maintenance and they transit to astrocyte production with age. Notch2 blocks NSC entry into the cell cycle by inducing Id4 expression, and inhibits Ascl1 transcription, thereby simultaneously preventing neuronal fate commitment. Id4 increases Hes5 expression by blocking its autorepression, and promotes astrocyte differentiation of NSCs. Increased Notch2 activity in ageing NSCs contributes to reduced neuron production and commitment to astrocytes differentiation.

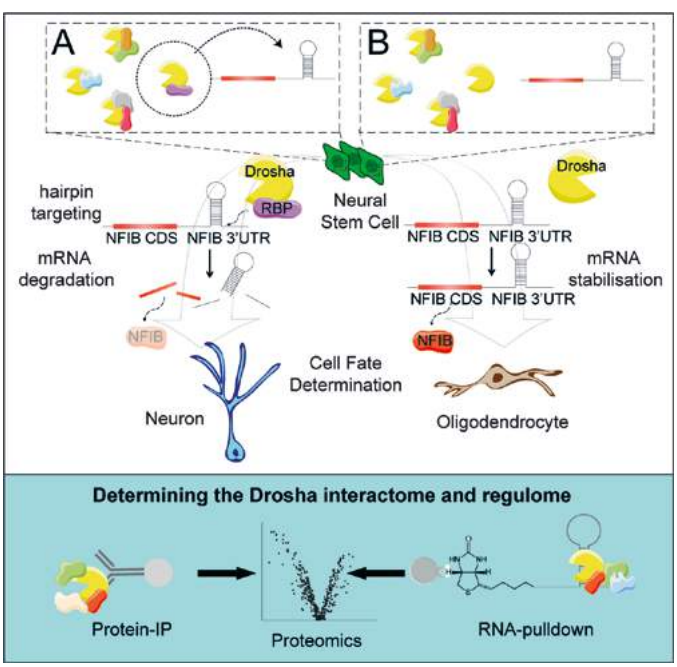

Fig. 2: Drosha regulates NSC fate by targeted cleavage of mRNAs of fate determining transcription factors. NFIB drives oligodendrocyte commitment of hippocampal NSCs, but its expression is repressed but Drosha cleavage of its mRNA. **A.** Cell-type specific regulation of Drosha activity is controlled by expression of cell-specific RNA binding protein (RBP) partners which target mRNAs in a sequence-specific fashion. **B.** Down-regulation of Drosha partners stabilizes the mRNA of targeted fate determining factors. Quantitative proteomics identified more than 140 novel Drosha interacting proteins and proteins that bind Drosha mRNA targets.

Selected Publications

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Zhang R, Boareto M, Engler A, Louvi A, Giachino C, Iber D, Taylor V (2019). Id4 downstream of Notch2 maintains neural stem cell quiescence in the adult hippocampus. Cell Rep. 28, 1485–1498.

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Fedele S, Collo G, Behr K, Bischofberger J, Müller S, Kunath T, Christensen K, Gündner AL, Graf M, Jagasia R, Taylor V (2017). Expansion of human midbrain floor plate progenitors from induced pluripotent stem cells increases dopaminergic neuron differentiation potential. Sci Rep. 7, 6036.

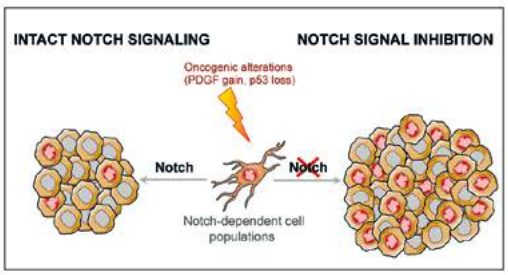

Fig. 3: Gliomas are the most common primary brain tumors in adults and the prognosis for patients is, in many cases, very poor. It has been proposed that gliomas could aberrantly hijack the same signaling pathways that allow normal NSCs to self-renew, thus enabling glioma cells to proliferate extensively and form the tumor. Unexpectedly, our studies indicate that Notch signaling, one major molecular pathway implicated in NSC self-renewal, can actually suppress the formation of some forms of brain tumor.

Developmental Genetics

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The Molecular and Cellular Basis of Developmental Robustness and Evolutionary Plasticity – Insights from Vertebrate Limb Bud Organogenesis

How an embryo develops from a single cell – the zygote – is one of the most fascinating biological processes. Recent research has uncovered the amazing self-regulatory properties of the gene regulatory networks (GRNs) and cellular interactions that drive organogenesis, which are a focus of our research. One property of self-regulation is robustness against genetic perturbations. Despite congenital malformations being a major cause of infant death, they are relatively rare considering the vast number of genes required for embryogenesis. A paradigm to study genetic robustness is the regulation of gene expression by cis-regulatory modules (CRMs) embedded in genomic landscapes. We have shown that Gremlin1 (Grem1) mediated BMP antagonism is pivotal to mouse organogenesis and its dynamic regulation in limb buds defines a key node in the self-regulatory signaling system controlling its development. The large Grem1 genomic landscape encodes the eight CRMs that orchestrate the Grem1 expression dynamics during limb bud development. These CRMs were functionally studied by reverse genetics using CRISPR/Cas9 genome editing in the mouse. While single CRM deletions did not alter limb development, deletion of all eight CRMs reproduces the Grem1 null phenotype. Combinatorial analysis uncovered the complex cis-regulatory logics and robustness of the dynamic Grem1 regulation during mouse limb bud development. We establish that these CRMs regulate Grem1 transcript levels in an additive manner while its spatial regulation depends on enhancer cooperativity. The latter provides Grem1 expression and digit development with cis-regulatory robustness as spatial alterations are the cause of digit fusions and loss. The observed phenotypes are very reminiscent of the changes in digit patterns that occurred during evolutionary diversification of mammalian limbs. Indeed, we discover that the Grem1 cis-regulatory landscape is evolutionary ancient and experimental evidence indicates that it provided the cis-regulatory plasticity for limb skeletal diversification during evolution. Two of the CRM enhancers are conserved from basal fishes to mammals and transgenic analysis reveals the substantial plasticity in their species-specific activities, which also provides insights into the molecular alterations underlying the fin-to-limb transition.

Another focus is the cellular analysis of the mechanisms controlling progenitor cell proliferation and specification in mouse limb buds. We initiated this analysis as little was known about the origin and molecular signatures of the limb bud mesenchymal progenitors (LMPs) that give rise to the chondrogenic primordia of the appendicular skeleton. The combination of flow cytometric analysis with transcription profiling revealed the molecular profiles of LMPs in limb buds. In particular, this analysis identified the most immature LMPs in early limb buds as Jagged1 (JAG1) positive cells located in the posterior-distal mesenchyme. The transcription pro-file of JAG1-positive LMPs and their functional manipulation in culture shows that they depend critically on morphogenetic SHH and FGF signaling. In particular, JAG1-positive LMPs are protected from apoptosis by GREM1-mediated BMP antagonism. This shows that the proliferation and survival LMPs in the distal limb bud mesenchyme is controlled by the SHH/GREM1/AER-FGF signaling system. At the same limb bud stage, the osteochondrogenic progenitors located in the core mesenchyme are already actively responding to BMP signaling, which induces their chondrogenic differentiation. This analysis identified the different LMP populations in early mouse limb buds and uncovers the spatially distinct response of cells to patterning, proliferation and differentiation signals.

These studies are complemented by cell sorting in combination with single cell RNA-seq and chromatin analysis to analyze GRN interactions in limb buds at cellular resolution. Finally, we use in depth bioinformatic analysis and simulations of mouse and chicken limb bud development to identify the shared and species-specific GRN interactions governing limb bud patterning and outgrowth.

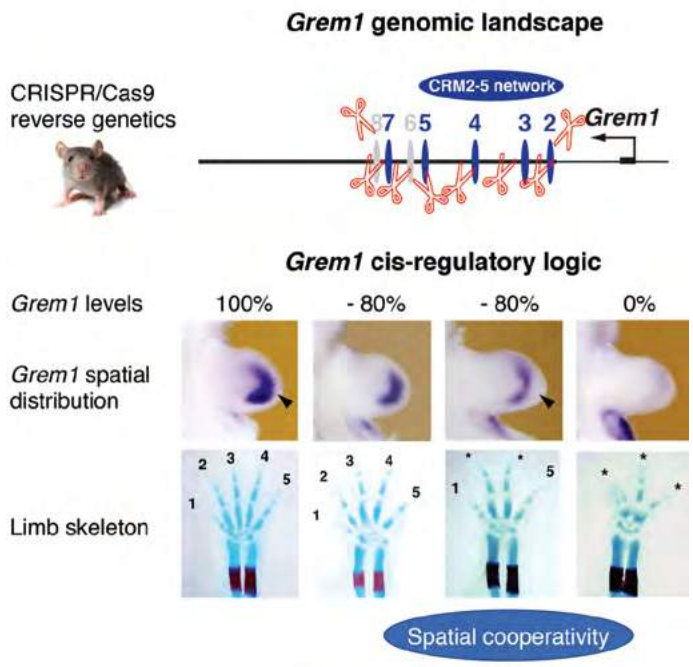

Fig. 1: Analysis of the *Grem1* cis-regulatory landscape by CRISPR/Cas) genome editing in mice. In the *Grem1* genomic landscape (upper scheme) an array of eight CRM was identified, several of which display strong enhancer activities in transgenic mouse limb buds (indicated in blue. The combinatorial analysis of these enhancers showed that CRM2-5 form an enhancer network that regulate Grem1 transcript levels in an additive and the spatial expression dynamics in a cooperative manner. Strikingly an 80 % reduction in Grem1 levels results in no digit phenotypes when the asymmetric spatial expression is maintained (lower panel). Only when this spatial cooperativity is broken – i. e. the expression becomes symmetric digit numbers are reduced and middle digits loose their asymmetry. Arrowheads indicate the wild-type and symmetric Grem1 expression domains, asterisks digits with phenotypes..

Selected Publications

Zuniga A and Zeller R (2020). Dynamic and self-regulatory interactions among gene regulatory networks control vertebrate limb bud morphogenesis. Curr Topics Dev Biol 139, 61–88.

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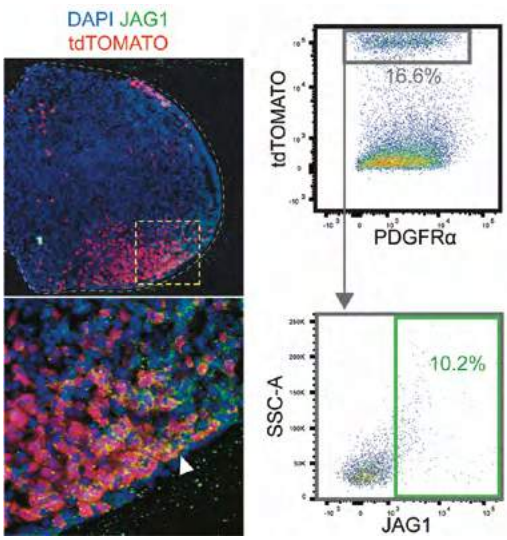

Fig. 2: Mapping LMPs and their descendants in mouse limb buds. Distribution of Shh-expressing cells (*Shh*-GFP, white arrowheads indicate the distal border) and tdTOMATO positive *Shh* descendants in a mouse forelimb bud (E10.5–E10.75). This pattern arose from permanent activation of the *Rosa26*tdTomato transgene by *Shh*GFPCre-induced recombination. The JAG1-positive LMPs are detected by specific antibodies. The overlap shows that only a small fraction of cells coexpress tdTOMATO (red) and JAG1 (green). White dashed lines outline the limb buds. Yellow dashed lines demarcate the regions enlarged in the lower panel. FACS analysis confirmed that about 10 % of the tdTOMATO-positive LMPs coexpress JAG1.

Oncology

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The major goal of this focal area is to foster research in the field of molecular and clinical oncology in Basel. In particular, we aim at bridging the gaps between basic, translational, and clinical oncology research ongoing at the University of Basel and the biotech and pharmaceutical industry in the Basel area. Ultimately, the focal area should enforce collaborative efforts and common projects between various research groups, research institutes and pharmaceutical industry and between different disciplines. An added value is seen in innovative research projects that eventually will be transferred to a clinical setting.

In the past years, the Focal Area of Research in Oncology has been chaired by Professor Gerhard Christofori, leader of the "Tumor Biology" group at the DBM, and by Professor Christoph Rochlitz, head of Clinical Oncology at the University Hospital. The program has now been reorganized with new leadership and initiatives, and adapted as Focal Area of Research in Oncology (FARO). It is now chaired by Professor Mohamed Bentires-Alj, head of the "Tumor Heterogeneity, Metastasis and Resistance" group, and by Sara Meyer, head of the "Myeloid Malignancies" group at DBM. The program focuses on two major topics: first to support basic, translational, and clinical research by generating opportunities for oncology research, for example by mentoring young investigators and hosting new recruitments within the DBM.

The second focus of the Focal Area Oncology is to increase communication between the various researchers, clinicians and pharmaceutical company representatives in Basel and to boost scientific exchange and technological collaboration, also with the other Focal Areas of the DBM. Towards this goal, monthly progress reports, one-day symposia and annual meetings are organized to offer platforms for the discussion of research progress and for the exchange of ideas. In addition, renowned international cancer researchers are invited to present lectures within the DBM Oncology Program Seminars, and impromptu Guest Seminars complete the seminar activities of the research program. Many members of FARO are also engaged in the Swiss-wide Personalized Health Initiative in Oncology which aims at implementing the nation-wide exchange and computational analysis of clinical data, at establishing common tumor boards and adequate biobanks, and at intensifying the cooperation between basic and clinical research. Many FARO members are also active in the Basel Breast Consortium (BBC) which integrates basic, translational and clinical research on breast cancer and is highly successful in fostering many translational research projects and in organizing progress report meetings, invited speakers lectures and annual conferences. Finally, specific advanced courses in experimental cancer research and in cell signaling are offered to Master and PhD students. Thus far, these communication activities have resulted into highly successful collaborations and research networks, manifested also by the accomplishments of several network grants and by the start-up of spin-off companies. Accordingly, many of these efforts are part of international and national research initiatives that cover innovative approaches towards cancer research and treatment, including research on cancer genetics and genetic instability, cancer epigenetics, angiogenesis and metastasis, signal transduction, cancer stem cells, tumor immunology and immunotherapy, tumor imaging and novel therapeutic regimen. Notably, a large number of clinical phase studies, including first-in-man tri-

als, have been and are taking place at the University Hospital of Basel. In the years to come, we still need to enforce scientific exchange between basic and patient-oriented research in order to facilitate the identification of clinical problems for the design of appropriate and innovative basic research approaches and, on the other hand, to further improve on the rapid translation of basic research results into clinical application.

Cancer Metastasis

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Investigating Metastasis Vulnerabilities through the Analysis of Circulating Tumor Cells

The formation of a metastatic disease accounts for more than 90% of cancer-associated death. Understanding the biological and molecular features of the metastatic process is key to identify new anti-metastasis therapies. Circulating tumor cells (CTCs) are cancer cells that have detached from a primary or metastatic tumor mass, have entered the blood circulation and are on their way to establishing new metastases at distant sites. CTCs can be found in the blood of patients as single cells or as multicellular clusters. We previously demonstrated that CTC clusters are primarily responsible for the establishment of metastasis at distant sites, and that they are 50 times more metastatic compared to single CTCs (Aceto *et al.,* Cell, 2014). Similarly, in cancer patients, the presence of CTC clusters in blood circulation denotes adverse clinical outcomes. These results point to the need to better characterize the biology of CTCs to gain more insights into the metastatic process and to identify new targets whose inhibition may impact the ability to form metastasis.

Recently, our group came across three major findings that highlight important features of metastasis biology. First, we discovered that clustering of CTCs leads to DNA methylation remodeling at critical (stemness-related) transcription factor binding sites, favoring metastasis seeding. We also identified FDA-approved drugs with the ability to target (dissociate) CTC clusters and suppress the metastatic spread of cancer in mouse models (Gkountela *et al.,* Cell, 2019). These results are rapidly translating to patients, as clinical trials with these inhibitors are now being conducted in breast cancer.

Second, we have discovered a new type of CTCs that was previously uncharacterized, i.e. those that travel in association with immune cells. With single cell parallel RNA and exome sequencing of CTCs from breast cancer patients and mouse models as well as CRISPR-based loss-of-function studies, we understood that CTCs most frequently partner with neutrophils, and that CTCs derived from CTC-neutrophil clusters feature recurrent mutations, higher proliferation rate and increased ability to initiate metastasis compared to CTCs that are not bound to neutrophils. We also uncovered that CTC-neutrophil clusters are held together through VCAM-1-dependent intercellular junctions, and that neutrophils secrete IL1beta and IL6 to boost CTC proliferation in the bloodstream (Szczerba *et al.,* Nature, 2019). These findings were not only key to the identification of ta new route of metastatic dissemination, but also because they represent one of the first examples whereby the interplay between cancer cells and immune cells occurs away from the primary tumor site, yet determines disease outcome.

Third, we asked what are the molecular triggers that promote the intravasation of CTC clusters and CTC-neutrophil clusters into the bloodstream from the primary tumor site. We found that intra-tumor hypoxia is localized within well-defined areas of the primary tumor, and that cell-cell junctions are upregulated in hypoxic tumor cells. In turn, this promotes the ability of hypoxic cells to intravasate as CTC clusters and CTC-neutrophil clusters, leading to accelerated metastasis formation. In contrast, treatment with EphrinB2 improves tumor vascularization and decreases hypoxia, leading to a reduced shedding rate of clustered CTCs and suppression of metastasis (Donato *et al.,* Cell Reports, 2020).

Together, recent results from our laboratory have contributed to a better understanding of CTC biology and vulnerabilities of the metastatic process (Figure 1). Our research is now focused on increasing the translational potential of our findings and testing new therapeutic approaches in preclinical models. In collaboration with clinicians at the University Hospital Basel we routinely profile CTCs isolated from the blood of cancer patients, aiming to define their key molecular features

and drug response patterns, while experiments with cancer models in the laboratory are now focused to learn about CTC release patterns and the requirement of specific genes along the metastatic cascade.

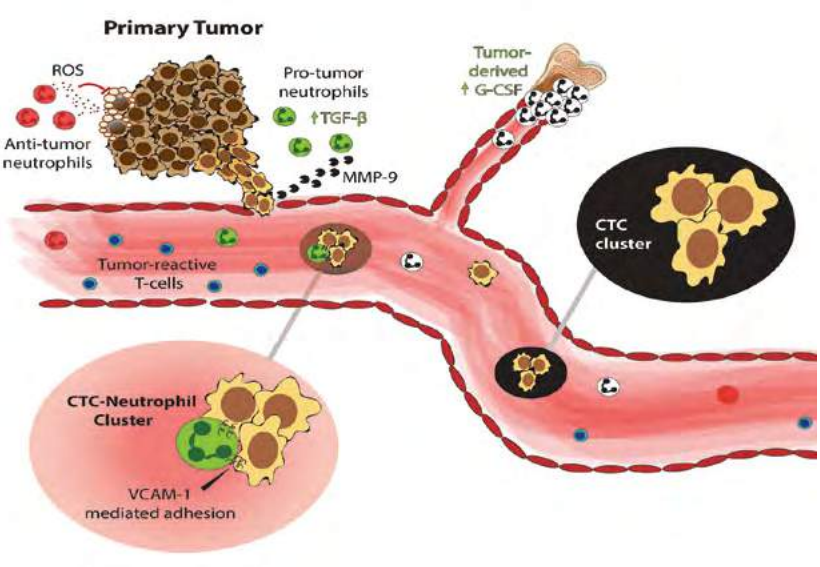

Fig. 1: Primary tumor cells are capable to intravasate as single circulating tumor cells (CTCs), CTC clusters or CTC-neutrophil clusters. Our recent data has highlighted both CTC clusters and CTC-neutrophil clusters as key players in the metastatic cascade. While the presence of clustered CTCs denotes a poor outcome in breast cancer patients, successful targeting of CTC clusters and CTC-neutrophil clusters suppresses metastasis development in preclinical models. Source: Saini, Szczerba and Aceto, Cancer Research, 2019.

Connection to Clinical Practice

Prof. Dr. Christoph Rochlitz
Prof. Dr. Alfred Zippelius
Prof. Dr. Walter Weber
Prof. Dr. Viola Heinzelmann
PD Dr. Marcus Vetter
Prof. Dr. Christian Kurzeder
Prof. Dr. Heinz Läubli

University Hospital Basel

Isolation of circulating tumor cells from the blood of cancer patients

The analysis of circulating tumor cells (CTCs) is an exceptional opportunity to study the biology of human cancer metastasis from minimally invasive biopsies, i.e. blood samples. In collaboration with Prof. Dr. Christoph Rochlitz, Prof. Dr. Alfred Zippelius, Prof. Dr. Walter Weber, Prof. Dr. Viola Heinzelmann, PD Dr. Marcus Vetter, Prof. Dr. Christian Kurzeder, and Prof. Dr. Heinz Läubli at the University Hospital Basel, we routinely isolate and characterize CTCs from a variety of patients with metastatic cancers (e.g. breast cancer, ovarian cancer, lung cancer, melanoma). Upon isolation with microfluidic technologies, we profile CTCs in various ways, ranging from next-generation sequencing to drug testing. With our approach, we aim to establish state-of-the-art and clinically-relevant tools that will enable the identification of key vulnerabilities of the metastatic process.

Selected Publications

Donato C, Kunz L, Castro-Giner F, Paasinen-Sohns A, Strittmatter K, Szczerba BM, Scherrer R, Di Maggio N, Heusermann W, Biehlmaier O, Beisel C, Vetter M, Rochlitz C, Weber WP, Banfi A, Schroeder T & Aceto N. "Hypoxia triggers the intravasation of clustered circulating tumor cells". Cell Rep. Sep 8 2020.

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Tumor Heterogeneity, Metastasis and Resistance

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Mechanisms of breast tumor heterogeneity, metastasis and resistance: From Bedside to Bench to Bedside and back again

Breast cancer is the leading cause of cancer death in women and 2.1 million new patients are diagnosed with this disease annually. Although the overall survival rates for breast cancer have improved over the last decades, more than 600,000 lives are lost to this disease annually because of drug resistant metastases. A thorough understanding of both cancer cell intrinsic (i. e., cell autonomous) and extrinsic (i. e., non-cell autonomous) mechanisms of breast cancer progression is urgently needed to end this stalemate.

The thread connecting the research topics in my lab is tumor heterogeneity. We assess fundamental mechanisms that influence normal and neoplastic breast stem cells, metastasis, and resistance to targeted therapies at the molecular, cellular, and whole organism levels. These interdisciplinary projects seek to leverage a mechanistic insight into personalized therapy, which is a focus of the translational research that we pursue in close collaboration with clinicians (Fig. 1) (www.bentireslab.org).

M. Bentires-Alj is the founder and president of the European Network for Breast Development and Cancer (www.enbdc.org) that fosters global interactions between labs in these areas, and co-founder of the Basel Breast Consortium (www.BaselBC.org), which is committed to promoting local basic, clinical, and translational interdisciplinary research projects within Switzerland.

Glucocorticoids promote breast cancer metastasis

Transcriptional profiling of tumours and matched metastases revealed cancer-site specific phenotypes and increased glucocorticoid receptor (GR) activity in distant metastases. GR mediates the effects of stress hormones and synthetic derivatives. We show that increase in stress hormones during breast cancer progression resulted in GR activation at distant metastatic sites, increased colonization, and ultimately reduced survival. The data also reveal that GR activation decreases the efficacy of the widely used chemotherapy paclitaxel. Corticosteroids such as dexamethasone are widely used in the treatment of breast cancer to combat side-effects of chemotherapy and to treat symptoms related to advanced cancer. Our results suggest that GR activation increases heterogeneity and metastasis and, thus, call for caution in the use of glucocorticoids in the treatment of BC patients with cancer related complications (Obardovic, Nature 2019).

Fig. 1: Research areas within the Bentires-Alj lab: https://bentireslab.org/

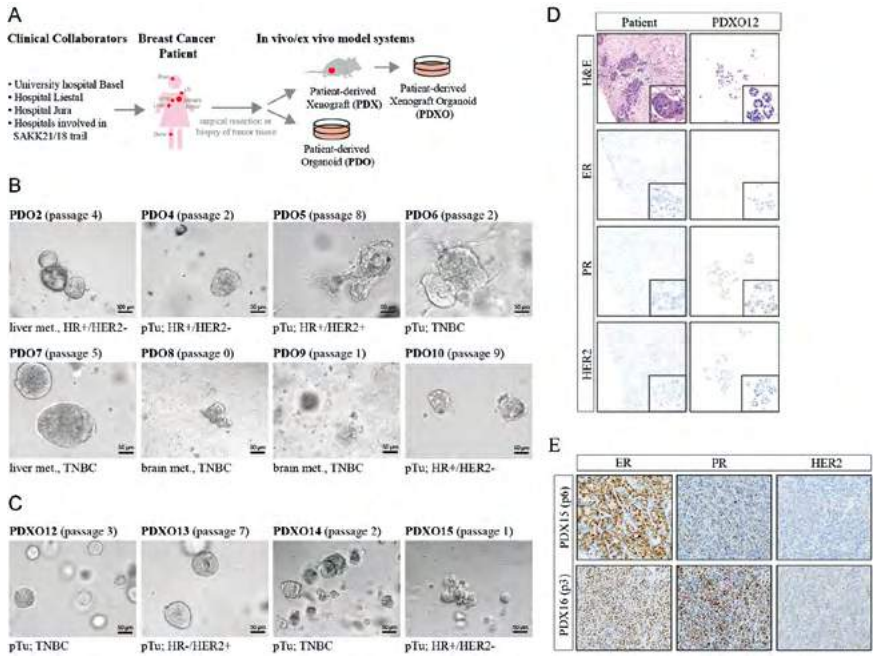

Fig. 2: Basel personalized breast cancer program: *Ex vivo* **and** *in vivo* **model systems from breast cancer patients.** A. Scheme displays our clinical collaborators and derived patient-derived organoids (PDO), patient-derived xenografts (PDX) and PDX-derived organoids (PDXO) models from different human primary breast tumors (pTu) and metastases (met). B,C. Representative bright field images of established PDO (B) and PDXO (C) cultures. D. Images of sections of a primary tumor and corresponding PDXO models. E. Images of sections of PDXs from ER+ breast tumors. Expression of ER, PR and HER2 was analyzed by IHC.

Hippo kinases LATS1/2 control human breast cell fate via crosstalk with ERα

Using a high-content confocal image-based shRNA screen for tumor suppressors regulating human breast cell fate, we have discovered that ablation of the Hippo kinases large tumor suppressors (LATS) 1 and 2 promotes luminal fate and increases the number of bipotent and luminal progenitors, the proposed cell-of-origin of most human breast cancers. Mechanistically, we revealed a crosstalk between Hippo and ERα signaling. In the presence of LATS, ERα was targeted for ubiquitination and DCAF1-dependent proteasomal degradation. Our findings reveal a non-canonical effect of LATS in the regulation of human breast cell fate (Britschgi, Nature 2017).

Swiss Personalized Oncology

The Swiss Personalized Oncology (SPO) driver project, part of the Swiss Personalized Health Network, is chaired by Profs. Bentires-Alj and Michielin (CHUV). SPO is a Switzerland-wide effort that aims at integrating clinical and molecular information from cancer patients, which should ultimately enable more precise diagnoses and thus treatments tailored to individual patients. SPO'S main goal is to achieve interoperability of the clinical and laboratory data from cancer patients in Switzerland.

Personalized breast cancer treatment

While the SPO is a nationwide effort, we have assembled, a local group of clinicians to make up a breast cancer personalized medicine team that should ultimately improve treatment of patients. Our goal is to collect patient samples and to use multiomics, combined with drug response profiling and computational analysis, in the assessment and modeling of cancer and tumor microenvironment heterogeneity in a longitudinal way (Fig. 2).

Connection to Clinical Practice

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Selected Publications

Obradović MMS, Hamelin B, Manevski N, Couto JP, Sethi A, Coissieux A, Münst S, Okamoto R, Kohler H, Schmidt A, Bentires-Alj M (2019). Glucocorticoids promote breast cancer metastasis. Nature 567, 540–54.

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Tumor Biology

Due to the retirement of Gerhard Christofori, the group will be closed by August 2021

Gerhard Christofori

Department of Biomedicine
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Eleni Panoussis
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*left during report period

Molecular dissection of malignant tumor progression, metastasis and therapy resistance

The vast majority of cancer patient deaths are due to the systemic dissemination of cancer cells throughout the body and the seeding and outgrowth of secondary tumors (metastases) in distant organs. One major objective of our research is the identification and characterization of the molecular pathways underlying the progression from differentiated benign tumor cells to invasive malignant cancer cells and to the seeding and outgrowth of metastasis in distant organs. Moreover, we have set out to delineate the genes and pathways that allow cancer cells to evade from current therapies. In addition to cultured tumor cell lines *in vitro*, we employ transplantation and transgenic mouse models of specific cancer types to determine causal connections between the expression of particular genes and the cellular changes during tumor progression, metastasis formation and therapy resistance *in vivo*.

In the past years we have learned that the development of malignant tumors is in part characterized by a tumor cell's capability to overcome cell-cell adhesion and to invade surrounding tissue by a process referred to as epithelial-mesenchymal-transition (EMT). An EMT underlies the conversion of epithelial, differentiated cells to mesenchymal, migratory and invasive cells. EMT occurs in multiple stages and is regulated by complex molecular networks regulating the expression of a large number of proteins, lncRNA and miRNA-encoding genes. Using dual recombinase lineage tracing approaches in transgenic mouse models, we have noted that hybrid intermediate stages of EMT represent the stages of highest cell plasticity which confers cancer cells with hallmarks of cancer stem cells and increased metastatic traits and drug resistance. For example, we have found that breast cancer cells undergoing an EMT and exhibiting high cell plasticity can be therapeutically forced to differentiate into post-mitotic adipocytes, thus eliminating invasive cells and limiting metastatic seeding. Investigating the regulatory circuits defining cell plasticity, we have established the epistatic nature of a network consisting of transcription factors, miRNAs and lncRNAs which act as master regulators not only in the initiation and execution of the morphogenic process of an EMT but also in providing survival signals to cancer cells and thus allowing cancer cells to seed and grow metastases in distant organs. With these experimental approaches we have also identified novel signaling pathways and epigenetic events occurring during EMT, which have been subsequently scrutinized for their potential use as therapeutic targets for preventing metastatic disease.

In a second line of research, we have investigated the molecular pathways underlying the development of evasive resistance to targeted cancer therapy. We have found that cancer cells shift from lethal autophagy during acute therapy to survival autophagy in therapy-resistant cells, thus overcoming cell death. Moreover, therapy-resistant cells appear to undergo a partial EMT and gain anti-oxidant activities which are critical in overcoming ferroptosis, a novel programmed cell death pathway involving reactive oxygen species and lethal lipid peroxidation. Finally, therapy resistant cells appear to shift their metabolism to glycolytic pathways. These pathways are specific for therapy resistant cells, and we have shown in preclinical experiments that they offer suitable therapeutic targets for overcoming resistance to conventional therapies.

Lea & Tamar Studio, © DBM

Fig. 1: Trans-differentiation therapy of metastatic breast cancer. Cartoon to exemplify the therapeutic conversion (trans-differentiation) of "dangerous" highly proliferating and metastatic breast cancer cells with high cell plasticity into "harmless" fat cells (adipocytes) which have stopped to proliferate and can no more contribute to metastasis formation (see Ishay-Ronen *et al.* Cancer Cell, 2019).

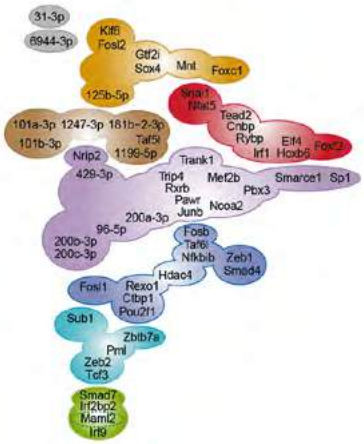

Fig. 2: Cloud model of the hierarchic regulatory circuits driving EMT. The hierarchical landscape of the regulatory circuits steering an epithelial-mesenchymal transition (EMT) was identified using computational analysis by nested effects models (NEMs). Within these models, transcription factors and miRNAs with similar effects were grouped in clouds and the factors in the top clouds have broader impact on EMT than the factors in the bottom clouds (see Mayer-Schaller *et al.,* Developmental Cell, 2019).

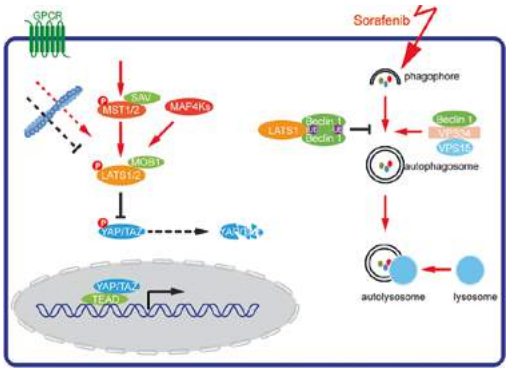

Fig. 3: Overcoming lethal autophagy underlies resistance to Sorafenib therapy of hepatocellular carcinoma. Sorafenib treatment of hepatocellular carcinoma cells leads to lethal autophagy which is overcome by the Hippo signaling pathway effector kinase LATS1 in a kinase-independent manner. Schematic representation of the role of LATS1 in canonical Hippo signaling (left side) and of its non-canonical role in repressing sorafenib-induced autophagy (right). LATS1-induced K27-linked ubiquitination of Beclin-1 on K32 and K263 results into its inactivation by self-dimerization and thus to an inhibition of autophagy (see Tang *et al.,* Nature Communications, 2019).

Selected Publications

Saxena M, Kalathur RKR, Rubinstein N, Vettiger A, Sugiyama N, Neutzner M, Coto-Llerena M, Kancherla V, Ercan C, Piscuoglio S, Fischer J, Fagiani E, Cantù C, Basler K and Christofori G (2020). Pygopus 2 – histone interaction is critical for de-differentiation and malignant breast cancer progression. Cancer Res. 80, 3631–3648.

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Connection to Clinical Practice

Markus Heim, Walter Weber

Department of Biomedicine, University Hospital Basel

Evasive resistance to targeted therapy and tumor heterogeneity

The development of resistance to targeted cancer therapy (evasive resistance) has appeared a major obstacle in treating cancer. In two network projects connecting patient care (Markus Heim), biomedical research (Mike Hall, Biozentrum) and computational biology (Niko Beerenwinkel and Jörg Stelling, D-BSSE, ETHZ, Basel), we have aimed at the molecular dissection of the pathways underlying the development of drug resistance to current cancer therapy. We have employed drug-sensitive cell lines and their drug-resistant counterparts, novel mouse models of hepatocellular carcinoma (HCC) to identify some of the molecular pathways underlying evasive resistance and to test first alternative therapies to overcome it. These projects have been supported by a European Research Council (ERC) Synergy Grant and by a SystemsX.ch MTD Grant.

In a network project in collaboration with the Department of Surgery of the University Hospital Basel (Walter Weber) and basic and computational researchers of the DBM and the Friedrich-Miescher-Institute in Basel (Mohammed Bentires-Alj and Michael Stadler), the University of Zürich (Bernd Bodenmiller) and IBM Rüschlikon (Maria Rodriguez), we have addressed basic questions regarding breast cancer cell heterogeneity in patients and in experimental models and we have learned about the regulatory networks driving EMT and metastasis formation. This project has been funded by a SystemsX.ch MTD Grant.

Ovarian Cancer Research

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Mechanisms of dissemination and molecular signatures for advanced diagnosis, outcome prediction, and tailored management of ovarian cancer

Key molecules in ovarian cancer dissemination

Peritoneal dissemination is a particular form of ovarian cancer metastasis which is the cause why the majority of patients are diagnosed at advanced FIGO stage accompanied with a poor patient's outcome. Identification of the molecular players involved in ovarian cancer (OC) dissemination can offer an approach to develop treatment strategies to improve clinical prognosis.

We have identified several cell surface markers that may promote the spreading of ovarian cancer. Here, we describe integrinα2 (ITGA2) as a key factor for cancer cell adhesion to extracellular matrix protein collagen that promotes metastasis to the omentum as demonstrated by *in vitro* assays in gene-edited cancer cell lines and *ex vivo* using patient-derived tumor cells. Moreover, we also demonstrate that ITGA2 promotes directed cell migration and mesothelial clearance in co-culture systems. Mechanistically, the oncogenic properties rely on ITGA2-dependent phosphorylation of focal adhesion kinase and activation mitogen-activated protein kinase pathways (*Huang et al., 2020;* Fig. 1). In a collaboration with Leonor David (University of Porto, Portugal) we show that mesothelin (MSLN), which is overexpressed in primary and matched peritoneal metastasis of high-grade serous carcinomas, promoted invasion of tumor cells through the mesothelial cell layer *in vitro*. Intraperitoneal xenografts established with MSLN-high OC cell lines showed enhanced tumor burden and spread within the peritoneal cavity. MSLN is hence suggested as key player in OC progression by triggering peritoneal dissemination *(Coelho et al., 2020).*

Epithelial-to-mesenchymal transition (EMT) and its reverse MET are suggested to be key features of OC metastasis and comprise cellular and molecular processes essential for local tumor growth, dissemination, and establishment of metastases at distant sites. We found that loss globoside glycosphingolipids (GSL) through genomic deletion of the key enzyme *A4GALT* induced EMT in OC cells, associated with loss of E-cadherin expression (through epigenetic silencing of *CDH1*) and cell-cell adhesion and increased chemoresistance (*Jacob et al., 2018*). Our current focus is to understand the role of GSL in MET, identify associated signaling pathways and study the expression of GSLs in patient-derived cells. In collaboration

Selected Publications

Huang YL, Liang CY, Ritz D, Coelho R, Septiadi D, Estermann M, Cumin C, Rimmer N, Schötzau A, Núñez López M, Fedier A, Konantz M, Vlajnic T, Calabrese D, Lengerke C, David L, Rothen-Rutishauser B, Jacob F, Heinzelmann-Schwarz V (2020). Collagen-rich omentum is a premetastatic niche for integrin α2-mediated peritoneal metastasis. eLife.9:e59442. doi: 10.7554/eLife.59442.

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Heinzelmann-Schwarz V, Knipprath Mészaros A, Stadlmann S, Jacob F, Schoetzau A, Russell K, Friedlander M, Singer G, Vetter M (2018). Letrozole may be a valuable maintenance treatment in high-grade serous ovarian cancer patients. Gynecol Oncol. 148:79–85.

with Arun Everest-Dass and Mark von Itzstein (Institute for Glycomics, Griffith University, Australia), we have established MALDI imaging to study spatial distribution of GSLs in matched and longitudinal tissue samples.

New molecular signatures towards early detection, outcome prediction, and tailored management of ovarian cancer

The identification of markers (signatures) for early and accurate diagnosis and reliable outcome prediction are the key to optimal management of ovarian cancer. In the era of precision medicine, where we transition from organ-based diagnosis towards individual genetically-linked diseases, the tailoring of treatment in cancer becomes increasingly important. This is particularly true for high-grade advanced stage serous adenocarcinomas comprising malignant tumors of the ovary (OC), fallopian tube (TC) and peritoneum (PC). These diseases currently are managed similarly, but our study using transcriptomic and next-generation sequencing data and validation by immunohistochemistry in various patient cohorts indicate that OC and PC are epidemiologically and molecularly distinct disease entities: PC relapsed earlier, had a distinctively different gene signature, and showed a different sensitivity to standard chemotherapy drugs compared to OC (*Jacob et al., 2020)*. A preceding study characterized the N- and O-glycome of these two disease entities using tissue glycomics and revealed also distinct glycomic signatures i.e. proteins are differently and uniquely glycosylated in OC versus PC *(Anugraham et al., 2017)*.

Additional studies from our own group evaluated candidate ovarian cancer detection and outcome markers for HGSOC. Among them the expression of maternal embryonic leucine-zipper kinase (MELK) correlated with poor survival *(Kohler et al., 2017)*, whereas LATS expression was not associated with outcome in ovarian cancer patients *(Montavon et al., 2019)*.

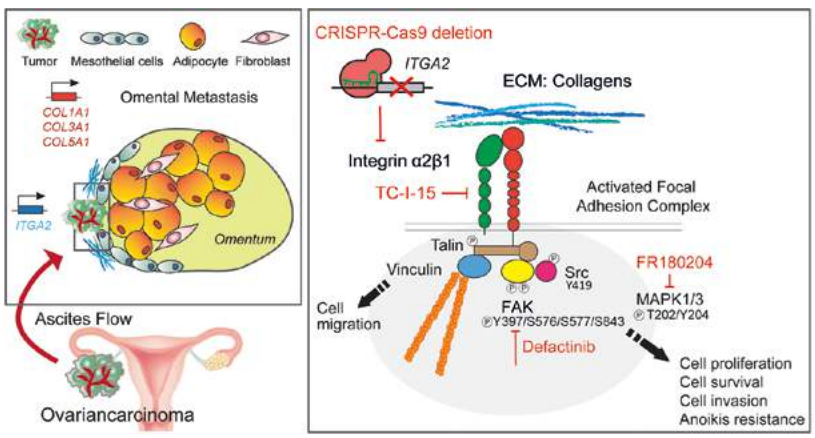

Fig 1: Schematic representation of ITGA2-collagen dependent signaling axis in ovarian cancer metastasis

Left: Cancer cells shed of from primary ovarian tumor are passively (via ascites) disseminate into the peritoneal cavity and establish a metastatic tumor in the omentum (omental metastasis). Integrinα2 (ITGA2) triggers ovarian cancer cell adhesion to collagen-rich omentum, promotes directed cell migration, anoikis resistance, mesothelial clearance, and peritoneal metastasis through the activation of MAPK and FAK signaling axis.

Right: This process can be inhibited at several levels by deletion of ITGA2 function (disrupts interaction with collagen), by integrinα2β1 inhibitor TC-I-15 (dimerization failure with Integrinβ1), and by inhibition of focal adhesion kinase FAK and mitogen-activated protein kinase MAPK (blocks signaling multiple cellular processes). From: *Huang et al., 2020. eLife.9:e59442. doi: 10.7554/eLife.59442.*

Connection to Clinical Practice

Prof. Viola Heinzelmann-Schwarz
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Precision medicine in ovarian cancer management

The tailoring of treatment in cancer is a pivotal for improved treatment regimens. In this respect, one study shows a superior outcome of patients with Malignant mixed Mullerian tumors originating from the endometrium (MMMT-E) treated with platinum/anthracycline or ifosfamide regimen as compared to those treated with platinum/taxanes regimens, suggesting that the previous shift from anthracycline or ifosfamide-based towards taxane-based chemotherapy for MMMT-E (possibly also for MMMT of the ovary) may be worth reviewing *(Heinzelmann-Schwarz et al., 2020).* In addition, the potential of immunotherapy for patients with advanced cervical cancer is highlighted by the persistent complete response after third-line treatment for relapsed chemotherapy-resistant cervical cancer *(Baettig et al., 2019).* In regards to ovarian cancer, our data suggest Letrozole maintenance treatment improving recurrence-free interval *(Heinzelmann-Schwarz et al., 2018).* These data are the basis for our initiated MATAO-trial, a phase III multicenter international clinical trial to evaluate the efficacy of Letrozole maintenance therapy after standard surgical and chemotherapy treatment in patients with newly diagnosed ER- positive epithelial OC *(PI: Prof. Heinzelmann-Schwarz).*

We are also part of the Tumor Profiler (TuPro) Consortium, an integrated, multi-omic, functional tumor profiling platform for clinical decision support, and currently evaluate the use of various state-of-the-art platforms (www.medrxiv.org/content/10.1101/2020.02.13.20017921v1).

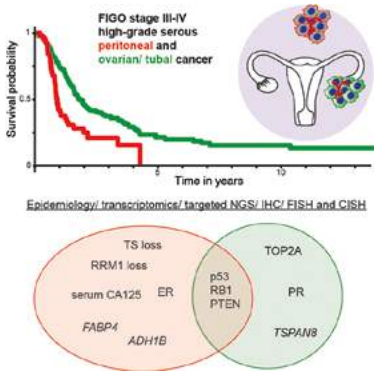

Fig 2: Serous peritoneal cancer is more aggressive than high grade advanced stage serous ovarian cancer. Both cancers display distinct molecular signatures. From: *Jacob et al., Mol. Oncol. 2020.doi: 10.1002/1878–0261.12811.*

Brain Tumor Immunotherapy and Tumor Biology

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Lorine Wachsmuth* (Undergraduate Student)

*left during report period

Combined Microglia Modulation and Tumor Targeting to Combat Glioblastoma

In 2018, we founded the Brain Tumor Immunotherapy (BTIT) research group, which closely collaborates with the Brain Tumor Biology group (BTB) to the point that a clearcut thematic distinction is not meaningful for the purpose of this report. Glioblastoma (GBM) is a devastating brain tumor devoid of curative treatment options. Cells in the tumor microenvironment (TME), especially tumor-associated microglia, play a pivotal role in tumor development and support (1). Targeting microglia in combination with other modalities is a promising therapeutic strategy to control the disease.

Microglia modulation and adaptive immunity.
We have setup genetically modified immunocompetent mouse strains to genetically activate or deplete microglia in the tumor context. We found significant survival benefits when microglia was genetically activated. *In vitro*, we have optimized microglia phagocytosis assays, and are now able to perform them in reproducible manner using *in vivo* imaging and flow-cytometry based methods. This also applies to human GBM derived microglia, which enables us to assess the interaction/phagocytic capacity of microglia and GBM cells in a patient-matched way. Specifically, we are investigating the role of potential don't eat me signals, specifically Siglec receptors and Sirpa/CD47, on microglia, in the context of GBM. We analyzed Siglec expression in GBM associated microglia and found a correlation of *SIGLEC9* expression with overall survival. We have established mouse colonies to specifically delete *SiglecE* on microglia or overexpress human *SIGLEC9.* Phagocytosis assays blocking Siglec-E or Siglec-H enhanced tumor cell phagocytosis. Moreover, tumor cell phagocytosis was enhanced when we combined Siglec blockade with Sirpa-CD47 disruption. In the next years, we are especially interested in the role and interaction of microglia with T-cells that infiltrate into the tumor but are severely exhausted. We will thoroughly characterize the immune compartment in the mouse tumor models under question by multidimensional analysis. We hypothesize that "overphagocytosis" of GBM cells by microglia would lead to an intratumoral-cross presentation of neoantigens which in consequence could lead to tumor-reactive T-cells.

Microglia modulation and tumor specific CAR T cells.
We have generated and tested several batches of EGFRvIII-specific human CAR T cells. In parallel we have setup a CRISPR based approach to place the EGFRvIII CAR directly under the control of the TRAC promoter to become independent of lentiviral integration artifacts and potentially improve efficacy of the T-cells. Next, we will combine the CART treatment with microglia modulation, especially anti-CD47 treatment, but also other modifiers of microglia activity. In parallel, we have backcrossed the *Sall1-GFP* reporter mouse to an NSG background and will be able to perform cranial window experiments to visualize the interplay of pharmacologically modulated microglia, grafted tumor cells and intratumoral CARTs in detail. We aim to streamline the CAR production to fit GMP standards in line with a current initiative at our hospital. Moreover, modified CAR constructs that reprogram the GBM (TME) have been generated.

Microglia phenotype in GBM regions: region specific treatment responses.
We acquired a large biobank of navigated, clinically annotated brain tumor samples, specifically from viable tumor center and non-contrast enhancing, infiltrated periphery. We performed single-cell RNAseq analysis (Fig. 1) and established 3D perfusion bioreactor cultures of a vast array of these samples, to (1) pinpoint the differences of microglia and other immune components between center and periphery at baseline, and to assess the local response of the TME to combinations of microglia modulators and T-cell checkpoint inhibitors.
Using a multidimensional microscopy platform (CODEX, collaboration with Christian Schuerch, Stanford) for formalin fixed, paraffin embedded tissue, we established a 50-marker panel to gain unprecendent insight into the plasticity of the iTME under different treatment paradigms. The data of 8 patients is currently analyzed on our high-performance computing platform and will give us exciting information on how microglia and T-cells are shaping in different therapeutic settings and tumor regions (Fig. 2).

Figures ▶

Connection to Clinical Practice ▶

Selected Publications

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Brain Tumor Immunotherapy and Tumor Biology

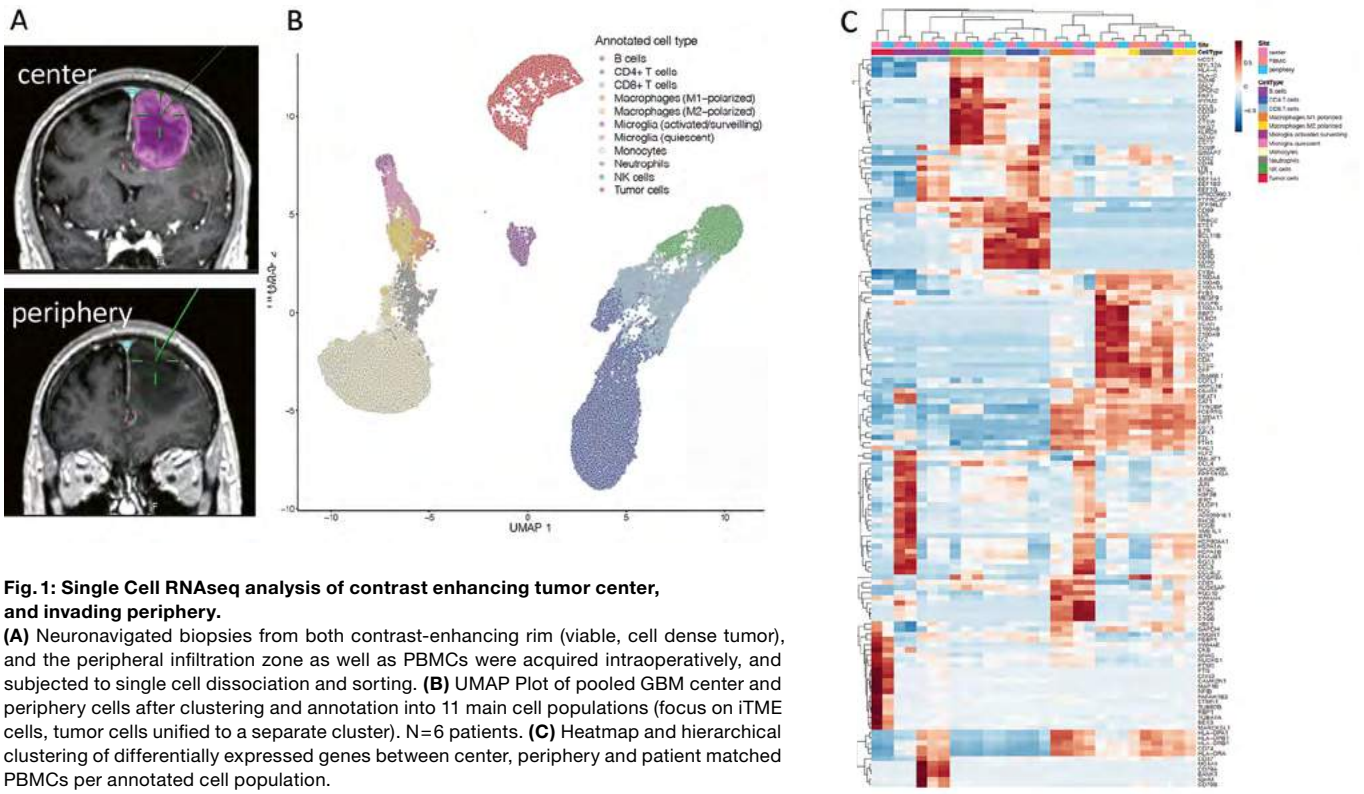


Fig. 1: Single Cell RNAseq analysis of contrast enhancing tumor center, and invading periphery.
(A) Neuronavigated biopsies from both contrast-enhancing rim (viable, cell dense tumor), and the peripheral infiltration zone as well as PBMCs were acquired intraoperatively, and subjected to single cell dissociation and sorting. **(B)** UMAP Plot of pooled GBM center and periphery cells after clustering and annotation into 11 main cell populations (focus on iTME cells, tumor cells unified to a separate cluster). N=6 patients. **(C)** Heatmap and hierarchical clustering of differentially expressed genes between center, periphery and patient matched PBMCs per annotated cell population.

Fig. 2: Multidimensional CODEX analysis allows iTME visualization and single-cell analysis of GBM patient-derived GBM bioreactor samples in different treatment settings.
A 50 immune and tumor marker panel was established to stain scaffolded patient-derived GBM bio-reactor samples after 7 d of immunomodulatory treatments at once (Center of figure, H&E stain). The downstream analysis pipeline consisted in segmentation and clustering/annotation of the iTME components. Examples of annotated cell types and their specific marker profiles are displayed derived from the multidimensional immunofluorescence microscopy data.

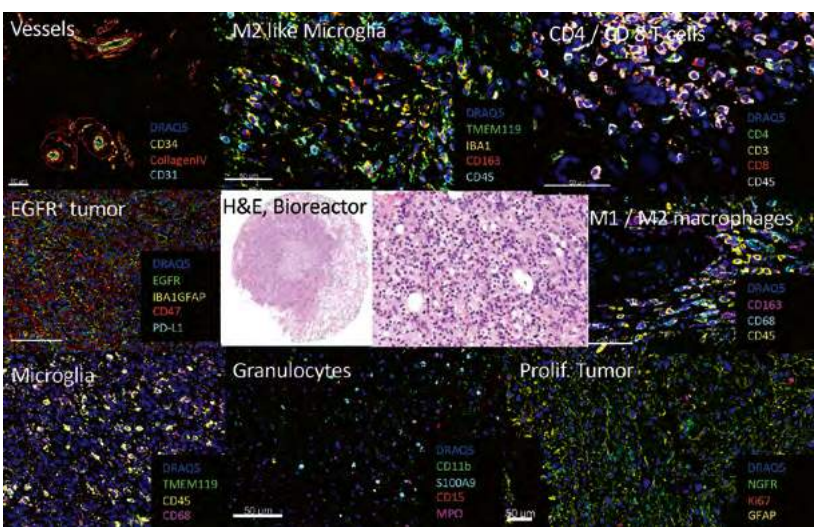
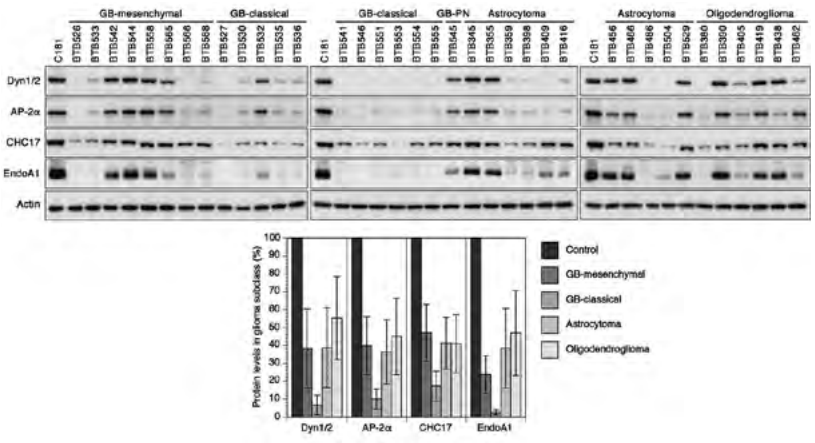


Fig. 3: Quantitative proteomics reveals reduction of endocytic machinery components in gliomas.
(From Buser *et al.,* 2019) Key endocytic machinery components (Dyn1/2, AP-2α, CHC17, EndoA1) are downregulated in various glioma subtypes, GB (classical), GB (mesenchymal), GB (PN), astrocytoma and oligodendroglioma. GB (classical), GB (mesenchymal), GB (PN) have been selected based on methylomic classifiers; astrocytoma have been selected based on the IDH1/2 mutation status and absence of 1p19q codel; oligodendroglioma have been selected based on IDH1/2 mutation status and 1p19q codel. Protein levels were quantified and plotted below in percent of the control sample of white matter mean and standard deviation of n=8 GB (IDHwt, mesenchymal), n=8 GB (IDHwt, classical), n=11 astrocytoma (IDHmut), and n=6 oligodendroglioma (IDHmut + 1p19q codel).



Connection to Clinical Practice

Prof. Gregor Hutter, Prof. Luigi Mariani
Neurosurgery, University Hospital Basel

Towards personalized glioma treatment

Having direct access to the neurosurgical operating theatre, we have been building a large biobank of clinically annotated brain tumor specimen and control samples. Using this repository, we are currently investigating the immunological differences between matched treatment-naïve primary and on-treatment recurrent GBM samples to deduct potential immunological interventions at recurrence. Indeed, several promising candidate genes expressed on tumor-associated microglia/macrophages and/or tumor cells are correlated with time to recurrence (manuscript in preparation).

In a proteomic study exploiting this biobank, we identified endocytic machinery components to be widely reduced in GBM samples, which might be an important and potentially targetable mechanism of enhanced oncogenic receptor signaling in GBM (Buser *et al.,* 2019, Fig. 3).

Generous support from the Department of Surgery at the University Basel and Pro Patient Forschungsstiftung enabled us to invest into a 3-dimensional *in vivo* culturing platform, which will allow us to tailor patient-specific immunotherapies in combination with tumor-targeting treatments. Using this approach, we hope to simulate the effect of patient-specific CAR T cells and combined microglia modulation directly on tumor tissue. The developed multi-dimensional analysis tools (CODEX, multiomics) will help in treatment stratification. Direct patient-specific response assessment should enable us to move faster towards clinical application of tailored, local iTME targeting treatments to improve brain tumor outcomes in the long term.

Prof. Luigi Mariani, Dr. Severina Leu
Neurosurgery, University Hospital Basel

Profiles from -omics analyses of gliomas have allowed to update and refine ‘classical’ histopathology, to lead to the 2016 WHO integrated classification of CNS tumors. Although newly defined subtypes can show distinct outcomes and responses to therapy, only few markers are currently available for only partial glioma classification. With the support of the Forschungsfonds of the University of Basel, we aim at identifying biomarkers specific for fast and reliable WHO glioma classification. To do so, we are currently performing wide-range proteomic and phospho-proteomic analyses of nearly 100 biopsies from adult glioma of all histologies and grades operated at Department of Neurosurgery. Identification of novel biomarkers is expected to provide novel tools for fast and reliable glioma classification, so that most appropriate therapeutic strategy could be applied, and longer term, may designate novel therapeutic targets.

Myocardial Research

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Cancer drug targets and the failing heart

Function of cancer-relevant kinases in the healthy and diseased heart

In the light of the increasing burden of cardiovascular disease observed in patients under and after chemotherapy (Ammon M *et al.,* J Card Fail 2013) and, more recently, targeted cancer treatment, we are investigating the function of cancer-relevant kinases and the impact of their inhibition in the healthy and injured heart. The goal of these studies is to gain novel insights into the molecular mechanisms of cardiotoxicity and cancer drug-associated cardiac side effects and to identify novel therapeutic targets for cardioprotection.

Our ongoing work focuses on fms-like tyrosine kinase 3 (Flt3), a prominent target of tyrosine kinase inhibitors (TKIs) administered to acute myeloid leukemia and solid tumor patients, in whom ensuing cardiomyopathies have been observed. We found that Flt3 is upregulated in the ischemically injured heart and that its activation via intramyocardial injection of its ligand confers cytoprotection and improves remodeling and function after myocardial infarction in mice (Pfister O *et al.,* J Am Coll Cardiol 2014). Using Flt3 ligand-deficient mice and mice treated with a Flt3-targeting TKI, we also uncovered a role of Flt3 in the maintenance and functionality of the cardiac side population (Della Verde *et al.,* submitted), a population enriched in cardiac progenitor cells (Pfister O *et al.,* Transl Res 2014), which could be relevant for patients with atherosclerosis and coronary artery disease. We further examined the effect of impaired Flt3- signaling on the outcome after myocardial infarction using Flt3-deficient and TKI-treated mice. We found very different effects depending on whether a genetic or pharmacological strategy was used, whereby the involved mechanisms appear related to both heart-intrinsic (pharmacological model) and heart-extrinsic actions of Flt3 (genetic model) (Monogiou Belik D, submitted, and Della Verde G *et al.,* unpublished).

We and others found that cancer drug toxicity is associated with cardiac microvascular rarefaction, which is at least in part due to the impaired endothelial differentiation potential of cardiac progenitor cells. These findings prompted us to further study the molecular mechanisms responsible for endothelial differentiation of cardiac progenitor cells. In this context, we identified the cell cycle regulator and tumor suppressor polo-like kinase 2 as an important regulator of cardiac cell fate in the early stages of endothelial lineage commitment (Mochizuki M *et al.,* J Am Heart Assoc 2017 and J Vis Exp 2019).

In summary, our findings on cancer relevant kinases in the heart provide novel insights into cardiac progenitor cell biology, are instructive regarding potential side effects of novel TKIs in the heart and could be therapeutically exploited to improve post-infarction remodeling and regeneration.

In our ongoing work, we now focus on non-coding RNAs in cardiac disease in a collaborative effort within COST Action CA 17129 CardioRNA (Robinson EL *et al.,* Noncoding RNA 2020, Pedrosa da Costa Gomez *et al.,* Circulation 2020, Pedrosa da Costa Gomez *et al.,* Noncoding RNA 2019).

Emerging concepts in heart failure with preserved ejection fraction (HFpEF)

HFpEF accounts for roughly half of all heart failure cases, but its pathophysiology is still poorly understood and no evidence-based guidelines for its treatment beyond the control of co- morbidities exist (Kuster GM and Pfister O, Swiss Med Wkly 2019). An emerging concept of HFpEF proposes that a pro-inflammatory state created by various co-morbidities including metabolic disease, diabetes, and hypertension, causes microvascular endothelial inflammation, which is associated with

the enhanced production of reactive oxygen species (ROS). We recently identified a contributory role of NOX1 to microvascular endothelial dysfunction and myocardial inflammation and remodeling in metabolically challenged mice (Xu *et al.,* under revision).

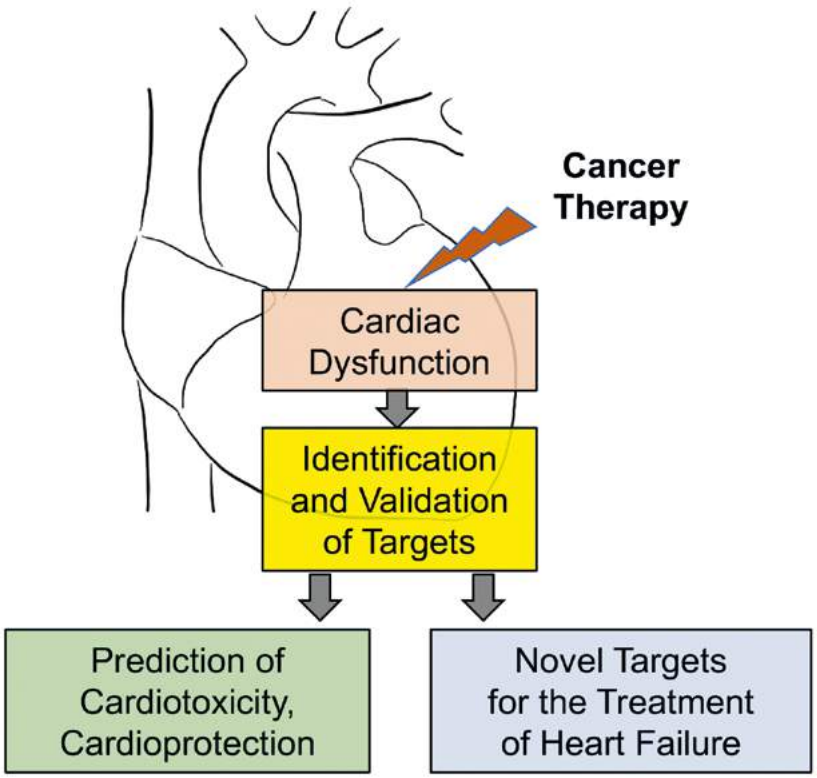

Fig. 1: The characterization of intended and unintended targets of cancer therapy and their downstream effectors in the heart is instructive regarding potential cardiovascular side effects and leads to the identification of novel candidate molecules that can be therapeutically exploited for cardioprotection in tumor patients or even treatment of heart failure in general.

Connection to Clinical Practice

Onco-Cardiology, a young and growing sub-specialty in cardiology

During the past decade, the still young and very dynamic field of Onco-Cardiology has established itself as a new sub-specialty of Cardiology. Whereas the focus at the beginning was mainly on the cardiotoxicity of classic chemotherapies such as anthracyclines, the field has grown significantly to include now all interfaces between cancer and cardiovascular disease from shared pathophysiology over common risk factors to the co-existence and interaction of both diseases. Rapid developments in the field of oncological drugs lead to a continuously large number of new approvals or new substances or substance classes administered within the scope of clinical trials. As a result, cardiovascular side effects in oncological patients will continue to be relevant in the future. Close interdisciplinary and multi-professional collaboration is essential in order to sustainably improve the survival of tumor patients, both with regard to the tumor and cardiovascular diseases. Current clinical and translational collaborations are ongoing with Medical Oncology, Hematology and the Breast Center of the University Hospital Basel.

Selected Publications

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Cancer Immunotherapy

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Improving cancer immunotherapy

Our main goal is to improve immunotherapy for cancer patients by using translational *in vitro* and *in vivo* tumor models, performing correlative analysis of patients treated with immunotherapy and conducting early clinical interventional trials (also see link to Medical Oncology).
One of our research foci is on the role of glycans and glycan-binding receptors in anti-cancer immunity. Glycans can mediate important interactions with immune cells and manipulation of glycans and glycan-binding receptors (lectins) bear a great potential to improve anti-tumor immune reactions. Glycan-mediated interactions in cancer immunology are significantly underexplored and could be used to improve anti-cancer immunity. Our group has studied the interaction between glycans that contain sialic acids (siaologlycans) and their interaction with Siglec receptors on immune cells and have demonstrated that this pathway can be targeted to augment T cell stimulation and tumor control. Current goals include improvement of cancer immunotherapy by modifying glycans in the tumor microenvironment and glycans of cellular products for adoptive cell therapies including genetically modified T cells.
An additional focus of our group is the improvement of immune checkpoint blockade and adoptive cellular therapies by investigating mechanisms and patterns of resistance to these therapies. To this end, we are investigating the tumor microenvironment as well as circulating immune cells in patients undergoing immune checkpoint blockade or adoptive T cell transfer. Identified pathways are further studied in the laboratory for their potential as new targets to improve antitumor immune responses.

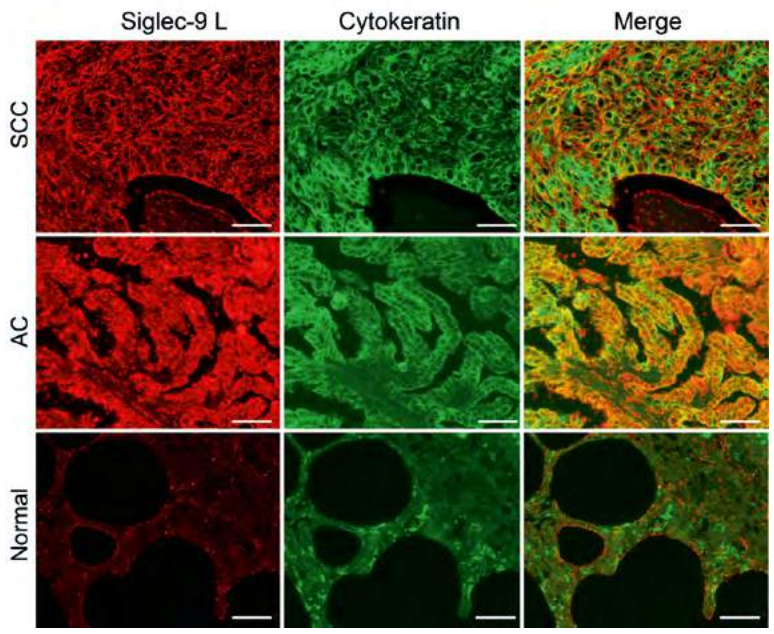

Fig. 1: Upregulation of Siglec-9 ligands in non-small cell lung cancer.
Squamous cell carcinoma (SCC), adenocarcinoma (AC) or normal lung tissue was stained with Siglec-9-Fc proteins (red) to detect Siglec-9 ligands and merged with cytokeratin staining to identify carcinoma cells. Siglec-9 ligands were found to be more often found in tumor tissue compared to normal tissue (from Stanczak *et al.,* J Clin Invest 2018).

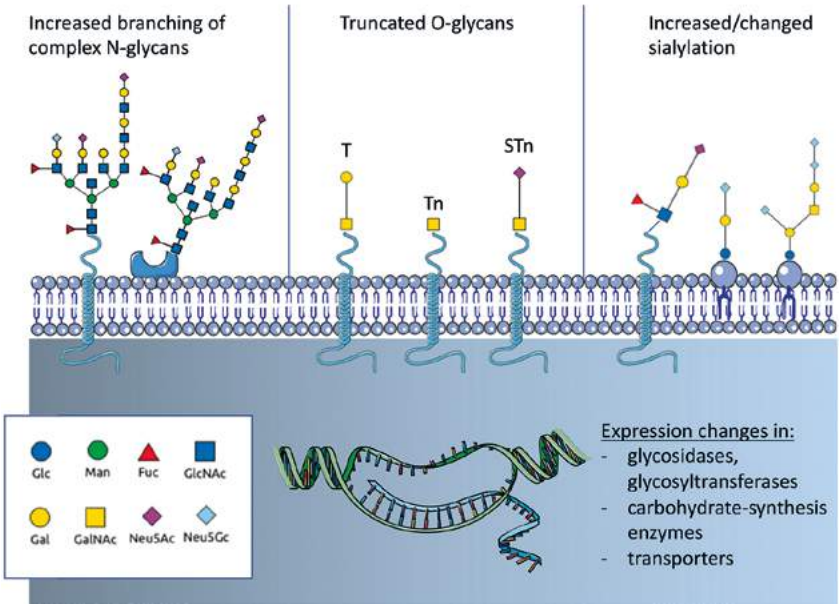

Fig. 3: Changes occurring in cancer-associated glycans.
Three main changes can be found in cancer that are regulated by genetic or epigenetic alterations in genes of glycan-modifying enzymes or enzymes involved in carbohydrate biosynthesis. N-glycans show often an increased branching due to increased MGAT5 expression. Another often observed change is the truncation of O-glycans and the exposure of new TACA including the T antigen, Tn antigen and the sialyl-Tn antigen (STn). In addition, changes of sialylation of both glycoproteins and glycolipids can be observed. Increased sialylation (hypersialylation) is often observed. The introduction of the non-human sialic acid Neu5Gc can also be observed. Glc, glucose; Man, mannose; Fuc, fucose; GlcNAc, N-acetyl-glucosamine; Gal, galactose; GalNAc, N-acetyl-galactosamine; N-acetyl-neuraminic acid; Neu5Gc, N-glycosyl-neuraminic acid (from Mantuano *et al.,* J Immunother Cancer 2020).

Selected Publications

Mantuano NR, Stanczak MA, de Araújo Oliveira I, Kirchhammer N, Filardy A, Monaco G, Christian Santos R, Carlos Fonseca A, Fontes M, de Souza Bastos Jr C, *et al.* (2020). Hyperglycemia enhances cancer immune evasion by inducing alternative macrophage polarization through increased O-GlcNAcylation. Cancer Immunol Res, 8, 1262–1272.

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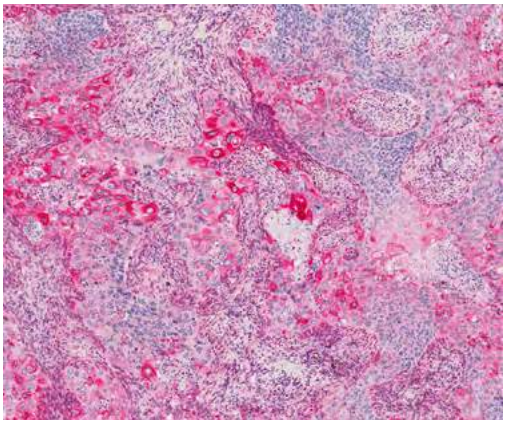

Fig. 2: HLA-F as a ligand for KIR3DS is present in lung cancer patients resistant to PD-1 blockade.
Immunohistochemical staining of lung adenocarcinoma tissue (form Trefny *et al.,* Clin Cancer Res 2019).compared to normal tissue (from Trefny *et al.,* Clin Cancer Res 2019).

Connection to Clinical Practice

Alfred Zippelius, Frank Stenner, Jakob Passweg
Department of Internal Medicine, Division of Oncology and Hematology, University Hospital Basel

Adoptive cell therapy for solid cancers

Adoptive cell therapy with TILs (tumor-infiltrating lymphocytes) for melanoma patients have been developed several years ago at the NIH. Clinical trials have shown high and very encouraging response rates depending on the stage and selection of patients. We have established and expansion protocol for the treatment of melanoma patient refractory to standard immune therapy with checkpoint inhibitors (and BRAF/MEK inhibition in BRAF mutated patients).

Our first planned clinical trial just recently started and will recruit patients. It includes an adapted classical expansion protocol and the application of IL-2 after the adoptive TIL transfer. In addition, we will perform a PD-1 blockade after stopping IL-2 treatment to render the tumor microenvironment more permissive for tumor-attacking T cells.

Our program will enable us to expand this treatment option to other tumor types. In addition, we are working to improve the expansion protocols and the specific expansion of tumor- recognizing T cells. Finally, the program will also allow for a direct translation of new genitically- modified T cell therapies into early clincical trials.

Myeloid Malignancies

Sara Meyer

Division of Hematology and
Department of Biomedicine
University Hospital Basel
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(Master student)

Mechanisms and targeting of oncogenic signaling in myeloproliferative neoplasms

Myeloproliferative neoplasms (MPN) are chronic leukemias with dysregulated production of mature myeloid cells. MPN occur as essential thrombocythemia with thrombocytosis, polycythemia vera with erythrocytosis, or myelofibrosis with increased megakaryocytes and marrow fibrosis. They progress to bone marrow failure or acute myeloid leukemia. Hematopoietic stem cell transplantation as a curative therapy is limited to a subset of patients. It is the goal of our studies to contribute to novel therapeutic approaches by targeting the molecular signaling driving these diseases.

MPN are characterized by dysregulated signaling of the JAK2 kinase due to acquired mutations in the JAK2 signaling pathway. JAK2 is a tyrosine kinase essential for hematopoiesis as the mediator of signaling from thrombopoietin, erythropoietin and GM-CSF receptors. JAK2 activates several signaling pathways including STAT transcription factors, phosphoinositide-3 kinase (PI3K) and mitogen activated protein kinase (MAPK) pathways, which promote cell proliferation. In MPN, JAK2 signaling is constitutively activated by mutations in JAK2, MPL or CALR. The central role of JAK2 signaling in MPN has led to the development of JAK2 inhibitors which act as ATP mimetics and stabilize JAK2 in the active form (type I inhibitors). Despite certain benefits, type I JAK inhibitors fail to reduce the MPN clone suggesting limited disease-modifying potential and induce resistance. To improve therapeutic targeting of JAK2 signaling, we are pursuing several approaches:

Targeting MAPK pathway activation

We found that MAPK signaling remains activated in MPN despite JAK2 inhibition. This suggests that compensatory activation of MAPK effectors bypass pharmacologic JAK2 blockade. We identified PDGFR signaling as a mediator of compensatory MAPK activation and dual targeting of JAK2 and MEK1/2, intermediate kinases in the MAPK pathway, showed superior therapeutic efficacy. Correction of splenomegaly and cytoses was improved by combined JAK2/MEK inhibition. Bone marrow fibrosis was reduced to an extent not seen with JAK2 inhibitors suggesting the MAPK pathway needs to be targeted for enhanced therapeutic efficacy.

More effective targeting of JAK2

A new mode of JAK2 inhibition has been reported which stabilizes the inactive form of JAK2 (type II inhibitors). We found high potency of type II JAK inhibition in preclinical MPN models. We observed decreased allele burden suggesting type II JAK inhibition could lead to a class of agents with disease-modifying potential. Resistance to type I JAK2 inhibitors is also abrogated. We are continuing our studies on type II JAK2 inhibition given the potential to lead to more potent, clone-directed JAK2 inhibitors.

Mechanisms of resistance to JAK2 inhibitors

Response to type I JAK2 inhibitors may be lost upon prolonged exposure, but JAK2 resistance mutations have not been found in patients. It has been shown that MPN cells reactivate JAK2 signaling by formation of JAK2 heterodimers with other JAK family members as JAK1 and TYK2. We found that this escape mechanism extends to type I JAK inhibitors in clinical development and observed cross-resistance. These molecular studies of resistance to JAK inhibitors may reveal new therapeutic targets, while studies on patient samples will provide insight into clinical JAK2 inhibitor resistance.

JAK2 signaling network

JAK2 activates STAT-, PI3K- and MAPK pathways and we have seen that combined inhibition of *e. g.* JAK2/Bcl2 or JAK2/MEK can increase benefit in JAK2-driven leukemia. We are investigating the JAK2 signaling network to delineate mechanisms limiting efficacy of JAK2 inhibitors to inform therapeutic strategies. We aim to extend these studies to other myeloid malignancies with suboptimal clinical benefit of tyrosine kinase inhibitors.

JAK2 signaling in thrombopoiesis

Efficacy of therapeutic targeting with JAK2 inhibitors is limited by on- and off-target toxicities. Thrombocytopenia is a relevant side effect of JAK2 inhibition. We have shown that JAK2 regulates megakaryopoiesis including formation of megakaryocyte-biased stem cells and are interested in differential effects of JAK2 inhibitors on thrombopoiesis.

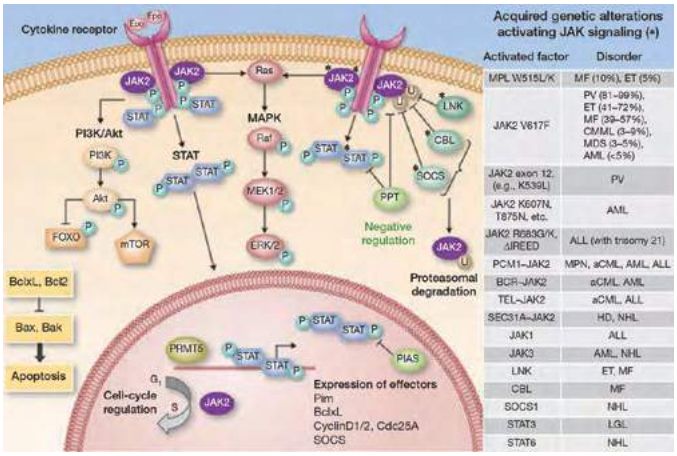

Fig. 1: Overview of JAK2 signaling. The JAK2 tyrosine kinase associates with hematopoietic cytokine receptors for EPO, TPO and GM-CSF. Upon ligand binding, JAK2 activates several signaling pathways including the STAT3 and STAT5 transcrip-tion factors, the PI3K/Akt pathway and the MAPK signaling pathway which includes RAS and the kinases RAF, MEK1/2 and ERK1/2. In MPN, JAK2 is constitutively activated by somatic mutations leading to excessive myeloid proliferation. The molecular interconnections between JAK2 and the downstream signaling pathways is not fully clarified. (Adapted from Meyer SC & Levine RL, Clin. Cancer Res. 2014)

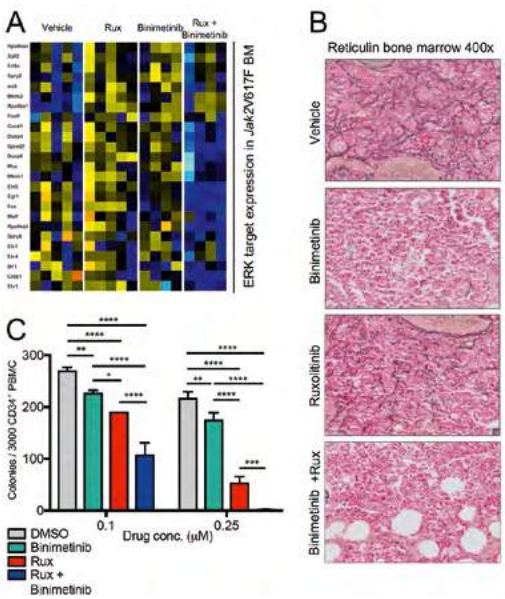

Fig. 2: Combined targeting of JAK2 and MEK provides therapeutic benefit in MPN *in vivo*. Pharmacologic inhibition of MEK by binimetinib and JAK2 by ruxolitinib is superior to ruxolitinib alone in reducing ERK target expression **(A)** and fibrosis in *Jak2*V617F mouse bone marrow **(B)**. Combined JAK2/MEK inhibition is also superior to ruxolitinib monotherapy in suppression of myeloid colony formation from MPN patient CD34+ cells **(C**, adapted from Stivala S, Codilupi T, Brkic S, Meyer SC. J Clin Invest 2019.).

Connection to Clinical Practice

Prof. Dr. J. R. Passweg
Prof. Dr. R. C. Skoda
Division of Hematology, University Hospital Basel

Characteristics of oncogenic signaling, therapeutic response and resistance in MPN patients

Our studies on oncogenic signaling and targeted therapeutic approaches in MPN are in close collaboration with Prof. R. Skoda who has established a long-term MPN patient cohort at University Hospital Basel, and Prof. J. Passweg, Head of the Division of Hematology at University Hospital Basel. We are studying clinical isolates of MPN patients with different mutational setup or at different stages of the disease for characteristics of oncogenic signaling and functional capacity of hematopoietic stem/progenitor cells. We are interested in the signaling dynamics in response to different therapies and upon development of resistance to conventional JAK2 inhibitors such as ruxolitinib. Collaborative studies with Prof. R. Levine based on the MPN cohort at Memorial Sloan Kettering Cancer Center New York, support these efforts. We aim to correlate the molecular findings with clinical characteristics of response or resistance to therapy in these MPN patients. These translational studies will facilitate potential clinical studies on improved targeting of JAK2 signaling in MPN in the longer term.

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Skin Biology

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*left during report period

Genodermatoses as a clue to cancer development

Epidermodysplasia verruciformis (EV) and ichthyosis with confetti (IWC), are genodermatoses serving as models for non-melanoma skin cancer (NMSC) development. Elucidating the mechanisms of these diseases will help to understand NMSC development in the general population.

Epidermodysplasia verruciformis (EV) is an autosomal recessive disease. EV patients develop plane wart-like lesions in childhood mainly on the neck and extremities. Most patients develop NMSC, mostly on UV-exposed areas. They are susceptible to beta-human papilloma virus (HPV). These HPV are harmless to the general population because they miss *E5,* a gene which is probably necessary for HPV to overcome the immune system. In about 50 % of patients, biallelic null mutations are found in *TMC6/EVER1* or *TMC8/EVER2.* Function of both proteins and the pathomechanism in EV are unknown. It is assumed that they are part of keratinocyte-intrinsic immunity, since EV patients are not susceptible to other infectious diseases.

We have expanded the phenotypical spectrum of EV by careful examination of patients. In collaboration with Casanova's group (Rockefeller University, NY; INSERM and Imagine Institute, Paris) we discovered *CIB1* (calcium and integrin binding 1) as a novel EV-associated gene. Functional studies showed the formation of a complex of both TMCs and CIB1. We generated a keratinocyte model using CRISPR-Cas9 enabling future functional studies of CIB1 independently of patient material.

Ichthyosis with confetti (IWC) is an autosomal dominant hereditary skin disorder. IWC patients suffer lifelong from erythroderma, but develop pale spots within the inflamed skin area, which look like healthy skin. All patients are carrier of a heterozygous keratin *(KRT) 1* or *KRT10* mutation which leads to a shifted reading-frame. We showed that the reading frame needs to be translated in an arginine-rich C-terminus of the keratin, leading to its nuclear accumulation instead of cytoplasmic localization (Fig. 2). It needs to be elucidated how the nuclear localization is associated with the disease-typical mitotic recombinations or gene conversions affecting the chromosome with the mutated KRT. This loss of heterozygosity leads to keratinocytes expressing the wildtype allele only. These cells present as pale spots on the skin. By clinical examination of patients and next-generation sequencing on fixed material from deceased patients, we showed that IWC patients have an increased risk of NMSC. Further functional analyses will be done to clarify how the IWC-causing pathomechanisms are related to NMSC and whether the same mechanisms are involved in NMSC in the general population.

As model to study skin diseases, we developed epidermal organoids. An organoid is a collection of organ-specific cells that develops from stem cells or organ progenitors and has the capability to recapitulate the function and architecture of the target organ. They are used for drug development and toxicity studies and in personalized medicine. They also have the potential to replace organ transplantation. In contrast to 2D keratinocyte cultures, epidermal organoids recapitulate the function and structure of the epidermis. By testing culture conditions, we have established Murine and Human Epidermal Organoids (HEO). HEO could be successfully generated from human foreskin keratinocytes (Fig. 3) and skin biopsies from healthy donors or patients.

While being necessary to protect us against dangers from the environment, innate immunity in the skin, when dysregulated, leads to various inflammatory dermatoses. Due to the complexity of innate immune responses and the plethora of insults our skin has to face, the physiology of inflammatory skin diseases is often not well known. Our current research projects are aimed at investigating the molecular events driving exacerbated innate immune reactions in the skin with a spe-

cial focus on hard to treat diseases such as rosacea, atopic dermatitis, pyoderma gangrenosum and hidradenitis suppurativa. Also, we are investigating the role of innate immunity in life threatening complications occurring after intake of certain medications, namely severe cutaneous adverse drug reactions.

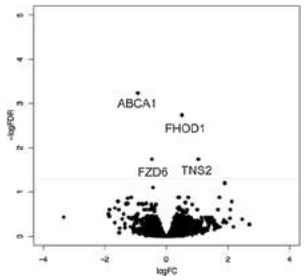

Fig. 1: RNAseq analysis of a high number of CIB1 knockouts with isogenic background showed small changes in expression level of few genes (Figure adapted from Imahorn *et al.,* 2020).

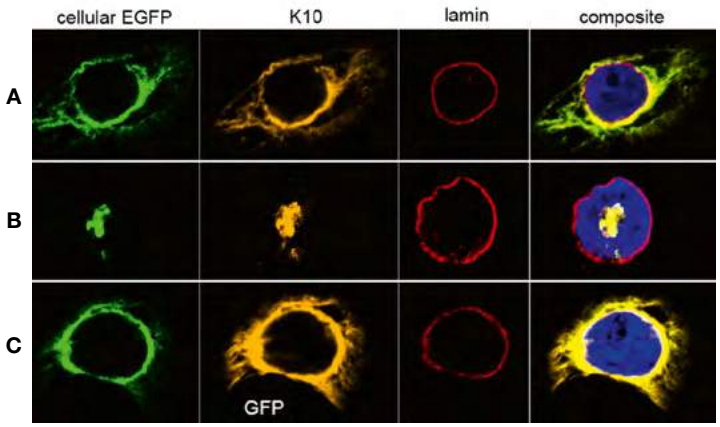

Fig. 2: Localization of various N-terminal GFP-labelled keratin 10 (K10) following transient transfection of a keratinocytes with plasmids encoding K10 with different C-termini. K10 was either detected by imaging of eGFP expressed from plasmid (cellular eGFP, green) or immunostaining with an anti-K10 or anti-GFP antibody (orange). The nuclear membrane was labelled with an anti-lamin antibody (red). DAPI (blue) was used for nuclear staining. **A.** K10 wildtype is localized in the cytoplasm of the keratinocyte. **B.** K10 with the IWC-typical arginine-rich C-terminus is localized in the nucleus of transfected keratinocytes. **C.** K10 with an alanine-rich C-terminus as the result of the alternative third reading frame is clearly localized in the nucleus. Immunostaining of K10 alanine was done using the anti-GFP antibody since this K10 was not detected by the anti-K10 antibody. (Figure adapted from Renz *et al.,* 2019).

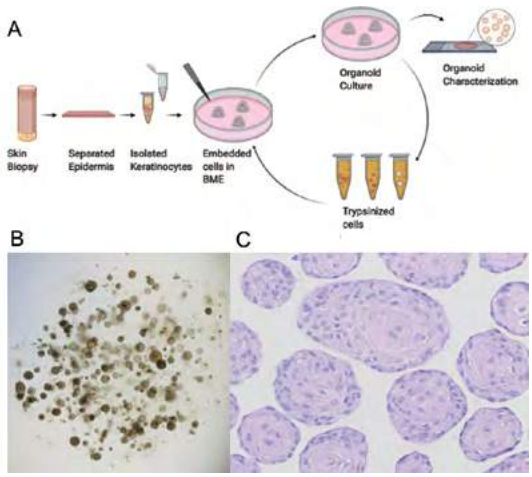

Fig. 3: Generation of human epidermal organoids recapitulating the epidermis structure.
A. Overview of the method.
B. Human organoids growing in Matrigel (light microscopy).
C. Hematoxylin & Eosin coloration of human epidermal organoids after 7 days of culture.

Connection to Clinical Practice

Prof. Dr. P. Itin (retired during period; laboratory head Dr. Burger)
Prof. Dr. A. Navarini (laboratory head Dr. Contassot)
Dermatology Department, USB

Skin inflammation in drug reactions, rosacea and other skin conditions

Until July 2020, the aim of our research was to identify mutations driving rare skin diseases and functionally investigate the proteins and their link to the phenotype observed in patients. Our research group is in transition due to the change of the research group leader. Whilst the aim of our research remains the same, namely to understand dermatologic conditions on the level of the pathophysiology, our focus is moving towards immunology. To this end, the labhead has changed from Dr. Bettina Burger to PD Dr. Emmanuel Contassot on the 1st of July 2020. We are currently building up research project involving the pathophysiology of drug reactions and the inflammatory skin disease rosacea. To this end, we closely work with the Dermatology Department to: Investigate the relevance of biological and genetic observations using biological material from patients and characterise the molecular mechanisms that mediate pathogenic events and their link with lesion development in patients.

Selected Publications

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Burger B, Ghosh A, Ng CKY, Piscuoglio S, Spoerri I, Itin PH, Greer K and Elbaum D (2020). Discovery of heterozygous KRT10 alterations in MAUIE cases underlines the importance of regular skin cancer screening in ichthyosis with confetti. The British journal of dermatology.

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Imahorn E, Yuksel Z, Spoerri I, Gurel G, Imhof C, Saracoglu ZN, Koku Aksu AE, Rady PL, Tyring SK, Kempf W *et al.* (2017). Novel TMC8 splice site mutation in epidermodysplasia verruciformis and review of HPV infections in patients with the disease. J Eur Acad Dermatol Venereol 31, 1722–1726.

Visceral Surgery and Precision Medicine

Salvatore Piscuoglio

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Dr. med. Stephanie Taha-Mehlitz* (Postdoc)
Kancherla Venkatesh (PhD Student)

*left during report period

Integrative approaches to augment precision medicine in cancer

Precision medicine is about getting the right treatment to the patients at the right time. Taking rectal cancer as an example, patients with intermediate-stage rectal cancer are typically treated with chemoradiotherapy followed by surgical excision to remove any residual disease. Post- surgery histologic analysis reveals that ~25% of the patients achieve complete response to chemoradiotherapy, meaning that they would not have needed surgical intervention. For the remaining patients that do not achieve complete response to chemoradiotherapy, alternative therapeutic options are desirable. Thus the identification of robust biomarkers that will precisely predict which patients would likely achieve good response to chemoradiotherapy, thus sparing them the unnecessary surgery, are urgently needed. On the other hand, model systems that reflect the biological behavior of the tumors in individual patients to test alternative therapeutic options in an *ex vivo* manner are essential. Our lab takes several complementary approaches to address outstanding challenges in precision oncology.

Ex vivo models for drug testing

Patient-derived organoids (PDOs) have been shown to retain the molecular features of the original tumors and to better resemble tumor heterogeneity than traditional two-dimensional cell culture methods derived from single cell clones. They are thus frequently used as *ex vivo* preclinical models for drug response prediction. In collaboration with the visceral surgeons at the Clarunis, we have initiated the prospective collection of patient tumors to establish a living biobank of PDOs. To date, we have successfully established a collection of ~100 PDOs (Fig. 1a). We have also established a protocol to test drugs and monitor response in real-time over five days. Using this protocol, we showed that 6-mercaptopurine effectively reduces cell growth and induces apoptosis in colorectal tumors with overexpression of ADSL, a gene with a critical role in purine synthesis (Fig. 1b).

Discovery of cancer vulnerabilities

The concept of synthetic lethality has helped extend precision oncology to enable the targeting of undruggable genes by disrupting their genetic interactors. For instance, GATA3 is mutated in 15–18% of estrogen-receptor positive breast cancer but is not targetable. By systematically interrogating a large-scale RNAi screen, we identified MDM2 as a top synthetic lethal interactor of GATA3. We found that pharmacological inhibition of MDM2 with idasanutlin reduces cell proliferation and induces apoptosis in GATA3-deficient cancers *in vitro* and in two independent *in vivo* models (zebrafish and chicken chorioallantoic membrane models). GATA3-mutant PDOs are also more sensitive to idasanutlin than GATA3-wild-type PDOs (Fig. 2a–b). With idasanutlin and other MDM2 inhibitors widely available, our findings can be rapidly translated into clinical trials to evaluate in-patient efficacy and GATA3 mutation status as a predictive biomarker of response to idasanutlin in breast cancer.

Cell-free DNA as a minimally invasive tumor surrogate

Precision medicine is only possible with tumor materials, and those that can be obtained through minimally invasive procedures (e. g. blood draw) are particularly desirable. Plasma- derived cell-free DNA (cfDNA) has been shown to reflect the genetic makeup of tumors and may serve as a tumor surrogate for mutation detection and disease monitoring during the course of therapy. cfDNA may be particularly useful as a genetic surrogate for tumors difficult to or not amenable to biopsy. This is important for hepatocellular carcinoma (HCC) as its diagnosis does not always require tissue biopsy; tumor tissue materials in inoperable patients are usually un-

available. The lack of tumor materials hinders the wider adoption of precision medicine in HCC. We found that genetic profiling of plasma-derived cfDNA was an adequate surrogate of primary HCC in patients with large tumor or metastatic disease (publication awarded the Swiss Foundation against Liver Cancer 2019 award). We are now investigating whether cfDNA may help disease monitoring in HCC (Fig. 3).

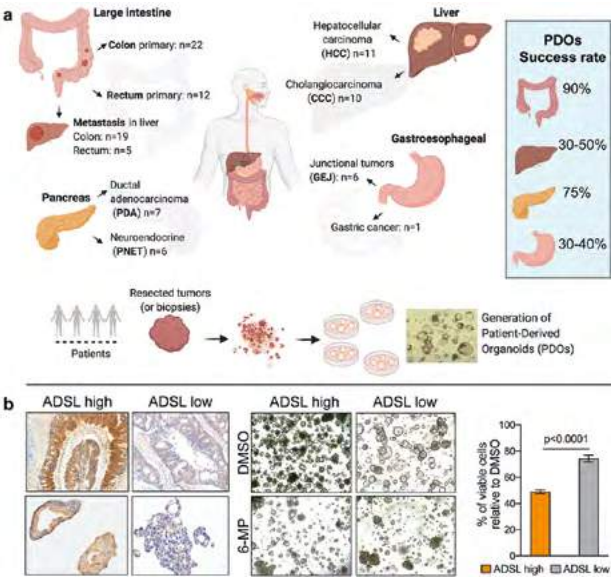

Fig. 1:
(a) We have optimized protocols to derive patient-derived organoids from tissue specimens. In collaboration with the surgeons at Clarunis, we have established ~100 organoids in our living biobank. **(b)** Our drug screening protocol in PDOs enabled us to demonstrate that ADSL overexpression is a biomarker of response to 6-mercaptopurine in colorectal tumors.

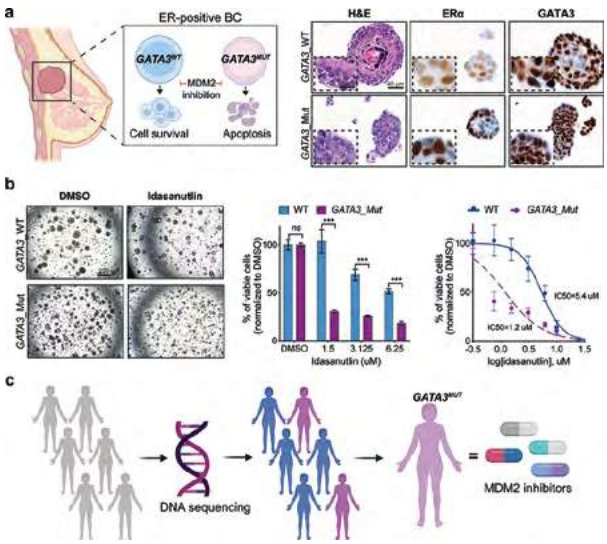

Fig. 2:
(a) MDM2 is a novel synthetic lethal target in *GATA3*-mutant estrogen receptor (ER)-positive breast cancer. Organoids derived from *GATA3*-wild-type (WT) and *GATA3*-mutant breast cancers. **(b)** *GATA3* mutations sensitize PDOs to idasanutlin treatment. **(c)** Genetic screening strategy to enable the precise targeting of the *GATA3*-mutant breast cancer.

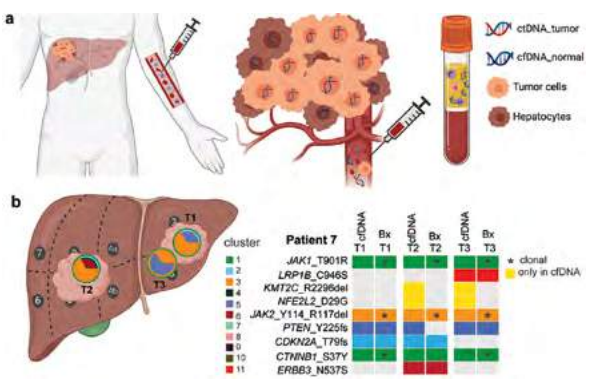

Fig. 3:
(a) Plasma-derived cell-free DNA as a tumor surrogate for mutation detection. **(b)** Longitudinal collection of cell-free DNA as a disease monitoring tool in hepatocellular carcinoma.

Connection to Clinical Practice

Prof Markus von Flüe and Prof Otto Kollmar
Clarunis Universitäres Bauchzentrum Basel

Generation of a living biobank for precision medicine

The availability of fresh tumor tissues directly from patients is critical for meaningful translational research on human cancer. With the surgery department at the Clarunis, we have established a clinical protocol to prospectively collect fresh tissues from biopsies and surgery that will allow us to establish a living PDO/patient-derived xenograft (PDX) biobank of visceral cancers (Fig. 1). The biobank, together with the collection of blood, lymphocytes and cfDNA, helps advance towards an integrated functional and multi-omics approach to support clinical decision making.

Selected Publications

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Genome Plasticity

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Genome dynamics in cell programming, aging and human disease

DNA in our cells is continuously damaged through its exposure to reactive agents of endogenous or environmental origin. Damage to DNA, however, does not only occur randomly by chemical reactions, but also on purpose, by the action of enzymes, to increase genetic variance or alter cell fate determining epigenetic marks, i.e., DNA methylation. Modifications of either kind occur thousands of times in our DNA every day and need to be controlled if genome integrity is to be maintained. We investigate molecular mechanisms underlying this dynamic instability of genomes. Over the past years, our research focus has been the role of DNA repair in DNA demethylation and its contribution to the patterning and maintenance of epigenetic programs – hence – cell identity. We have been following three main lines of investigation towards (i) unraveling the basic molecular mechanisms and function of active DNA demethylation, (ii) the relevance of DNA methylation control and stability for human aging and disease, and (iii) the impact of the environment on the stability of DNA methylation.

Shaping chromatin by DNA repair mediated DNA demethylation

An important long-term interest of our research has been a DNA repair pathway controlled by the "Thymine DNA Glycosylase" (TDG). TDG first caught our attention because of its ability to remove thymine (T) or uracil (U) when mismatched with guanine (G) in DNA. T•G and U•G mismatches arise frequently by hydrolytic deamination of cytosine (C) or 5-methylC (5mC) and, unless repaired, will give rise to C>T mutations, the most prevalent base substitution found in our genomes. While its enzymatic activity implicates TDG in the anti-mutagenic repair of these mismatches, our research led us to uncover a quite different function. It started with the unexpected observation that a genetic defect in TDG causes developmental failure in a mouse model, due to aberrant gene expression and DNA methylation patterning. Together with work of others on the biochemistry of trans-eleven-translocation (TET) proteins, these findings indicated TDG to act in a pathway for active DNA demethylation, operating through the oxidation of 5mC by TET and replacement of the oxidized 5mC with a C through TDG dependent DNA repair. We then found that TDG and TET indeed cooperate in differentiating cells to drive cyclic methylation and demethylation at specific gene regulatory sequences. We were able to show that TET1 and TDG physically and functionally interact to form an active DNA demethylase, and to proof by full biochemical reconstitution that the TET-TDG-repair system, coordinated by SUMO modification, is capable of productive DNA demethylation. Ongoing work addresses, amongst other questions, the "biology" of TDG driven DNA methylation/demethylation cycling, in particular its implicated role in shaping chromatin and gene expression states in differentiating cells.

(Epi)genetic maintenance by DNA repair

Aberrant DNA methylation contributes to tumorigenesis by deregulation of the genome, but exactly why and how such aberrations arise is largely unknown. Our aim is to identify and mechanistically understand genetic und environmental conditions modulating DNA methylation stability in human tissues. Investigating DNA methylation stability in the human colonic mucosa with a molecular epidemiological approach, we were able to decipher distinct patterns of age-dependent DNA methylation drift and found the rate of such DNA methylation change to be modulated by lifestyle factors, including BMI, medication and smoking. This work in healthy tissue allowed us then to derive cancer-specific patterns of aberrant DNA methylation and, subsequently, to separate on that basis subtypes of colon cancer

that evolve through different molecular pathways associated with and without a CpG-island methylator phenotpype (CIMP). Mechanistically, we were able to show CIMP in colon cancer to be a consequence of a malfunction in TET dependent active DNA demethylation, caused by BRAF-induced downregulation of TET1. Current work addresses the mechanism underlying this link between oncogenic signalling an epigenetic remodelling.

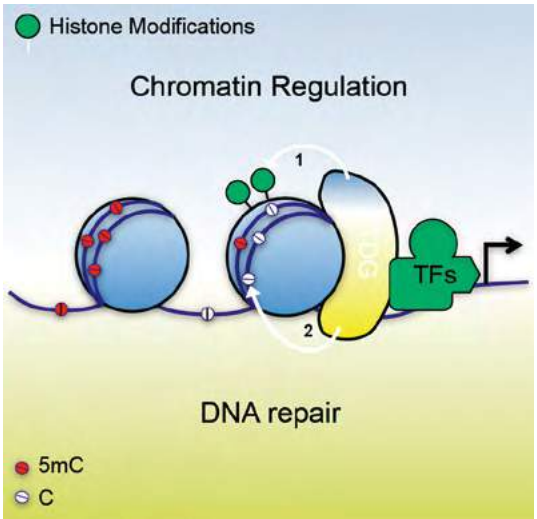

Fig. 1: TDG dependent DNA excision repair controls epigenetic states through DNA demethylation.

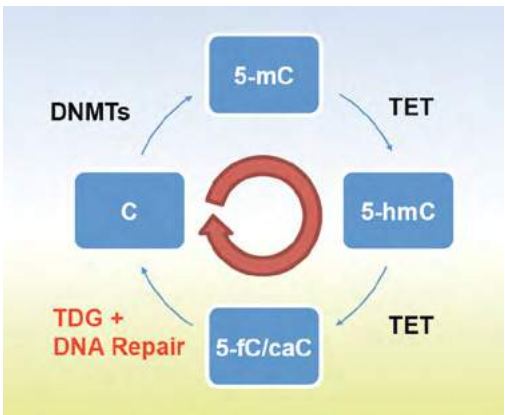

Fig. 2: TDG and TET hydroxylases cooperate in cyclic DNA methylation and active oxidative demethylation at CpG di-nucleotides in the genome. TDG excises 5-fC and 5-caC, thereby initiating excision repair incorporating an unmethylated C. 5-mC, 5-methylcytosine; 5-hmC, 5-hydroxymC; 5-fC, 5-formylC; 5-caC, 5 carbocylC.

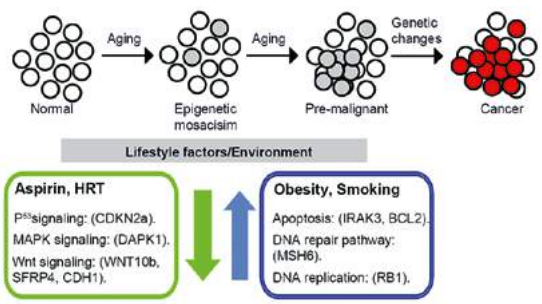

Fig. 3: Lifestyle factors modulate the rate of DNA methylation drift in the aging colonic mucosa and, by inference, early events of colorectal carcinogenesis.

Connection to Clinical Practice

PD Dr. Kaspar Truninger

Truninger is an Gastroenterologist leading the clinical parts of the cancer epigenetics projects.

Selected Publications

Noreen F, Chaber-Ciopinska A, Regula J, Schär P and Truninger K (2020). Longitudinal analysis of healthy colon establishes aspirin as a suppressor of cancer-related epigenetic aging. Clin Epigenet 12, 164.

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Manser M, Sater M, Schmid C, Noreen F, Murbach M, Kuster N, Schuermann D and Schär P (2017). ELF-MF exposure affects the robustness of epigenetic programming during granulopoiesis. Sci Rep 7, 43345.

Weber A, Krawczyk C, Robertson A, Kuśnierczyk A, Vågbø CB, Schuermann D, Klungland A and Schär P (2016). Biochemical reconstitution of TET1–TDG–BER-dependent active DNA demethylation reveals a highly coordinated mechanism. Nat. Commun. 7, 10806.

Childhood Leukemia

Jürg Schwaller

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Models and molecular mechanisms of acute myeloid leukemia (AML)

Our research aims to understand the cellular and molecular mechanisms of a human blood cancer called acute myeloid leukemia (AML). We focus on genetic lesions associated with particularly aggressive disease that, despite improved therapeutic options, remains incurable for most of the patients. Based on the rarity and genetic heterogeneity of the disease with limited access to primary material, we perform most of our studies in cell- and mouse models. During the last three years, we worked on two major subjects.

A) We studied the impact of the cellular origin and transforming potential of AML-associated fusion oncogenes by generating a series of inducible transgenic mouse lines (in collaboration with A. Peters, FMI, Basel and T. Mercher, Institute Gustave Roussy, Paris). We found that these fusions act as epigenetic regulators and induce a reversible leukemia in mice that closely phenocopies the human disease. Interestingly, induction of an MLL-AF9 fusion in hematopoietic stem cells (HSC) resulted in a more aggressive disease than activation in more committed progenitor cells. In contrast to MLL-AF9, the MLL- ENL fusion only resulted in leukemia when induced in HSC and early multipotent progenitors suggesting a particular window of hematopoietic transformation susceptibility (Stavropoulou *et al.,* 2018). The NUP98-MLL fusion is the only AML-associated MLL rearrangement in which the entire C-terminus of the protein is maintained. Induction of NUP98-MLL resulted in myelodysplastic syndromes and AML in mice (Fisher *et al.,* 2020). The ETO2-GLIS2 fusion gene is a molecular hallmark of acute megakaryoblastic leukemia (AMKL) almost exclusively affecting young children. Strikingly, ETO2-GLIS2 induction in mouse fetal HSC rapidly induced reversible AMKL, while expression in adult mouse BM cells resulted in long latency AML. Chromatin and transcriptomic analysis revealed that ETO2-GLIS2 rewired transcription factor activities in an ontogeny-dependent manner. Thus, we established the first *in vivo* model for ETO2-GLIS2-driven AMKL and showed that the phenotype of pediatric AML is determined by ontogeny-dependent susceptibility for transformation by particular oncogenic fusion genes (Lopez *et al.,* 2019).

B) Functional characterization of the nuclear interacting SET domain protein 1 (NSD1), a histone methyltransferase involved in a fusion oncogene in pediatric AML, led us to study acute erythroleukemia (AEL). Genetic inactivation of NSD1 in the hematopoietic system of the mouse unexpectedly resulted in development of a fully penetrant disease with several hallmarks of human AEL. Functional studies revealed that despite abundant expression of the erythroid transcriptional master regulator called GATA1, differentiation of Nsd1-/- erythroblasts was significantly impaired. Expression of wildtype but not a catalytically-inactive NSD1 mutant rescued differentiation associated with increased GATA1 chromatin occupancy and target gene activation. Collectively our work indicates that the NSD1 methyltransferase is a novel regulator of GATA1-controlled erythroid differentiation and leukemogenesis (Leonards *et al.,* 2020). AEL is a rare but very aggressive human cancer. To better understand its molecular pathology, we genetically characterized a series of world-wide collected primary AEL samples. We found at least three molecular subgroups including patients carrying TP53 mutations, epigenetic mutations, and others. We established a transcriptomics-based space in which, independently of the genetic subgroup, most AEL samples exhibited a unique mapping that was clearly different from other AML or MDS. In >25% of the cases, we found aberrant expression of transcriptional regulators related to impaired activity of GATA1. Ex-

pression of these factors immortalized murine erythroid progenitors *in vitro* and led to erythroid or erythroid/myeloid proliferations *in vivo*, phenocopying human AEL. This work indicates that AEL is a genetically heterogeneous disease with an erythroid identity that results in part from the aberrant activity of key erythroid transcription factors like GATA1 (Fagnan *et al.,* 2020).

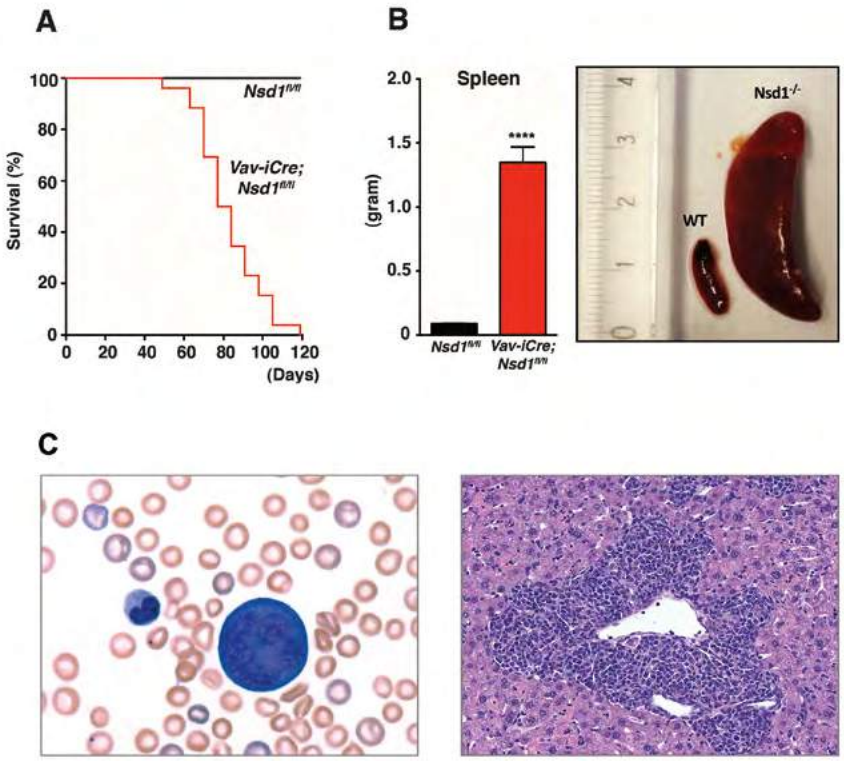

Fig. 1: Genetic inactivation of the NSD1 histone methyltransferase in the hematopoietic system of the mouse results in a fully penetrant disease that phenocopies human acute erythroleukemia.

A) Kaplan-Meier survival plot

B) Significant splenomegaly of diseased *Vav-iCre;Nsd1$^{fl/fl}$* (= *Nsd1$^{-/-}$*) mice

C) Left: peripheral blood smear of a diseased *Nsd1$^{-/-}$* mouse with a large dysplastic multinuclear erythroblast, a smaller myelocyte, reticulocytes and poorly globinized erythrocytes; right: liver section showing extensive infiltration by erythroblasts.

Selected Publications

Stavropoulou V, Almosailleakh M, Royo H, Spetz JF, Juge S, Brault L, Kopp P, Iacovino M, Kyba M, Tzankov A, *et al.* (2018). A Novel Inducible Mouse Model of MLL-ENL-driven Mixed-lineage Acute Leukemia. Hemasphere 2, e51.

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Molecular pathogenesis of myeloproliferative neoplasms

Myeloproliferative neoplasms (MPN) are a group of blood diseases characterized by aberrant proliferation of precursors of the myeloid, erythroid and megakaryocytic lineages. They represent clonal stem cell disorders with a tendency towards leukemic transformation. Currently, no curative therapy is available. MPNs comprise 3 entities: polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). The goal of our studies is to advance the understanding of the molecular events that initiate MPN and influence its progression to leukemia. A recurrent mutation *Janus kinase 2 (JAK2)* gene that substitutes a valine to phenylalanine at position 617 (*JAK2*-V617F) is present in a majority of patients with MPN. This mutation leads to activation of the Jak2 tyrosine kinase and represents a driver for the proliferation of hematopoietic cells. Activating mutations *Calreticulin (CALR)* and the *Thrombopoietin receptor (MPL)* genes represent other frequent driver events. Despite this progress, several questions remain unsolved including what determines whether a hematopoietic stem cell (HSC) after acquiring a driver gene mutation expands to initiate MPN disease, or stays inactive and eventually disappears, what determines the progression to myelofibrosis or acute leukemia, and how a single *JAK2*-V617F mutation causes three different MPN phenotypes. We are examining these questions by combining three approaches: molecular studies in patients with sporadic MPN, genetic analysis of familial MPN and transgenic mouse models that mimic the human disease.

Analysis of MPN disease initiation

The discovery of clonal hematopoiesis of indeterminate potential (CHIP) and the fact that *JAK2*-V617F is one of the most frequent CHIP mutations in healthy individuals showed that acquisition of *JAK2*-V617F not the rate-limiting step in MPN pathogenesis, as only a fraction of individuals who carry *JAK2*-V617F eventually develop MPN disease. We are examining which factors promote the expansion of the *JAK2*-mutant clone to MPN disease initiation (Fig. 1). We determined that additional mutations in epigenetic regulator genes, e. g. *Ezh2,* or *Dnmt3a,* or inflammatory signals (e. g. *IL-1β*), as well as inherited predisposition mutations can favor clonal expansion and MPN disease initiation.

Familial predisposition for MPN

Familial syndromes resembling MPN can be grouped into two classes:

1. Inherited disorders with high penetrance and polyclonal hematopoiesis ("class 1").
2. Hereditary predisposition to true MPN ("class 2"), with low penetrance, clonal hematopoiesis and occurrence of somatic mutations, e. g. in *JAK2*-V617F.

We identified for the first time a mutation in the erythropoietin *(EPO)* gene that causes familial polyclonal erythrocytosis with elevated erythropoietin levels. This mutation, a single-nucleotide deletion (c.32delG), introduces a frameshift in exon 2 that interrupts translation of the main *EPO* messenger RNA (mRNA) transcript but initiates excess production of erythropoietin from what is normally a noncoding EPO mRNA transcribed from an alternative promoter located in intron 1. Families with "class 2" phenotype are more common than generally assumed. These germ line mutations increase the likelihood of transition from *JAK2*-V617F CHIP to MPN disease. We are using genetic methods to identify such pre-disposing mutations.

Mouse models for MPN

We generated JAK2-V617F transgenic mice that express the human *JAK2*-V617F and develop MPN phenotype. A major focus of our research is to examine the nature of the MPN initiating stem cells and their interactions with the bone marrow

microenvironment. We demonstrated that MPN can be initiated by transplanting single hematopoietic stem cells that carry *JAK2*-V617F as the sole genetic alteration and that loss of function mutations in *Ezh2, Dnmt3a* promoted, while loss of *IL-1β,* the inflammatory master regulator, decreased MPN disease initiation from single HSCs. We are using our mouse models for pre-clinical screening of *Jak2* inhibitors and other potential therapeutic agents. We also found that mutant JAK2 induces metabolic reprogramming of hematopoietic cells causing increased energy requirement that can be targeted by inhibitors of metabolism (Rao et al 2019).

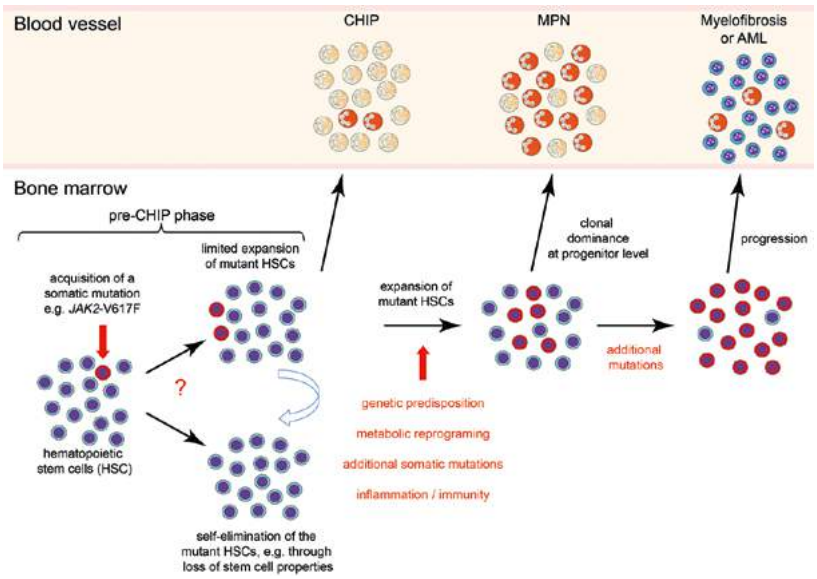

Fig. 1: Model of MPN disease initiation. Somatic mutations can occur in all cells including hematopoietic stem cells (HSCs). A single HSC in bone marrow that acquired a driver gene mutation (marked in red), e. g. *JAK2*-V617F, can either divide and increase the number of mutant HSCs, or divide and differentiate to mature cells of limited life span, thereby eliminating the mutant clone. This "pre-CHIP" phase is not yet detectable in peripheral blood. The *JAK2*-mutant clone has to expand to become self-sustaining and to generate sufficient numbers of mature blood cells to become detectable in peripheral blood (CHIP-phase). Further expansion and clonal dominance of the *JAK2*-mutant HSCs is required to initiate MPN disease characterized by increased numbers of erythrocytes and/or platelets (MPN-phase). Several factors (marked in red) can favor the transition from CHIP to MPN and the progression to myelofibrosis or acute leukemia (AML).

Connection to Clinical Practice

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New therapeutic approaches to treat MPN: From bench to bedside

A collaborative study with Dr. S. Mendez-Ferrer showed that a β3-adrenergic receptor agonist restored Nestin-positive cells within the stem cell niche, and thereby normalized blood counts and improved myelofibrosis in our *JAK2*-V617F MPN mouse model (Arranz *et al., Nature* 512:78-81, 2014). Based on these observations, we performed a clinical phase-II study with the β-3 sympathomimetic agonist Mirabegron in 39 *JAK2*-V617F-positive MPN patients (Drexler *et al.,* 2019). While the primary end point (reduction of *JAK2*-V617F allele burden of ≥ 50 %) was not reached, we observed increase in Nestin-positive niche cells and decrease in reticulin fibrosis in Mirabegron-treated patients. These results are encouraging and show that Mirabegron can modify the microenvironment where the *JAK2*-mutant stem cells are maintained and thereby diminish the fibrotic manifestations of MPN.

Selected Publications

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Targeting the PI3K/mTOR pathway in cancer, immunity and neurodegenerative disease

The phosphoinositide 3-kinase (PI3K) – mechanistic target of rapamycin (mTOR) axis is key to cancer progression, but also regulates inflammatory, allergic and metabolic events and plays a role in neurodegenerative disease. The four class I PI3Ks are the only PI3K family members to produce PtdIns(3,4,5)P_3, which acts a docking site for effector proteins with phosphoinositide-binding domains. While class IA PI3Ks associate with phosphorylated growth factor receptors and their substrates, the sole class IB, PI3Kγ, is activated by G protein-coupled receptors (GPCR). The PI3Kγ catalytic subunit p110γ is bound to either a p84 or p101 adapter subunit. We have demonstrated with various approaches that the p84 and p101 subunits have non-redundant functions, and that the full activation of the p84-p110γ complex requires activated, GTP-loaded Ras proteins. This makes mast cells, expressing exclusively p84, susceptible to drugs interfering with Ras membrane attachment, while macrophages with p84 and p101 maintain GPCR signaling [Fig. 1]. This suggests that targeting of p84-p110γ complexes provide a cell-selective path to alleviate allergic responses, without impairing host defense mechanisms (Jin *et al.,* 2020).

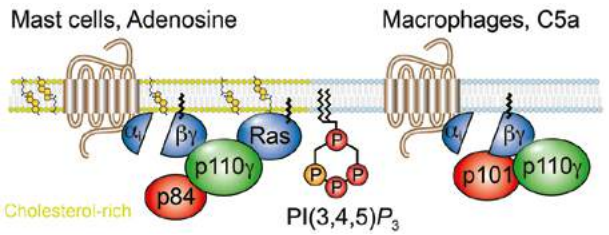

Fig. 1: Class IB PI3Kγ is activated downstream of activated GPCRs by Gβγ subunits of trimeric G proteins. Its catalytic subunit p110γ exists at the plasma membrane in two complexes, either bound to the adapter subunit p84 (also dubbed p87^{PIKAP}) or p101. The p84-containing complex operates in a cholesterol-rich submembrane compartment and requires activated Ras to produce phosphoinositide (3,4,5)-tris phosphate [PI(3,4,5)P_3]. Using isoprenylation inhibitors of Ras, we could demonstrate sensitivity in mast cell PI3Kγ signaling operating via p84, and resistance on macrophages with both p101 and p84 (Jin *et al.,* 2020).

Due to numerous oncogenic inputs that activate PI3Ks in cancer, PI3Ks have been recognized as valuable drug targets. In spite of major efforts, only a handful of PI3K inhibitors (PI3Ki) have been approved up-to-date. Besides the investigation of mechanisms of PI3K isoform activation in cancer, inflammation and allergy, we have developed a number of drug-like molecules targeting the PI3K-mTOR pathway. Of these, the PQR309/bimiralisib pan-PI3Ki (Beaufils *et al.,* 2017) has been explored in phase II clinical trials in solid tumors and lymphoma. A consequence of targeting all class I PI3Ks are mechanism-based systemic feedbacks loops, such as drug-induced hyperglycemia and compensatory hyperinsulinemia. Especially the latter interferes with optimal drug action of PI3Kis, and might occur because of a simultaneous inhibition of PI3Kα and PI3Kβ. Moreover, we have elucidated off-target effects of PI3K inhibitors that are chemically closely related to PQR309: while BKM120/buparlisib and PQR309 have similar potencies as PI3K inhibitors, BKM120 also interacts with tubulin. In consequence, the dominant BKM120-induced cell fate in 66-cell lines was mitotic arrest. A subsequent structural, chemical and biological analysis revealed how BKM120 binds to the colchicine-binding pocket of tubulin, an off-target interaction that is structurally prevented in PQR309. Exploration of PQR309/BKM120 target engagement also revealed a corrected orientation of BKM120 in PI3K [Fig. 2; (Bohnacker *et al.,* 2017)]. These

investigations spurred to the discovery of novel microtubule disrupting agents, and the development of dual PI3K/mTOR (PQR514, PQR530) and highly selective mTOR kinase inhibitors (mTORKi), such as PQR620 (Rageot *et al.,* 2018) and its metabolically stabler follow-up compound PQR626 (Borsari *et al.,* 2020).

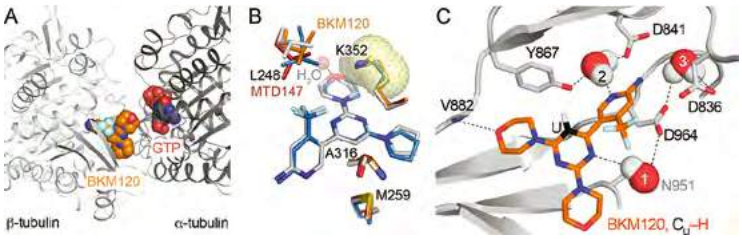

Fig. 2: BKM120 is a PI3K inhibitor that has entered >80 clinical trials. **A)** In (Bohnacker *et al.,* 2017) we showed that BKM120 interacts with microtubules and binds to the so-called colchicine-binding site on β-tubulin, explaining the subsequent depolymerization of microtubules **B)** A combination of chemical structure function relation (SAR) and X-Ray protein structure studies determined the exact rotational positioning of BKM120 and location of MTD147 in tubulin. **C)** The studies in **B)** triggered a review of a previously published BKM120/PI3K structure, which we identified as a low affinity binding mode. The correct orientation of BKM120 in PI3K shown here depicts important conserved water molecule interactions, which form an interactive water network required for efficient binding (Bohnacker *et al.,* 2017)

In contrast to pan-PI3Kis, PQR620 and PQR626 did not provoke hyperinsulinemia, and seem well tolerated. These compounds were therefore successfully used in animal models to attenuate lymphoma and ovarian cancer. As PQR620 and PQR626 are brain permeable, they were evaluated in other diseases emerging from an overactivated mTOR pathway (TORopathies). In patients with Tuberous sclerosis complex (TSC) mutated, benign hyperplastic lesions (hamartomas) are present in brain, kidney, heart, skin, lung, and liver. Morbidity is often dominated by neurological effects, including subependymal nodules (SENs >90 %), subependymal giant cell astrocytomas (SEGAs <20 %), mental impairment, and epilepsy (~90 %). PQR620 and PQR626 displayed an excellent efficiency in the attenuation of epileptic seizures in a TSC-induced (GFAP-Cre x $Tsc1^{flox/flox}$) mouse model with frequent spontaneous seizures [Fig. 3]. The elimination of seizures in the mouse TSC null model above, and an increased seizure threshold in a mouse model of chronic epilepsy (Brandt *et al.,* 2018) are a clear demonstration of the efficacy of mTORKi action in the central nervous system.

Selected Publications

Borsari C, Keles E, Rageot D, Treyer A, Bohnacker T, Bissegger L, De Pascale M, Melone A, Sriramaratnam R, Beaufils F, Hamburger M, Hebeisen P, Löscher W, Fabbro D, Hillmann P and Wymann MP (2020). 4-(Difluoromethyl)-5-(4-((3R,5S)-3,5-dimethylmorpholino)-6-((R)-3-methylmorpholino) 1,3,5-triazin-2-yl)pyridin-2-amine (PQR626), a Potent, Orally Available, and Brain-Penetrant mTOR Inhibitor for the Treatment of Neurological Disorders. J Med Chem, 63, 13595–13617.

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Beaufils F, Cmiljanovic N, Cmiljanovic V, Bohnacker T, Melone A, Marone R, Jackson E, Zhang X, Sele A, Borsari C, Mestan J, Hebeisen P, Hillmann P, Giese B, Zvelebil M, Fabbro D, Williams RL, Rageot D and Wymann MP (2017). 5-(4,6-Dimorpholino-1,3,5 -triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (PQR309), a Potent, Brain-Penetrant, Orally Bioavailable, Pan-Class I PI3K/mTOR Inhibitor as Clinical Candidate in Oncology. J Med Chem 60, 7524–7538.

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Connection to Clinical Practice

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PI3K and mTOR inhibitors in clinical trials

The development of drugs targeting PI3K and mTOR kinase is an intense area in pharmaceutical industry. A spin-off company of the University of Basel, PIQUR Therapeutics, has completed phase I clinical trials with PQR309. PQR309 is a potent, brain penetrable pan-PI3K inhibitor with moderate action on mTOR kinase activity. Initial studies showed hyperglycemia, an adverse effect typical for this class of compounds, which could be attenuated by intermittent dosing schedules. Phase II studies have been carried out in lymphomas, solid tumors, and in a drug combination trial using PQR309 with eribulin (piqur.com; clinicaltrials.gov). Recently, a topical formulation of PQR309 has been developed to be tested in cutaneous T-Cell Lymphoma (CTCL) and plaque psoriasis (PPSO).

Funding by Swiss CTI and Innosuisse has promoted research at University of Basel and allowed the generation of a number of novel lead compounds targeting PI3K and mTOR with defined selectivity profiles. Besides cancer, other TORopathies were explored, including Tuberous sclerosis complex (TSC). Another collaboration with AstraZeneca (Gothenburg, Sweden) elucidated a novel class of PI3Kγ inhibitors with a novel mode of action involving conformational changes of the PI3Kγ catalytic subunit. These inhibitors are destined to unleash myeloid cells' anti-tumoral responses.

The currently established chemical space at UniBas provides further target specificities and opportunities, which are currently explored. Further questions aim to understand the biology of tumor drug resistance to PI3K/mTOR inhibitors, and include novel tools generated for chemical genetics.

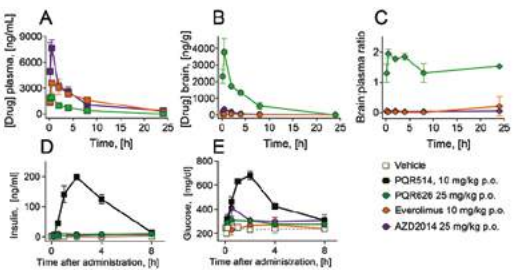

Fig. 3: A) PQR626 (Borsari *et al.,* 2020) displays a good pharmacology with a bit shorter half-life in rodents as compared to PQR620 (Rageot *et al.,* 2018). **B, C)** PQR626 shows a high brain:plasma distribution as compared to Everolimus and AZD2014, and is thus expected to cause less systemic side effects when targeting the CNS. **D, E)** Unlike a potent pan-PI3Ki (PQR514), mTOR inhibitors did not cause hyperinsulinemia or elevated plasma glucose levels.

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Immune modulation in cancer: implications for novel cancer therapies

Exploiting the immune system for cancer has become a paradigm-shifting therapeutic arsenal in oncology. Thus, cancer immunotherapy is increasingly considered to be one of the most important advances in the field of medicine following outstanding clinical successes with adoptive T cell therapies or blockade of immune checkpoints (Nobel Price in Medicine, 2018). Yet, therapeutic benefits are currently limited to a minority of treated patients and many patients are either refractory ab initio or develop resistance to such therapies, through yet poorly understood mechanisms. Our research group is a translational science laboratory in cancer immunology and immunotherapy. We are applying basic science research in immunocompetent murine tumor models and primary human tumor specimens and translating our discoveries and knowledge directly into early clinical testing (clinical trial unit including a phase I unit).

The understanding of cellular and molecular mechanisms of primary and acquired resistance to checkpoint blockade therapy allows for designing novel combination immunotherapy approaches to overcome these resistance mechanisms. In the last years, our research has been dedicated to mechanistically understand the immuno-modulating capabilities of novel anti- cancer therapies in order to pave the way for rationally designed treatment algorithms. We have recently provided insights into the therapeutic activity of immune-modifying chemotherapy that can elicit strong anti-tumor immunity in patients and mouse models. In addition, we showed that resistance to immunotherapy can be successfully overcome by synergistic combinations of immunotherapeutic agents and approaches specifically targeting immune-suppressive pathways. Figure 1 provides an overview with references.

A major barrier for effective cancer immunotherapy is intra-tumoral immune cell exhaustion. A comprehensive understanding of molecular initiators and promoters of T cell exhaustion is key to develop more effective strategies to restore antitumor immunity. Our group is interested in dissecting mechanisms underpinning T and NK cell exhaustion in human cancer patients; accordingly, recent work elucidated the diversity and functional impact of inhibitory T cell receptors expressed in cancer patients. To develop strategies to overcome tumor-induced T cell dysfunction, immunotherapeutic agents endowed with specific immune-activating capacities have been evaluated to induce a functional T cell recovery, thereby enhancing the effector functions in tumor-infiltrating immune cells. Figure 2 provides an overview with references.

We are currently working on implementing emerging technologies for multidimensional characterisation of the tumor microenvironment. E. g. CODEX is a novel multiplex imaging platform, which is capable of providing information on expression of up to 50 markers from a single tissue slide coupled with spatial coordinates of the cells (Figure 3). It is an excellent tool to study immune cells in their in situ environment. In addition, CyTOF (mass cytometry) is a multi parameter tool allowing for detailed quantification to study the cell subsets in suspension. Therefore, combining CyTOF with CODEX allows for through immune and tumour cell characterisation, also in the samples where material for analysis is limited.

Further work includes clinical research activities embedded into the Immunotherapy network at the Cancer Center of the University hospital Basel (Sebastian, BMC Cancer 2014; Conen, Dermatology 2014; Läubli, J Immunther Cancer 2015; Conen, Dermatology 2015; Kölzer, J immunother Cancer 2016; Koelzer, J Immunother Cancer 2016; Müller, Cancer Immunol Immunother 2016; Läubli, J Immunther Cancer 2017; Ortega, J Immunother Cancer 2018; Läubli, J Immunother Cancer 2018; Läubli, J Immunother Cancer 2018; Ortega, SMW 2019; Läubli, Virchows Arch 2019).

Fig. 1

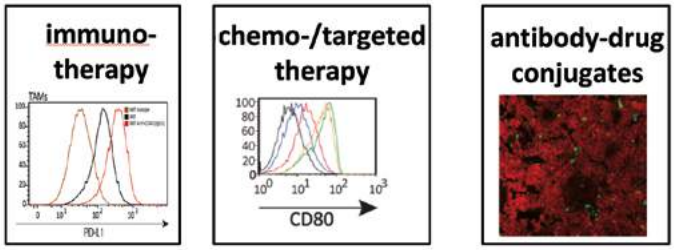

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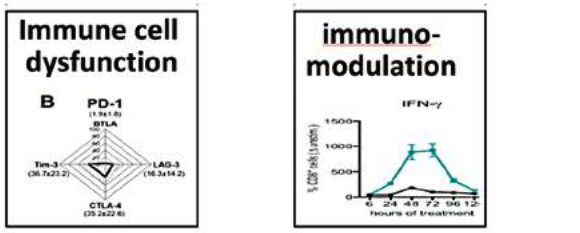
Fig. 2



- *Thommen, Cancer Immunol Res 2015*
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- *Trefny , Cancer Immunol Immunother 2020*
- *Schreiner, Onco-immunology 2015*
- *Xue, J Natl Cancer Instit 2015*
- *Kallert, Nat Comm 2018*
- *Claus, Science Translat Med 2020*
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Selected Publications

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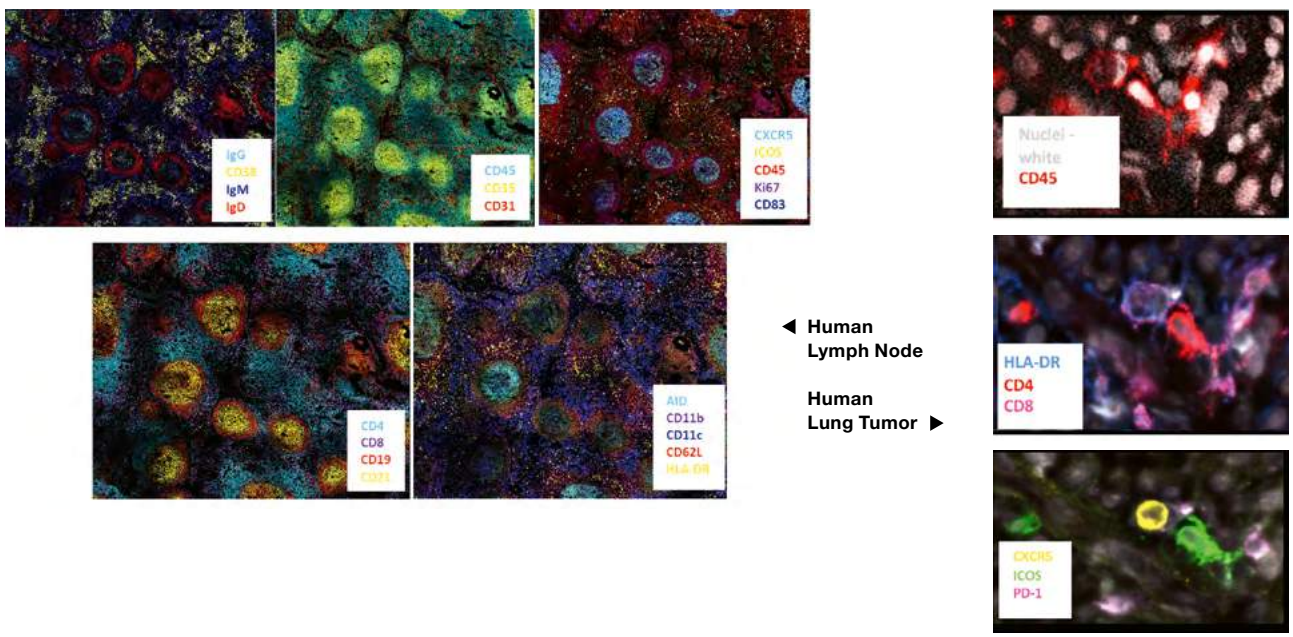
Thommen DS, Koelzer VH, Herzig P, Roller A. Trefny M, Dimeloe S, Kiialainen A, Hanhart J, Schill C, Hess C, *et al.* (2018). A transcriptionally and functionally distinct PD-1(+) CD8(+) T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade. Nat Med. 2018 Jul;24(7):994–1004.

Fig. 3



◀ **Human Lymph Node**

Human Lung Tumor ▶

Immunology

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The Immunology Focal Area comprises 31 Principal Investigators, which participate in the University of Basel Immunology Community (uBICo) group. uBICo promotes scientific collaboration, training of PhD students and organizes weekly Immunomeetings, an annual retreat, the PhD-club and seminars presented by distinguished guest speakers.

Significant basic immunological questions are investigated. Important topics are: i) the mechanisms of thymic development and the role of thymic epithelial cells with focus on their genetic and epigenetic control; ii) The role of T follicular helper memory cells and their use as ideal candidate targets for innovative vaccines; iii) the regulation of lymphocyte trafficking, with emphasis on the role of the direction and nature of chemokine gradients; iv) the function of small regulatory microRNAs and of miR-17~92 on T cell co-stimulation and fine-tuning of the T cell response to antigen; v) the relevance of Innate Lymphoid Cells, the mechanisms how they recognize and kill target cells, how their antigen presentation is influenced by tissue-specific signalling cascades.

Another main topic is the influence of cellular metabolism on the immune response. Seminal work showed that in T cells the metabolic state changes over time, and influences both their early response and late diminished function. T cell metabolic changes are facilitated by a dynamic physical association of cellular organelles and of cytoplasmic enzymes.
Changes in cellular metabolism occurring within cells which become T cell targets is also object of studies. Alterations in key metabolic pathways may lead to the accumulation of unique metabolites, which bind the antigen-presenting molecule MR1 and stimulate metabolite-specific MR1-restricted T cells. These novel T cells are gaining great interest because mostly tumor cells accumulate the stimulatory metabolites and thus are primary targets of this type of immune response. A direct correlation between innate immunity with metabolism regulation is being investigated in diabetes patients. The role of inflammatory processes in the failure of insulin production was demonstrated and the close association of metabolic stress with IL-1β-mediated immune response provided novel understanding of the pathogenesis of type 2 diabetes.

Many translational studies address the mechanisms of disease and innovative immunotherapy approaches.
Liver and gut diseases are main topics. Predictive biomarkers for response to treatments in Hepatocarcinoma (HCC) are studied using combination of molecular and bioinformatic approaches. Organoid models of HCCs are used for drug screening and to reveal phenotype-genotype correlations with clinical data.
Another investigated liver disorder is non-alcoholic fatty liver disease. The capacity of various hepatic cells in presenting microbial metabolite antigens to Mucosal Associated Invariant T cells is under scrutiny.
Patients with cirrhosis have been studied to define the role of attenuated immune response to microbial challenge. This curbed immune response has been associated to increased numbers of monocytic myeloid-derived suppressor cells expressing TAM receptors. Inflammatory bowel disease is being studied with a focus on metabolite-sensing receptors in macrophages and intestinal epithelial cells,

possibly relating microbial metabolites to disease pathogenesis. A link of colon macrophage numbers with glucose homeostasis was clearly documented, inferring a role of these cells as sensors of local microenvironment.

Autoimmune diseases such as Multiple Sclerosis (MS) and Systemic Lupus Erythematosus (SLE) are also investigated. In MS patients during infections, autoreactive B cells can be activated upon co-capture of microbial and self-membrane antigens. In MS, neurofilament light chain has been validated as marker of neuronal damage to measure disease activity and drug response. In SLE, molecular mimicry is a mechanism activating C1q-reactive B cells due to the striking sequence homology between a major linear epitope of C1q and an antigenic site of Epstein Barr Virus. In SLE patients another important alteration is reduced disposal of apoptotic cells, which in turn promotes immunogenicity of self-antigens that usually remain intracellularly.

The immunology of infectious diseases represents another major focus.

Compelling studies revealed that upon yearly influenza vaccinations protective immunity is affected by the previous vaccination history. Prospective studies address whether adaptations in the vaccine formulation recruit naïve B cells and broaden the immune repertoire, or instead mostly boost the pre-existing immunity, thus skewing the response.

Epidemiological studies focus on transmission events. The infection with human influenza viruses, and most recently the pandemic SARSCoV-2 are being investigated, with emphasis on spatio-temporal dynamics. A new assay based on microbial genome sequencing and bioinformatic analysis has been established to very rapidly predict antibiotic resistance.

Cellular immunotherapy is being implemented in patients with severe infections with Cytomegalovirus and Epstein Barr virus. Virus-specific T cells from immunocompromised patients are expanded and reinfused, thus reducing the outcomes of such infections.

Other topics are the HIV-1 reservoir formation, stability and dynamics during early therapy of patients with HIV infection. These studies revealed that the main contributors to HIV-1 persistence reside outside circulating blood cells.

Primary immunodeficiencies, also known as inborn errors of immunity, are being molecularly characterised. Novel disease-causing immune gene variants have been identified and personalised treatment strategies have been devised in such patients.

Cell engineering and immunotherapy of cancer are also fields of main investigations. Novel approaches to gene engineering have been established. TCR gene transfer has been validated in animal models of cancer. Finally, clinical trials with NK and T cells have been approved and are in progress.

Translational Immunology

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Balancing immunity: Autoimmunity, immunosuppression, Infection and Vaccination

The translational immunology lab focuses on human immunology. We are interested in antigen-specific immune responses in the context vaccinations and autoimmune disease.

Evolution of the humoral immune response following repeated seasonal influenza vaccination

Viruses mutate and thereby evade the host immunity. If this happens at a high rate, as in influenza, such 'escape' is a major challenge for vaccine design. An influenza vaccine protecting us from all potentially occurring viral variants remains the holy grail of influenza vaccine research. The current influenza vaccination strategy of yearly vaccination with adapted strains aims to counteract viral escape. To better understand the factors influencing vaccine responses in healthy and immunosuppressed individuals, we study the immune responses following influenza vaccination in these subjects. In the setting of seasonal influenza vaccination, we found that in immunosuppressed subjects (i.e. HIV infection) the response profiles (i.e. a multidimensional vector that includes time and antigen specificity) are similar to those in healthy, whereas the magnitude of the response is dampened (Berger CT. Human Vaccine Immunother, 2015). In a follow-up study on healthy subjects we could show that the vaccine response to the influenza vaccine is moreover strongly affected by the previous vaccination history. We found evidence that the vaccine response can become skewed, rendering the subject prone to viral escape (Bigler, M. B. et al. (in preparation)).

We are currently expanding these findings in a prospective clinical study of repeated annual influenza vaccination over three consecutive seasons from 2018–2021. We investigate the evolution of the B cell responses by immunophenotyping and B cell receptor sequencing, and by defining the antibody functions and cross-reactivity. Specifically, we aim to dissect whether adaptations in the vaccine formulation recruit new naïve B cells to the overall influenza response (i.e. broaden the response) or mainly boost/adapt the preexisting immunity (i.e. skew the response). Using a systems approach, this data may allow formulating predictions based on the pre-vaccination profile and repertoire. This may help identifying (i) who is in need for yearly vaccination, and (ii) which antigenic difference between subsequent vaccinations induce diversification of the vaccine response. Ultimately, we aim to apply this towards more personalized rather than one-size-fits-all vaccination strategies, to reduce the risk of vaccine failure.

The immunological targets in autoimmune vasculitis

Autoimmune diseases occur when the immune system attacks self-proteins. Understanding the target of the immune response in autoimmune disease may enable developing therapies interfering with the cause of immunopathogenesis directly. Target identification moreover allows developing tools to measure autoimmunity. Clinically relevant autoantibodies have been described in various autoimmune disease. Immunological biomarkers in predominantly T cell-mediated autoimmune diseases have not yet been established for clinical use.

Giant cell arteritis (GCA) is a T cell-mediated, inflammatory disease of unknown etiology. GCA exclusively affects the large arteries. Disease manifests as an inflammatory syndrome and ischemic symptoms resulting from stenosis of inflamed arteries. There is strong evidence that T cells play an important role in disease induction and/or maintenance. The pathogenesis remains, however, unknown. One of the goals of our lab is to unravel the events leading to disease and more specifically the immunological target of the T cells. We study this within the framework

of a prospective single-center GCA cohort at the university hospital Basel that we are running with the rheumatology clinic. All patients seen at our institution with clinical suspicion of GCA are enrolled. The cohort-data entails a comprehensive set of clinical, routine laboratory, pathological (biopsy), and vascular diagnostic (ultrasound duplex studies and PET studies) information, as well as the longitudinal biobanking of blood and serum samples. This cohort is a precious source to address translational research questions (e.g. Kistner A *et al.,* Rheumatology 2017; Berger CT *et al.,* Rheumatology 2018; Berger CT *et al.,* Annals of the Rheumatic Diseases 2019).

The main current focus is to analyze the inflammatory infiltrate in the artery biopsies of GCA patients. We use next-generation sequencing of the TCRαβ repertoire to identify the expansion of dominant T cell clones in biopsies from patients. Using the collected information on the TCR repertoire, we then aim to identify the target of the expanded T cell clones. To do so, we established a workflow to transfect the identified TCRαβ of expanded T cells into TCRαβ-deficient Jurkat. The thereby generated set of transfected TCRαβ-Jurkat cells is used as reporter cell lines to screen against putative targets of the transfected TCR. For this antigen discovery studies we use an unsupervised ('MHC class II ligandome of artery tissue') and a supervised (viral antigen) screening approach (Bigler MB *et al.,* Arthritis and Rheumatology 2018). Identifying the source of the antigen that T cells recognize in GCA will inform on the potential disease-causing processes. This may pave the way for novel approaches (i) to prevent GCA by identifying subjects at risk, and (ii) to develop immune-therapies aimed at improving antigen-specific tolerance.

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Connection to Clinical Practice

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The Swiss Giant Cell Arteritis Cohort

Giant cell arteritis (GCA) is the most prevalent of the primary vasculitis syndromes with an increasing disease incidence. Patients typically present with constitutional symptoms, headache, and a systemic inflammatory syndrome. To date therapy of GCA is based largely on steroids, and guided by parameters reflecting disease activity only partially, as indicated by recent imaging-studies. Furthermore, intensity and duration of steroid therapy remain a matter of debate, and no consensus exists in defining remission. Both GCA itself and the steroid based therapy are associated with significant morbidity. Improving diagnostic accuracy and monitoring of disease activity thus would be of great importance. To study these clinical problems, we established in 2011 a prospective interdisciplinary cohort of patients with GCA at the University Hospital Basel. Since 2020, we co-lead a Swiss Cohort for GCA that involves all University Hospitals in Switzerland. In the Relevant clinical data, laboratory parameters, serum and peripheral blood mononuclear cells from all patients are collected at longitudinal time-points. Vascular disease activity is assessed using new technologies such as color-coded duplex ultrasound and positron emission tomography. Thereby we aim at integrating clinical data, imaging studies, and extended immunological and histomorphological assessments for a more detailed understanding of the immunopathogenesis of GCA. This may help to (i) further develop precise, ideally non-invasive, tools to diagnose and monitor disease activity, and (ii) generate strategies towards interfering with specific pathways associated with disease activity and/or complications.

Translational Hepatology

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Molecular mechanisms of immuneparesis in patients with cirrhosis

Cirrhosis of the liver is a systemic inflammatory condition depicted by its high morbidity and mortality and raising prevalence worldwide. There is no treatment option other than transplantation, applicable to only a minority of patients. Infectious complications are highly frequent and independent predictors of adverse prognosis – being the leading cause of acute decompensation, "acute-on-chronic" liver failure (ACLF) and death. The distinct infection susceptibility in patients with cirrhosis has been attributed to a state termed immuneparesis defined by attenuated immune responses to microbial challenge. A detailed understanding of the mechanisms underlying immuneparesis is desired in order to identify prognostic markers and define potential future immunotherapeutic targets that may enhance immune responses and reduce recurrent infection, need for liver transplantation and death.

Our research group seeks to decipher the pathophysiology of immuneparesis in relation to monocyte and macrophage differentiation and function in patients with cirrhosis. Over the previous years we identified specific immune-suppressive and immune-regulatory monocytic subsets accumulating in the systemic circulation along with disease progression of cirrhosis where they attenuated responses to microbial challenge.

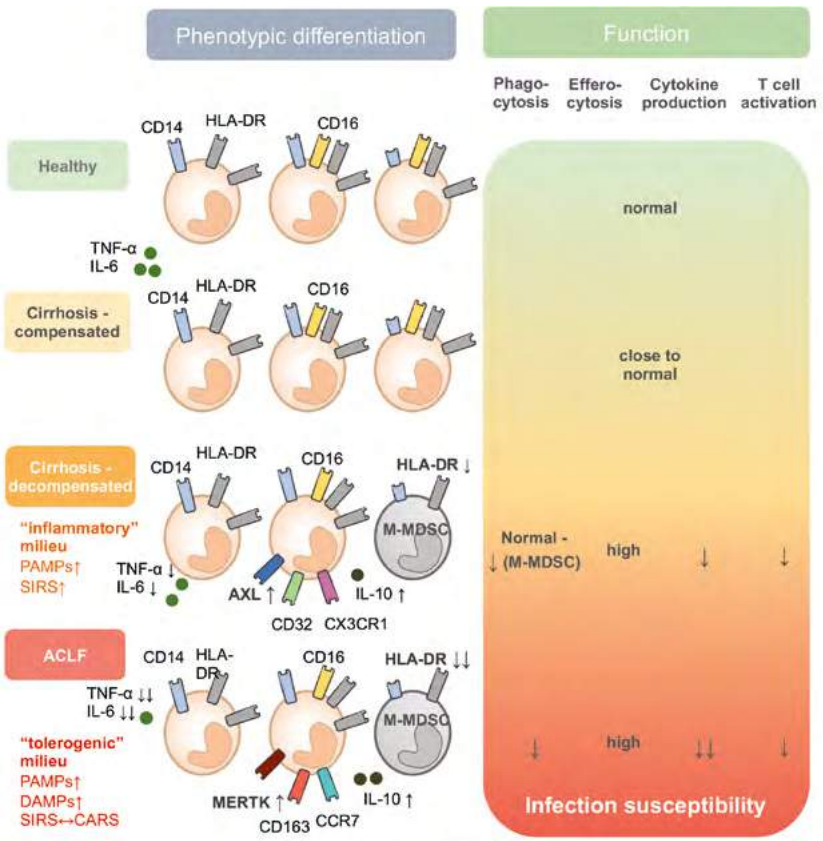
Immune suppression by monocytic myeloid-derived suppressor cells (M-MDSC)

In association with infectious morbidity and mortality reduced expression of the MHC class II receptor human leucocyte antigen (HLA)-DR on circulating monocytes from patients with advanced cirrhosis had been observed a decade ago. The mechanism underlying infection susceptibility remained indeterminate. We recently described that expression of HLA-DR on circulating monocytic cells gradually decreased while severity of cirrhosis increased, and was attributed to the generation of M-MDSC (CD14+CD15–CD11b+HLA-DR–). Functionally, circulating M-MDSCs from patients with cirrhosis *ex vivo* were typified by distinct immunosuppressive properties, i.e. reduced T cell activation, TNF-α and IL-6 production in response to toll-like receptor (TLR) stimulation and phagocytic capacity. M-MDSC accumulated in response to systemic inflammatory responses (SIRS) and circulating pathogen-associated molecular patterns (PAMPs). *In vitro* the immune stimulant poly(I:C), reduced abundance of suppressive M-MDSC and augmented their antimicrobial function.

Immune regulation by TAM receptors

Also, we specifically focussed on the regulatory function of tyrosine kinases of the TAM receptor family (Tyro-3, AXL and MERTK). TAM receptors are expressed on monocytes and macrophages and play a pivotal role in regulating innate immune responses to microbial challenge by inhibiting TLR signalling and immune homeostasis by promoting efferocytosis, i.e. phagocytosis of apoptotic cells. We have recently discovered the expansion of circulating immune-regulatory AXL- and MERTK-expressing monocyte subsets in patients with cirrhosis at different stages of disease that were characterised by preserved phagocytosis of bacteria, enhanced efferocytosis but suppressed cytokine responses (TNF-α and IL-6) to lipopolysaccharide and attenuated T cell activation. AXL expressing cells accumulated in response to phagocytosis of bacteria, efferocytosis and PAMP exposure. MERTK- and AXL- inhibition, respectively, restored cytokine responses *in vitro*.
In the circulation of patients with advanced stages of cirrhosis these described dysfunctional monocytic cell populations prevailed over their functional counter-

parts and explain reduced capacity to repel microbial challenge and infection susceptibility. Since proof of principle experiments revealed that these immune functions were modifiable, we further investigate whether targeted immune modulatory therapies may restore innate immune responses of monocytes from patients with cirrhosis in the future. Importantly, our observations also indicate that these cells evolve in a highly compartment specific manner, and initiated our current and ongoing project entitled “Diversity and compartmentalisation of monocytes & macrophages and immuneparesis in patients with cirrhosis”.



Differentiation of circulating monocytic cells along with disease severity of cirrhosis. Classically monocytes have been subdivided into $CD14^{++}CD16^{-}$ (classical), $CD14^{++}CD16^{+}$ (intermediate), and $CD14^{+}CD16^{++}$ (non-classical) subsets. Paralleling progression of cirrhosis towards decompensation and acute-on-chronic liver failure (ACLF), distinct immune-regulatory and immune-suppressive monocytic subsets accumulate and displace functionally intact monocytic cells and hereby may relate to increased infection susceptibility. Immune-suppressive monocytic myeloid-derived suppressor cells (M-MDSC) expanded during progression to decompensated stages and represented half of all circulating $CD14^{+}$ cells in ACLF. During decompensation distinct stage-specific immune-regulatory subsets expanded such as $CD14^{++}CD16^{+}$, $CD14^{+}CD16^{high}HLA\text{-}DR^{high}AXL^{+}$ in a predominantly inflammatory milieu, and $CD14^{+}CD16^{high}HLA\text{-}DR^{high}CD163^{+}MERTK^{+}$ in a predominantly tolerogenic milieu such as ACLF. Adapted from Bernsmeier *et al.,* J Hepatol, 2020.

PAMP, Pathogen-associated molecular pattern.
DAMP, Damage-associated molecular pattern.
SIRS, systemic inflammatory response.
CARS, compensatory anti-inflammatory response syndrome.

Selected Publications

Bernsmeier C, van der Merwe S and Périanin, A (2020). Innate immune cells in cirrhosis. J. Hepatol. 73(1), 186–201.

Brenig R, Pop OT, Triantafyllou E, Geng A, Singanayagam A, Perez-Shibayama C, Besse L, Cupovic J, Künzler P, Boldanova T *et al.* (2020). Expression of AXL receptor tyrosine kinase relates to monocyte dysfunction and severity of cirrhosis. Life Science Alliance 3(1): e201900465.

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Translational Diabetes

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Gut mucosal immunity in metabolic disease

Diabetes is a serious and growing health problem, affecting 463 million people worldwide in 2019. Chronic inflammation is a hallmark in the pathogenesis of type 2 diabetes and obesity. However, the initiating mechanisms of glucose dysregulation and inflammation in obesity remain poorly understood.

Our research focuses on gut mucosal immunity as a potential starting point of inflammation and glucose dysregulation in metabolic disease. Thereby, we are interested in elucidating the role of the mucosal immune system, especially intestinal macrophages. Intestinal macrophages constitute the largest macrophage compartment within the body and could serve as crucial "sensors" of environmental or external factors (i. e., food intake or environmental toxins such as air pollutants or cigarette smoke particles) for the host's immune system. We are interested in how intestinal macrophages respond to such environmental stressors and how their response ultimately affects glucose homeostasis and systemic inflammation.

We found that pro-inflammatory/ monocyte-derived colonic macrophages are elevated in mice fed a high fat diet, suggesting a link between colon macrophage numbers and glucose homeostasis. Indeed, we were able to establish a direct link between colon macrophages and glucose metabolism as colon-specific macrophage depletion ameliorated glycemic control and beta-cell function.

Besides classical risk factors like unhealthy food or sedentary lifestyle, also environmental toxins like air pollution or cigarette smoke increase the risk for type 2 diabetes. We showed that air pollution particles mediate diabetes via the gastrointestinal tract rather than via lung exposure as previously thought. Oral exposure to pollutants occurs via mucociliary clearance of particles from the airways with subsequent swallowing of the particles. Particles reaching the gastrointestinal tract caused a distinct inflammatory shift of colon macrophages. This local gut inflammation was associated with impaired insulin secretion and glucose intolerance. Similarly, we are assessing how cigarette smoke particles and e-liquids from e-cigarettes impact on mucosal gut immunity and glucose homeostasis. Also, we are studying the differential effects of air pollution particles on atherosclerosis when they are administered via lung or gut exposure.

In addition, we are also interested in therapeutic aspects of gut mucosal immunity. As weight- loss surgeries are associated with a rapid improvement in glucose homeostasis, we aim to address the question whether weight loss has beneficial effects on gut mucosal immunity and hence glucose tolerance.

In sum, the aim of our laboratory is to better understand the changes of gut mucosal immunity upon environmental stimuli and how this connects with glucose intolerance and systemic inflammation in metabolic disease to potentially find immune-modulatory treatments.

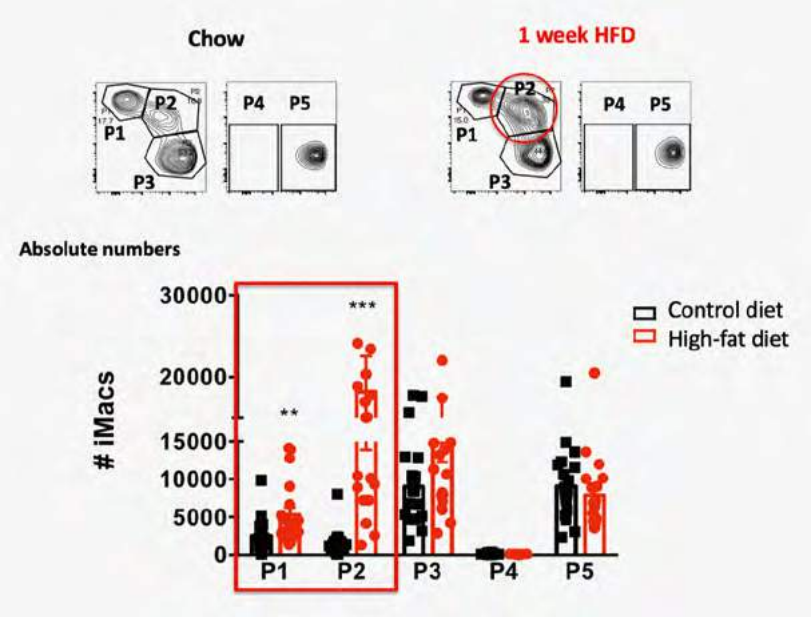

Fig. 1: Pro-inflammatory colon macrophages are elevated following high-fat diet.
Top panel: Representative flow cytometry of colon macrophage subpopulations P1-P5 subpopulations in a mouse fed standard chow or 1 week high-fat diet.
Bottom panel: Absolute numbers (#) of pro-inflammatory (P1, P2, P3) and anti-inflammatory/resident colon macrophage subpopulations (P4, P5) in mice fed standard chow or high-fat diet.

Connection to Clinical Practice

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Human intestinal macrophages in metabolic disease

In order to translate our findings to human disease, we compare human gut biopsies of patients with different environmental "toxins" (i.e., normal weight versus overweight individuals or smokers versus non-smokers). We found an inflammatory shift in intestinal macrophages in obese individuals, similar to our findings in obese mice. To assess whether these changes in gut innate immunity are reversible, we plan to study intestinal macrophages from individuals before and after weight loss surgery. The ultimate goal is to potentially find immunemodulatory treatments at the interface between the environment and the host's metabolism.

Selected Publications

Schneider R, Kraljevic M, Peterli R, Rohm TV, Klasen JM, Cavelti-Weder C and Delko T (2020). GLP-1 Analogues as a Complementary Therapy in Patients after Metabolic Surgery: a Systematic Review and Qualitative Synthesis. Obes Surg 30, 3561–3569.

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Experimental Immunology

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*left during report period

MR1-restricted T cell recognition of metabolite antigens in cancer, infections and autoimmune diseases

T lymphocytes recognize a variety of antigens and exert important functions in immune response. The activation of T cells is mediated by engagement of the T cell receptor (TCR) that recognizes antigens on the surface of antigen-presenting cells. T cells may recognize antigens of different chemical composition, including short peptides, lipids, and small metabolites. Upon interaction of complexes formed by antigen-presenting molecules and antigens with TCR, T cells become activated and exert their effector functions.

We study the nature of the antigens that stimulate T cells. Recently, we have focused on a new population of T cells that we identified and called MR1T cells and that recognize endogenous metabolites presented by the antigen-presenting molecule MR1. We found that MR1T cells use a polyclonal TCR gene repertoire, they have different functional capabilities, including killer and helper functions, and are present in healthy individuals with frequencies similar to those of peptide-specific T cells. They also show different gene regulatory mechanisms, thus indicating that they are a functionally heterogeneous population of T cells, resembling adaptive T cells specific for peptide or lipid antigens. An important characteristic of MR1T cells is that they mostly recognize tumor cells and not healthy cells. This unexpected tumor recognition bias is due to the preferential accumulation of unique metabolite antigens within tumor cells. Our laboratory has started a multi-disciplinary approach to identify the nature of these novel tumor antigens using molecular approaches to reveal genes relevant to metabolite accumulation. We also have established tools to perform HPLC separation of metabolites from tumor cells, which are then tested for their stimulatory capacity and structure by mass spectrometry and NMR. We have generated a large number of MR1T cell clones that have been tested against >50 tumor cell lines. These studies revealed that MR1T cells recognize patterns of tumor cells. Transfer of TCR genes confirmed TCR specificity. Furthermore, tumor cells were also grouped according to their capacity to stimulate most or only some of tested MR1T cells. We interpret these findings with the presence of MR1T TCR that recognize metabolite antigens shared among many tumors, and with the presence of multiple types of metabolic alterations that occur in tumor cells. The combination of both induces a pattern-type recognition of tumor cells by MR1T cells.

These findings have raised major interest in using MR1T cells in novel types of anti-tumor cell therapy. This is justified by several reasons as follows, i) the metabolites stimulating individual MR1T cells accumulate in many tumor types, independently of their tissue origin; ii) metabolite antigens cannot be readily modified by tumor cells, limiting recognition escape associated with antigen modification as the case with peptide antigens; iii) MR1 is ubiquitously expressed and even tumor cells expressing very low levels of MR1 on their membrane may efficiently stimulate specific MR1T cells; iv) the MR1 gene is not polymorphic and thus the same MR1T TCR recognizes tumors from different individuals; v) MR1T cells show killer and helper functions, which are both required for optimal anti-tumor cell therapy.

Current studies are addressing the nature of the stimulatory antigens, the regulation of metabolic pathways relevant to generation and accumulation of MR1T-stumulatory metabolites, the identification of the cellular compartments where metabolites are generated and how they are transported to those where they can meet MR1 protein, and the nature of the co-stimulatory/inhibitory molecules that control the activation of MR1T cells. Ad hoc animal models are being exploited to investigate their capacity to recognize and control tumor expansion *in vivo*.

MR1T cells have the function of surveying the metabolic integrity of other cells and may prevent accumulation of metabolic alterations leading to dysregulated cell proliferation. Their use in novel tumor cell therapy approaches may represent a natural outcome of future translational applications.

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Clinical Neuro-immunology

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Molecular and immunological analysis of Multiple Sclerosis

Our research focuses on the molecular and immunological analysis of multiple sclerosis (MS), an inflammatory and neurodegenerative disease of the central nervous system (CNS), and number one cause of neurological disability in young adulthood. We pursue two main research lines: 1) Relevance of B-cells and antibodies in MS pathogenesis. 2) Exploration and validation of biomarkers in cerebrospinal fluid and blood as tools for therapeutic decision making for persons with MS. Both approaches provide novel tools for monitoring the efficacy of current and emerging therapies of MS.

B cells and their targets in MS (Derfuss group)
B-cells have a major role in the pathogenesis of MS. Depletion of B-cells leads to a remarkable amelioration of the disease. The mechanisms by which B-cells impact MS are however incompletely understood. Our research focuses on the identification of novel B-cell autoantigens and the characterization of the interaction of auto-aggressive B-cells with the CNS. We could show that antibodies against native myelin oligodendrocyte glycoprotein (MOG) identify a subset of patients with neuromyelitis optica and are also found in SLE patients with CNS involvement. Using transgenic animal models, we were able to prove a new concept how infection could lead to the development of autoantibodies like those against MOG. We identified the co-capture of membrane antigens by the B cell receptor as a key step in initiating an autoimmune response in the context of an infection. This work is now continued by analyzing the capacity of B cells to migrate to peripheral tissues including the CNS and harvest their cognate and non-cognate antigens from the tissue. The phenomenon of membrane capture can also be used to purify B cells of a certain specificity from blood (Fig. 1) and to identify novel B cell autoantigens in MS.

Defining biomarkers for disease progression and therapy response (Kuhle group)
Despite modern MS therapy almost completely suppresses acute disease activity ("relapses"), chronic worsening of neurological functions ("progression") continues to affect almost all persons with MS. Neurofilament light chain (NfL) is a biofluid marker of neuronal damage and has been established by us as a blood-based precision medicine tool to measure disease activity and drug response (Fig. 2), and to predict the long-term outcome of disability on the group level. We pursue now to establish NfL as a diagnostic tool for individual patients for therapeutic decision making. We aim to better characterize the pathophysiology of NfL based on innovative MRI techniques and to establish a normative data base from controls over eight decades of age to be used as reference values for individual testing. Further, we investigate other biofluid markers to contextualise NfL signals with regard to state and stage of MS, and for differential diagnosis vis-à-vis other inflammatory neurological diseases. This project is based on patient information and biological samples from the Swiss MS Cohort Study, a consortium of Swiss academic MS centres founded in 2012, and a number of international collaborations in Europe and the US.

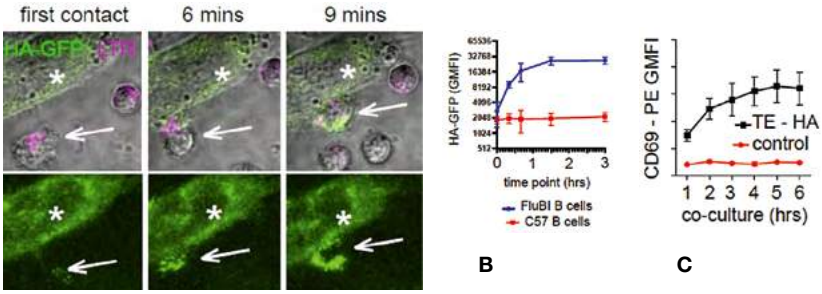

Fig. 1: Antigen Extraction from Membrane by Cognate B cells
(A) Live Cell Imaging of membrane antigen capture. Hemagglutinin-specific FluBI mouse B cells (white arrows, labeled magenta LTR) are added to cells (white asterisks) expressing a fusion protein of hemagglutinin with a cytoplasmic GFP (HA-GFP, green). Images show the initial contact between a B cell and an antigenic target cell, then the same location at 6 and 9 minutes later. The lower panels show only the GFP channel to show capture of antigen. **(B)** Extraction of membrane expressed HA-GFP by antigen-specific or antigen-irrelevant B cells. HA-specific FluBI B cells were labeled with Cell Trace Violet (CTV), mixed with unlabeled, antigen irrelevant mouse B cells at a ratio of 1:10, and added to an adherent layer of cells stably transfected with membrane-expressed HA-GFP. At the indicated time points, the B cells were retrieved and interrogated by flow cytometry. The FluBI cells were separated from unspecific B cells by CTV label, and GFP levels were compared between the two cell types. Points and bars show mean and standard deviation of the geometric mean GFP fluorescence. **(C)** Time-course of CD69 upregulation. HA-specific FluBI mouse B cells were exposed to HA-expressing TE HA, or HA-non-expressing control cells for the indicated times, and then retrieved, immunolabeled for B220 and CD69 and measured by flow cytometry. Vertical axis shows the geometric mean immunofluorescence intensity and SEM of the anti-CD69

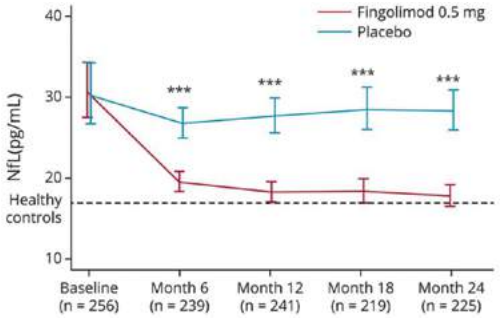

Fig. 2: NfL is the first blood-based measure to quantitate the neuroprotective effect of MStherapy
Geometric means of plasma NfL with 95 % confidence intervals. Dotted line represents plasma NfL concentration in healthy controls. ***p < 0.0001. n = number of patients.

Selected Publications

Khalil, M, Pirpamer L, Hofer E, Voortman MM, Barro C, Leppert D, Benkert P, Ropele S, Enzinger C, Fazekas F, Schmidt R, Kuhle J. (2020. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. Nat. Commun., 11, 812.

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Connection to Clinical Practice

Our two research groups are closely connected to the MS centre, the Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB) and the Outpatient Clinic of the Department of Neurology, University Hospital Basel that provides care for more than 1300 MS patients per year. This provides access to a population of MS-patients in different stages and states of disease, treated with all state-of-the-art therapies. The close collaboration with the Translational Imaging in Neurology (ThINk) group at the Department of Biomedical Engineering, the Medical Image Analysis Centre (MIAC) and the Division of Neuroradiology enables characterization of patients with cutting edge neuroimaging techniques. The Clinical MS Research Group plays a key role in conceptualising and conducting international therapeutic trials to bring novel therapies to persons with MS. These trials provide unique possibilities for a translational medicine approach by connecting basic research and clinical studies for a better understanding of disease, and specifically for progressive MS.

The development of biomarkers needs prospective, standardized, and high-quality clinical and neuroradiological data from large patient cohorts to allow for validation on the individual patient level, and hence application in clinical practice as Precision Medicine tools. The Swiss MS Cohort Study (SMSC), initiated in 2012 and coordinated by our MS Group since then, is the mainstay of research efforts in Clinical Neuroimmunology; it provides an internationally unique long-term follow-up of over 1200 Swiss MS patients with clinical and MRI data, and blood and cerebrospinal fluid samples for biomarker research.

Diabetes Research

Immune-mediated response to nutrition in physiology and pathology

Our research aims at the understanding of the pathogenesis of type 2 diabetes. We could identify an inflammatory process underlying failure of insulin production in this disease. Thereby we could showed that metabolic stress induces an IL-1β mediated immune response. We confirmed our hypothesis in clinical studies showing that modulation of the immune system may improve metabolism in patients with type 2 diabetes. The work has contributed to the concept that the innate immune system is an integral component in the regulation of metabolism, i. e. immunometabolism.

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Hepprich M*, Wiedemann SJ*, Schelker BL, Trinh B, Stärkle A, Geigges M, Löliger J, Böni- Schnetzler M, Rudofsky G, Donath MY (2020). Postprandial Hypoglycemia in Patients After Gastric Bypass Surgery Is Mediated by Glucose-Induced IL-1β. CELL Metabolism 31:699–709.

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Applied Microbiology Research

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Towards a systems understanding of key host-pathogen interactions, from molecules to populations

Hosts and pathogens share complex interactions across scales from molecules to populations. The Applied Microbiology Research group aims to understand these various levels of interactions by the identification of factors involved, with a systems biological approach. To do so we use techniques including cutting edge molecular techniques, high throughput pathogen genome sequencing, and mass spectrometry. Key findings and applications are translated into clinical applications to improve patient diagnostics of infections.

Transmission of clinically relevant viruses.
We study transmission events in the context of local outbreaks and global transmission using human influenza viruses, and most recently the pandemic SARS-CoV-2. For both viruses, we have established whole genome sequencing (WGS) and analysis pipelines and humoral immune assays. Together with our collaborating partners, we explore transmission events and spatio-temporal dynamics and models across the Basel region. With these tools we investigate viral evolution in clinically relevant contexts, such as the role of superspreading events, the effect of socioeconomics and transportation, and treatment of hospitalized patients. We explore specific mutations in the viral genome as markers for epidemiological modelling and detection of antiviral resistance.

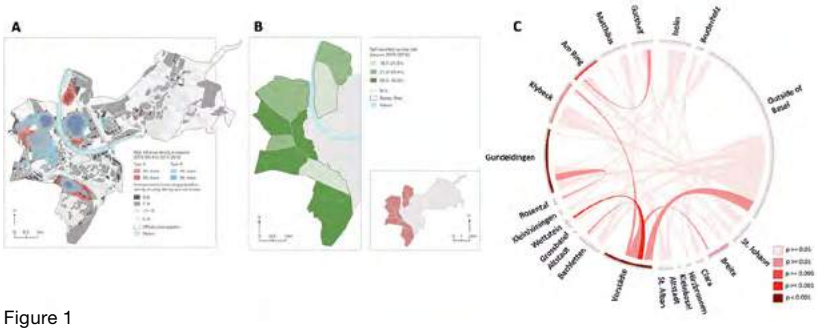

Figure 1

Transmission of clinically relevant bacteria.
We use WGS (Illumina and Oxford Nanopore) and metagenomic approaches in order to describe genetic relatedness and evolution between and within hosts. Bacterial pathogens of interest include multi-drug resistant bacteria such as ESBL- and Carbapenemase-producing and hypervirulent Enterobacteriaceae, Vancomycin resistant *Enterococcus faecium, Clostridioides difficile, Legionella pneumophila,* and Methicillin resistant *Staphylococcus aureus,* as well as interesting clinical outbreaks. Recently we have described a new bacterial species – *Mycobacterium basiliense.* A fundamental tool which we are constructing is the NRP72-funded Swiss Pathogen Surveillance Platform (www.spsp.ch): collaborating with the Universities and University Hospitals of Basel, Geneva and Lausanne, VetSuisse (University of Bern and Zurich) and the Swiss Institute for Bioinformatics, this is an interoperable molecular and classical epidemiological database for WGS and metadata sharing. This work will be extended from MRSA to multiple clinically relevant pathogens – including previously mentioned respiratory viruses.

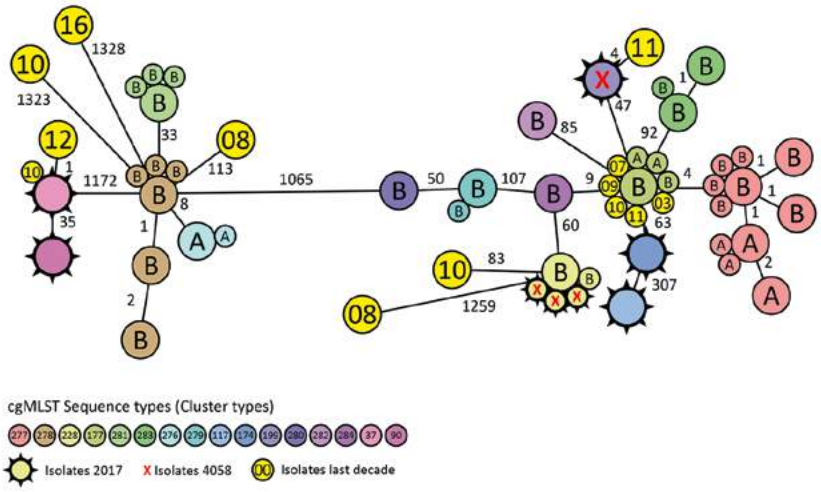

Figure 2

Understanding pathogens and populations.
Our research group also focuses on pathogen dynamics and prediction of invasiveness within a single host. In a SNF-funded project, we are also developing metagenomic tools to determine MDR colonization status of hospital patients directly from swabs, aiming to monitor microbiota changes over time within the patient during hospitalization. In a Gebert-Rüf funded project, we look into the dynamics of ESBL *E. coli* colonization and carriage in healthy individuals who travelled to high endemic regions. Our goal is to identify (i) microbiological factors affecting whether the subject remains colonized or spontaneously clears the pathogen and (ii) which pan-sensitive natural microbial displace resistant bacteria such as ESBL *E. coli*. Finally, we also study the factors driving invasiveness of colonizing *E. coli* isolates causing pyelonephritis and uro-sepsis. We use WGS data to predict ribosomal marker masses in order to determine phylogroups in MALDI-TOF MS spectra. These phylogroups allow the prediction of clinical phenotypes.

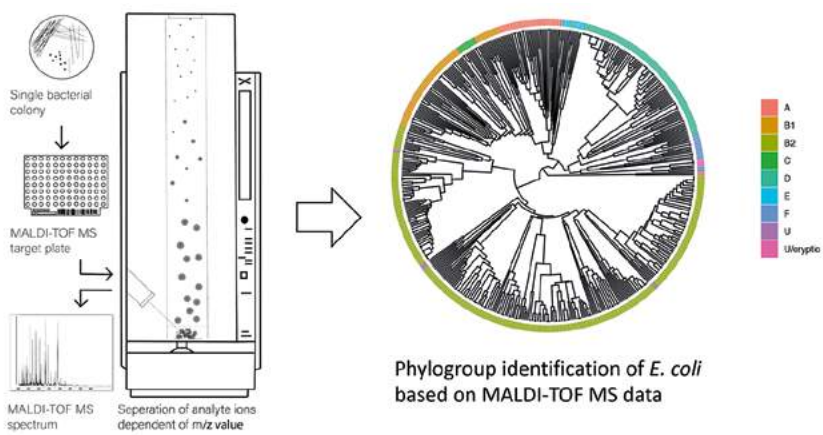

Figure 3

Connection to Clinical Practice

Prof. Manuel Battegay and team
Infectious Diseases and Hospital Epidemiology

Bridging pathogen characterization to clinical application

Being embedded in the division of Clinical Bacteriology and Mycology provides access to clinical isolates, and interesting cases. Together with colleagues from the Division of Infectious Diseases and Hospital Epidemiology, we explore these patients and use the new discoveries and insights to improve the diagnostic process. In parallel, there is a constant need to accelerate diagnostics, providing the best of new technologies for patients, and much of our work also focuses on this aspect. We want to translate our findings into clinical practice, developing novel diagnostic strategies and preventive measurements to reduce pathogen transmission and expedite patient treatment.
An example is the combination of mass-spectrometry and antibiotic resistance profiles. Using machine learning, we have developed together with Prof. Karsten Borgwardt (ETH Zurich) an algorithm to predict antibiotic resistance about 24h before classical phenotypic assays.

Selected Publications

Egli A, Schrenzel J, Greub G. Digital microbiology. Clin Microbiol Infect. 2020 Oct;26(10):1324-1331. doi: 10.1016/j.cmi.2020.06.023. Epub 2020 Jun 27.

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Liver Immunology

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Characterization of mucosal-associated invariant T (MAIT) cells in liver diseases

Mucosal-associated invariant T (MAIT) cells represent the most abundant T cell type in human liver. MAIT cells respond to bacterial metabolites presented by MHC-like molecule MR1 on antigen (Ag)-presenting cells (APCs). In mouse models, activated liver MAIT cells were described as profibrogenic and MAIT cells from patients with liver cirrhosis showed functional alterations consistent with pro-fibrotic functions. Gut dysbiosis has also been implicated in progressive liver fibrosis in fatty liver disease in mice. Since liver MAIT cells respond to bacterial metabolites and exhibit pro-fibrotic properties, they likely also contribute to pathogenesis of non-alcoholic fatty liver disease (NAFLD). In our research, we investigate which cells in the human liver are involved in MAIT cell activation and how their profibrogenic function could be prevented. We also study influence of the gut microbiome on the phenotype of MAIT cells, with an emphasis on a pathogenic role of MAIT cells in fibrosis and NAFLD.

We found that several classes of primary liver cells, including hepatocytes, hepatic stellate cells (HSCs), liver endothelial and biliary epithelial cells, have the capacity to present bacterial Ag to MAIT cells. Liver cells exposed to bacterial Ag precursor had the capacity to generate active Ag endogenously. The identified interaction between HSCs and MAIT cells supports the pro- fibrogenic function of these cells. The finding that activated liver MAIT cells produce large amounts of IL-17, suggests the involvement of this pro-fibrotic cytokine in liver disease pathogenesis. The observed repression of MAIT cell activation by non-stimulatory MR1 ligands creates a therapeutic opportunity to interfere with MAIT cell pro-fibrogenic properties.

To better understand the role of MAIT cell stimulation in liver disease, we are currently studying molecular signatures of MAIT cells derived from liver in comparison to colon and blood and we are also correlating MAIT cell phenotypes with the gut microbiome of patients with liver diseases.

Mechanisms of MAIT cell regulation in the liver – physiological functions and pro-fibrotic properties

We assessed the localization of MAIT cells by immunofluorescence staining of cryopreserved human liver tissue and found them to dispersedly localize within the liver parenchyma, thus being in close contact to cells within the sinusoidal compartment (Fig. 1). We have found that distinct primary liver cell types, including hepatocytes, HSCs, liver sinusoidal endothelial cells (LSECs), and biliary epithelial cells (BECs), act as strong drivers of MAIT cell activation, with the potential of increasing liver fibrogenesis (Fig. 2). Presentation occurred in response to both pure synthetic Ag 5-OP-RU (5-(2-oxopropylideneamino)-6-D-ribitylaminouracil) and bacterial lysate from E. coli. Presentation capacities differed markedly among the investigated liver cell types, with hepatocytes being the most efficient liver-derived APCs (data not shown).

MAIT cell activation was prevented by pre-treating APCs with the non-stimulatory MR1 ligands 6-formylpterin (6-FP) and Acetyl-6-FP and was diminished in the presence of the acetylsalicylic acid derivative 5-formylsalicylic acid (data not shown). These findings create a therapeutic opportunity to prevent pro-fibrogenic properties of MAIT cells. Human polyclonal liver-derived MAIT cells produced large amounts of Interleukin 17 (IL-17), a cytokine with strong pro-fibrotic properties, when interacting with distinct liver-derived APCs, including hepatocytes and HSCs. Moreover, liver cells exposed to an Ag precursor (5-A-RU) had the capacity to generate active Ag 5-OP-RU, as assessed by Ag-presentation assays and mass spectrometry (data not shown).

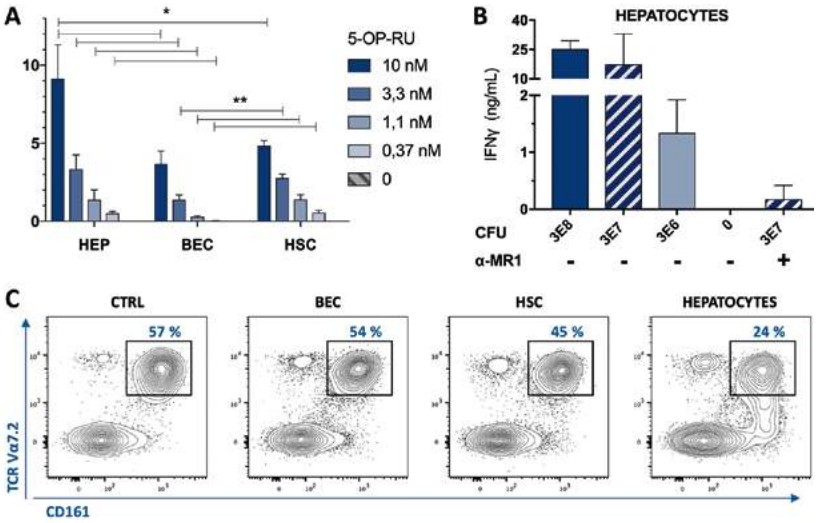

Fig. 1: MAIT cells localize dispersedly to the parenchymal space in healthy human liver. **(A)** Representative IF analysis of tissue section from a liver biopsy without histopathological abnormalities. Co-localization of CD3, TCR Vα7.2 and IL18-Rα (see higher magnification lower panels) identifies MAIT cells (yellow arrow heads). White arrow and blue arrow heads point at portal field and central veins, respectively. Lower panels also show MAIT cells in proximity of TCR Vα7.2- and IL18-Rα-negative T cells. **(B)** Percentages of MAIT cells and non-MAIT Vα7.2+ cells versus total CD3+ T cells in healthy human liver (n = 8), assessed as shown in (A). ** $P < 0.01$, non-paired Welch t-test.

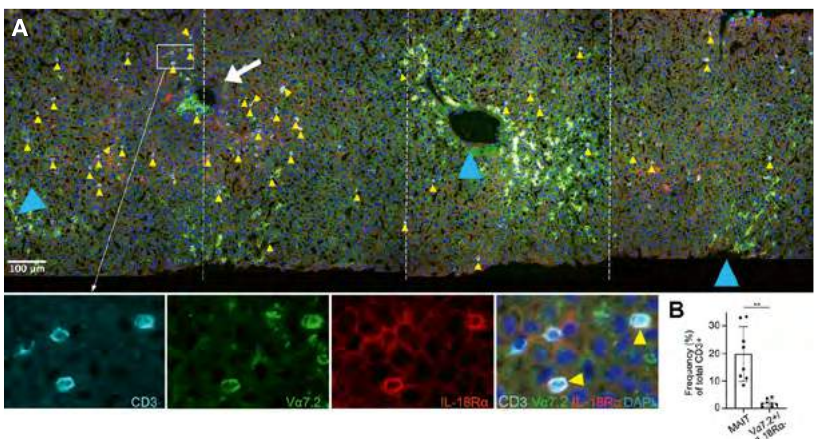

Fig. 2: Robust MAIT cell activation in response to interactions with primary human liver cells.
Synthetic antige (Ag) 5-OP-RU (A), and E. coli lysate (B) titration on liver-derived cells, including hepatocytes (HEP), BEC, and HSC, used as Ag-presenting cells (APCs). IFN-γ production by a liver-derived MAIT cell line **(A)** and blood-derived MAIT cell clone **(B)** is depicted. MR-1 dependence of the activation process was confirmed by MR1-blocking antibodies. **(C)** Cell surface staining for MAIT cell markers CD161 and Vα7.2 in response to distinct liver-derived APCs exposed to 5 nM 5-OP-RU. The left panel corresponds to the negative control (CTRL) lacking the APC. Primary blood-derived Vα7.2+ CD161++ cells were enriched by negative selection.

Connection to Clinical Practice

Characterization of liver- and gut-derived human MAIT cells

Most liver diseases are characterized by an inflammatory response in the liver, driven by numerous triggering conditions, such as exposure to alcohol, excess fat, medication, infection or autoimmunity. A prolonged inflammatory state leads to progressive fibrosis that can result in liver cirrhosis associated with serious complications including loss of liver function or development of hepatocellular carcinoma.

Since liver MAIT cells respond to bacterial metabolites and exhibit pro-fibrotic properties, they likely also contribute to pathogenesis of various liver diseases. To date, only few studies have addressed a role of these cells in human liver tissue and using primary human material.

Our projects are being performed in close collaboration with the Department of Gastroenterology/Hepatology at the Basel University Medical Clinic in Liestal (PD Dr. E. Burri and Prof. J. Leuppi), the Visceral Surgery Department at the Kantonsspital Baselland (Prof. R. Rosenberg), the Divisions of Gastroenterology/Hepatology and Visceral surgery, Clarunis University Center for Gastrointestinal and Liver Diseases (Prof. M. Heim and Prof. O. Kollmar), the Department of Interventional Radiology of the University Hospital Basel (Prof. C. Zech), and with the laboratories of Prof. D. Stroka and Prof. A. Macpherson, Department of Biomedical Research, University Hospital Bern.

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Developmental Immunology

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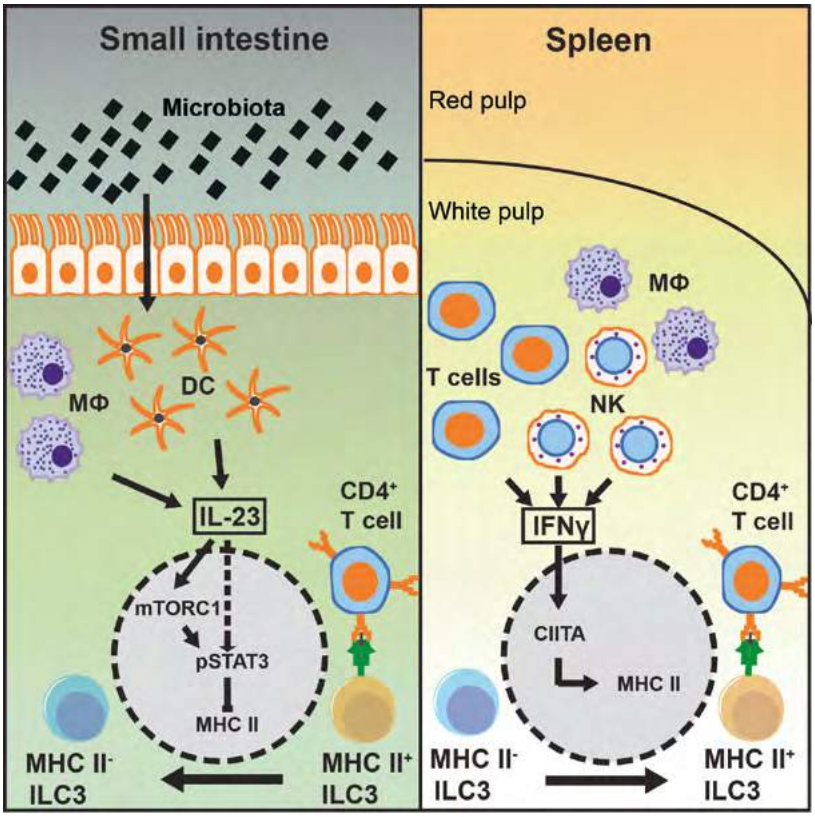
Development and immune functions of innate lymphoid cells

In the last decade, we have gained substantial knowledge on the function of innate lymphoid cells (ILCs), a group of immune cells, which immediately respond to "danger signals" with the release of cytokines. They protect mucosal surfaces in the gut and lung, but are also involved in diseases such as inflammatory bowel disease, asthma and cancer. Our previous research has shed light on how ILCs were regulated by environmental cytokines. More recent work has demonstrated that ILC3s have tissue-restricted properties and a metastable transcriptional signature. The identification of molecular pathways that regulate ILC differentiation and function is essential for a better understanding of how ILCs contribute to protective or pathological responses.
ILCs, unlike adaptive lymphocytes do not express variable antigen receptors that serve as master activators in T and B cells. Instead ILCs sense the environment by a concerted action of surface molecules, and the outcome of ILC responses depend on the integration and cooperation of different downstream signaling pathways. We defined a new role of NKp46, an activating receptor expressed by all ILC1s and a subset of ILC3s. We found that the expression of TRAIL, a TNF superfamily member with known tumoricidal function, depends on NKp46. Lack of NKp46 lead to the reduction of normal levels of TRAIL expression on the surface of ILCs. The reduced cytotoxic potential of NKp46-deficient ILC1s towards TRAIL-receptor positive targets provide an additional role for NKp46 in tumor surveillance.

Another focus of our research is the regulation of T-cell immune responses by group 3 ILCs. Tissue-specific factors regulate the expression of transcripts associated with MHC class II antigen presentation in ILC3s. Splenic ILC3s are relatively efficient antigen presenting cells, whereas ILC3s of the small intestine are poor in presenting antigen and stimulating T cells. We identified tissue specific signaling cascades that affect the antigen presentation by ILC3s. The intestinal microbiota induces the release of IL-23 by myeloid cells, which silences the expression of MHC class II in ILC3s, thereby reducing their capacity to present antigen. Moreover, mTORC1 and STAT3 phosphorylation are part of the IL-23-signaling cascade responsible for downregulation of MHC class II (Figure 1). Altogether this might be essential to maintain immunological tolerance at barrier tissues like the intestine. In contrast in the spleen IFN-gamma induces the expression of MHC class II molecules, thereby increasing the antigen presenting capacity of ILC3. Both signaling cascades might be relevant to balance T-cell tolerance and immune reaction by affecting antigen presentation by ILC3s. Our current interest is to better understand the tissue-specific sub-localization and the cellular interaction of ILC3s with the adaptive immune system.
In a third line of research, we investigate ILC development. ILCs like all hematopoietic cells develop from hematopoietic stem cells. However, the sequence of developmental stages and molecular events that lead to the generation of ILC- committed progenitors as well as the exact identity of such cells remains poorly defined. Using a systemic approach including single cell molecular and bioinformatical analysis, we are able to reconstruct developmental trajectories from a hematopoietic stem cell into an ILC progenitor or alternative developmental lineages. With a comprehensive molecular map of developmental transitions that result in the generation of a committed ILC progenitor we are now dissecting the role of individual genes and signaling pathways that control ILC lineage specification.



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Hepatology

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Hepatocellular Carcinoma and Chronic Hepatitis

Worldwide, liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death, with an estimated 854,000 new cases and 810,000 deaths per year. 90 % of liver cancers are hepatocellular carcinomas (HCCs). Over 95 % of HCCs develop on the background of chronic liver disease and indeed, more than 80 % of HCCs occur in cirrhotic livers. Treatment options for advanced stage HCCs are still very limited, and a better understanding of the molecular and cellular pathogenesis of HCCs is urgently needed. In the framework of a clinical study protocol we generated a clinically annotated tumor- and liver-biopsy biobank and blood bank. This unique research resource is being used to study the molecular and cellular pathogenesis of HCC with the aim to generate clinically meaningful molecular classifications, to identify predictive biomarkers for response to treatments, and to identify new therapeutic targets and strategies. A major obstacle in preclinical drug development is the lack of appropriate cell culture model systems. Current *in vitro* cell culture models of HCC are based on conventional hepatoma and hepatocarcinoma cell lines that fail to recapitulate key features of tumor tissues such as three-dimensional tumor architecture, cellular heterogeneity, and cell-cell interactions. We have developed a pipeline to generate and characterize organoid models of HCCs (Nuciforo *et al.,* 2018). These HCC organoids maintain the histological and genomic features of their originating tumors during long-term culturing for up to 32 weeks. The models can be used for preclinical drug screenings and testing and to generate phenotype-genotype correlations tables (Fig. 1). HCC tumor biopsies can also be used to generate xenograft mouse models (Blumer *et al.,* 2019). Again, these models closely resemble the originating tumors and can be serially passaged. Xenograft mouse models preserve the heterogeneity of HCCs and are a valuable research tool for preclinical drug testing.

The most important underlying liver diseases that predispose to HCC are chronic hepatitis B and chronic hepatitis C, alcoholic liver disease, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis. Our lab has a long-standing research interest in viral hepatitis with a special focus on innate immune responses to viral hepatitis. The host response to hepatitis C is controlled by a genetic polymorphism of the interferon lambda (IFNL) gene locus. Paradoxically, individuals who cannot produce IFNL4 due to a frameshift mutation in the IFNL4 gene have a better immune response to HCV and can control and eliminate the viral infection. On the other side, individuals with a wild-type IFNL4 usually cannot eliminate the virus and develop chronic hepatitis that can lead to cirrhosis, despite a strong induction of hundreds of IFN-stimulated genes (Boldanova *et al.,* 2017). This so called "IFN lambda 4 paradox" is currently not understood, and is a focus of ongoing research in the lab.

Contrary to HCV, hepatitis B virus (HBV) does not stimulate the induction of an interferon response in the liver. Using liver biopsies of patients with HBV infections, we could show that this lack of innate immune response is not due to an active inhibition of sensory pathways or interferon expression by HBV, but because HBV is a "stealth virus", i. e. HBV is not recognized by pathogen associated molecular patterns (PAMP) receptors, most likely because of a very low expression of cGAS and STING in hepatocytes, two components of the intracellular sensory pathway that detects viral DNA (Suslov *et al.,* 2018; Baumann *et al.,* unpublished). Ongoing projects in the lab investigate the molecular mechanisms that control HBV viral replication in chronic hepatitis B, with a main focus on disease stage transitions during the natural history of chronic hepatitis B.

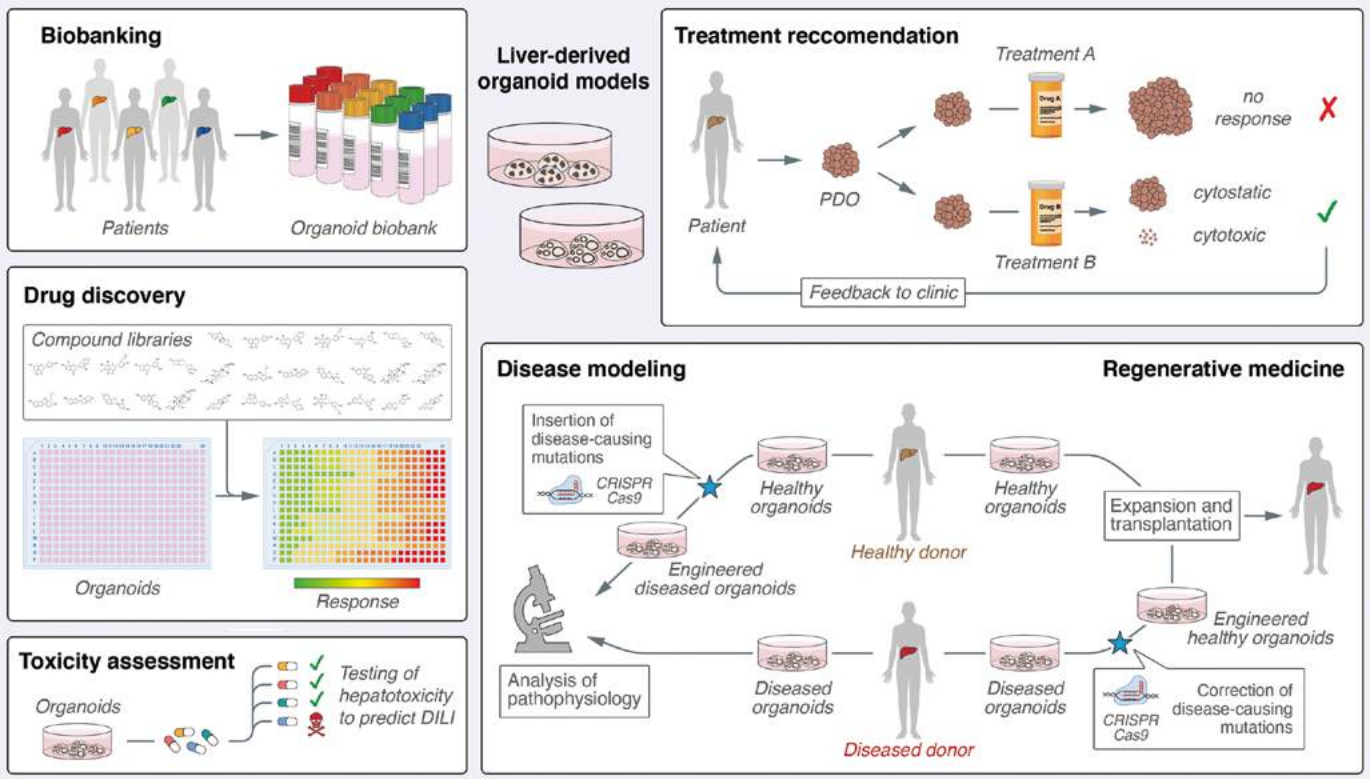

Fig. 1: Translational applications of liver-derived organoid models.
Patient-derived organoid biobanks are important resources for applications in academic research and drug development. Organoid models of liver disease can be directly generated from diseased donors or alternatively from healthy donors following CRISPR/Cas9-mediated insertion of disease-causing mutations, e. g. for the study of monogenic liver diseases or liver cancer. Organoid-based drug discovery allows a more physiological assessment of drug sensitivity and hepatotoxicity facilitating the selection of potent drugs with a safe profile. Patient-derived organoids could support clinicians during the therapy decision-making process by predicting the efficacy of different treatments for the same indication. Finally, organoid-based cell therapies represent an alternative to liver transplantation for various diseases, in particular monogenic liver diseases that can be corrected with genome editing methods. CRISPR/Cas9, clustered regularly interspaced short palindromic repeats/CRISPR associated protein 9; DILI, drug-induced liver injury; PDO, patient derived organoid.

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Di Blasi D, Boldanova T, Mori L, Terracciano L, Heim MH and De Libero G (2020). Unique T-Cell Populations Define Immune-Inflamed Hepatocellular Carcinoma. Cell Mol Gastroenterol Hepatol 9, 195–218.

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Immuno-biology

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Immunometabolic regulation of adaptive immunity in health and disease

Our research is focused on basic and translational aspects of lymphocyte function and its metabolic basis. Conceptually, our recent work has led us to propose the idea that a spectrum of immune cell metabolic states can provide a basis for categorizing diseases (Fig. 1).

In that scheme, acute resolving infection represents properly regulated cellular metabolism. Exploring this notion experimentally, we tested how acetate – a short chain fatty acid – is regulating T cell metabolism during resolving infection in mice. We found that acetate transiently increases in the blood circulation upon acute infection. This leads to acetylation of the enzyme GAPDH in memory CD8+ T cells, which enhances their glycolytic switch and interlinked inflammatory capacity. At sites of prolonged inflammation, by contrast, acetate accumulates but now catalyzes glutaminase activity and develops suppressive capacity by buffering calcium (Balmer *et al.* Immunity 2016 and Cell Metabolism 2020). These findings support the idea of an orchestrated early hypermetabolic-, followed by a hypometabolic T cell state jointly enabling resolution of acute infection.

Two disease categories were investigated to further probe our metabolism-centric categorization scheme (Fig. 1), namely cancer and primary antibody deficiency (PAD). In cancer patients, we investigated how tumor-derived TGF-β suppresses the key antitumor function of CD4+ T cells, IFN-γ production. Suppression required expression and phosphorylation of Smad proteins in the TGF-β signaling pathway – but not their nuclear translocation, and it depended on oxygen availability, suggesting a metabolic basis for these effects. Indeed, TGF-β substantially impaired the ATP-coupled respiration of CD4+ T cells and specifically inhibited mitochondrial complex V (ATP synthase) activity. Inhibition of ATP synthase alone was sufficient to impair IFN-γ production by CD4+ T cells. These results suggest

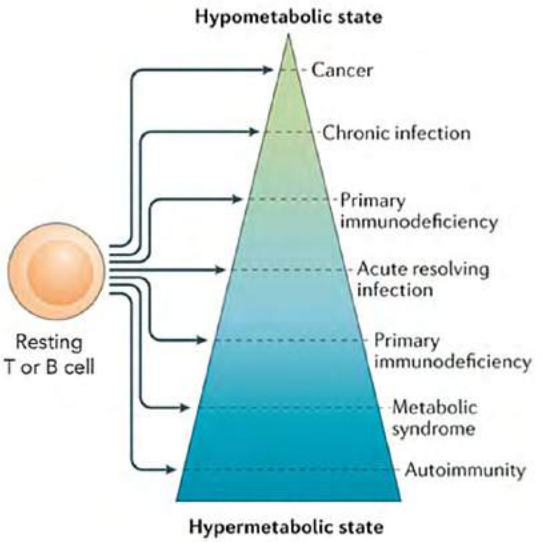

Fig. 1:
From Bantug *et al.,* Nat Rev Immunol 2018 Jan;18(1):19–34

that TGF-β targets T cell metabolism directly, diminishing T cell function by driving a hypometabolic phenotype (Dimeloe *et al.* Science Signaling 2019). In PAD, we previously found that loss-of-function mutations can lead to immunodeficiency by causing a hypometabolic T cell phenotype (Kolev *et al.,* Immunity 2015). In the current reporting period we built on this observation and prospectively screened glycolysis and mitochondrial respiration in B cells from patients with PAD. The highest oxygen consumption rate values were detected in three study participants with persistent polyclonal B cell lymphocytosis (PPBL). Exome sequencing identified germline mutations in SDHA, which encodes succinate dehydrogenase subunit A, in all three patients with PPBL. SDHA gain-of-function led to accumulation of fumarate in PPBL B cells, which engaged the KEAP1-Nrf2 system to drive the transcription of genes encoding inflammatory cytokines. In a single patient trial, blocking the activity of the cytokine interleukin-6 *in vivo* prevented systemic inflammation and ameliorated clinical disease. Overall, this study thus identified a hypermetabolic phenotype, driving pathological mitochondrial retrograde signaling, as a disease modifier in PAD (Burgener *et al.* Nat. Imm., 2019) (Fig. 2).

In our basic research efforts we aimed to understand, at the molecular level, how glycolysis is linked to the rapid response of memory CD8+ T cells (Gubser *et al.,* Nat. Imm., 2013). We found that rapid activation of AKT by mTORC2 leads to inhibition of GSK3β at mitochondria- endoplasmic reticulum (ER) junctions. This enabled recruitment of hexokinase I (HK-I) to the voltage-dependent anion channel (VDAC) on mitochondria. Binding of HK-I to VDAC promoted respiration by facilitating metabolite flux into mitochondria. Glucose tracing pinpointed pyruvate oxidation in mitochondria, which was the metabolic requirement for rapid generation of IFN-γ in memory T cells. Subcellular organization of mTORC2-AKT-GSK3β at mitochondria-ER contact sites, promoting HK-I recruitment to VDAC, thus underpins the metabolic reprogramming needed for memory CD8+ T cells to rapidly acquire effector function (Bantug *et al.* Immunity 2018), (Fig. 3).

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Balmer ML, Ma EH, Thompson AJ, Epple R, Unterstab G, Lötscher J, Dehio P, Schürch CM, Warncke JD, Perrin G *et al.* (2020). Memory CD8+ T Cells Balance Pro- and Anti- inflammatory Activity by Reprogramming Cellular Acetate Handling at Sites of Infection. Cell Metabolism 32, 457–467.e5.

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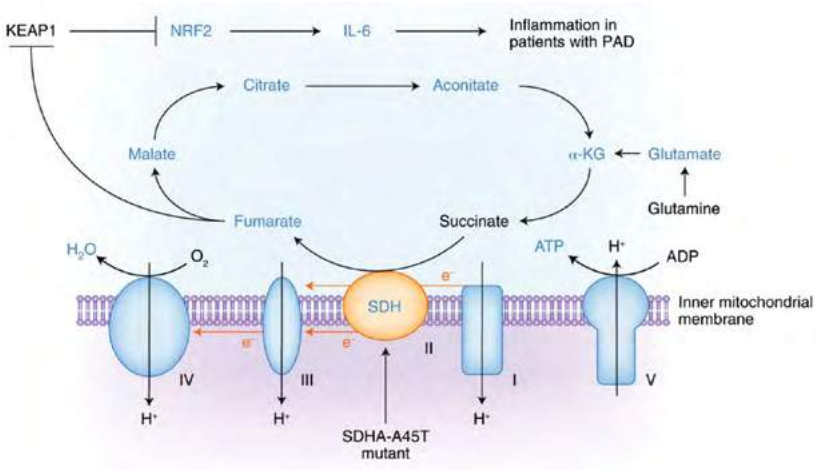

Fig. 2:
From Zeng H and Chi H. Nat Immunol 2019 Oct;20(10):1264–1266

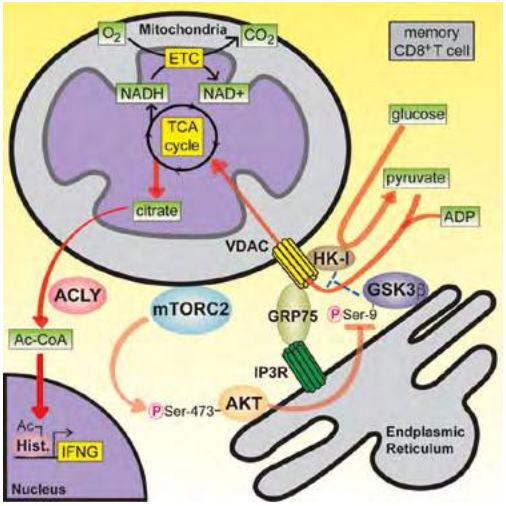

Fig. 3:
From Bantug *et al.,* Immunity 2018 Mar 20; 48(3): 542–555

Transplantation and Clinical Virology (TCV)

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Missing immunity and Viral Diseases

The research group "Transplantation and Clinical Virology" focuses on translational aspects of clinically relevant virus infections in humans. Our approach includes contrasting acute versus chronic viral infections with respect to pathogenesis and immune control using community-acquired respiratory viruses (CARVs) versus persisting human herpesviruses or human polyomaviruses in immunologically naïve, in immunodeficient, or in immunosuppressed patients.

Regarding CARVs, we have been actively engaged in several studies characterizing the epidemiology and impact in solid organ transplantation (SOT) patients participating in the Swiss Transplant Cohort Study (STCS) and in hematopoietic stem cell transplant (HSCT) patients. We contributed to prospective studies of lung transplant recipients and to evaluating a novel antiviral drug (presatovir) targeting fusion of respiratory syncytial virus in HSCT patients. We reviewed the available literature and contributed to CARV- and CoVID19-guidelines in the framework of ECIL and EHA. The year 2020 has been dominated by the SARS-CoV-2 pandemic for which we established a robust in-house assay to diagnose patients and identified its rapid replacing all commonly circulating CARVs (Leuzinger et al. 2020; **Fig.1**).

Regarding human herpesviruses, cytomegalovirus (CMV), herpes simplex virus (HSV) and Epstein-Barr virus (EBV) are the most relevant challenges. Epidemiology and impact have been evaluated in collaborations with the STCS and locally with Profs Schaub/Steiger. We established phenotypic acyclovir resistance testing for HSV, genotypic resistance for HSV and CMV including the new drug (letermovir). We established CMV-DNAemia as the major form of plasma CMV loads resulting from naked unprotected viral genome fragments. This explains the long-known difficulty of CMV culture from blood as opposed to broncho-alveolar lavage fluids despite high CMV-DNA loads. Our observations have pathophysiological, diagnostic, and therapeutic relevance, and entered the international TTS consensus guidelines on CMV management in SOT.

Regarding human polyomaviruses, we focus on BK polyomavirus (BKPyV) and characterized its epidemiology and impact in collaborations nationally with the STCS, locally with Profs Schaub/Steiger in kidney transplant patients as well as internationally, with the pediatric kidney and HSCT programs in Helsinki, Finland. We improved BKPyV-detection establishing that BKPyV-DNAemia is the major form of "viremia" in transplant patients similar to CMV. These observations impact concepts regarding the use of neutralizing antibodies for protection and therapy. Together with Prof Parmjeet Randhawa, Pittsburgh (PA, USA) and AST-IDCOP, we provided the 2019 clinical guideline on BKPyV in kidney transplantation.

Our experimental virology studies focus on BKPyV in primary human renal tubular epithelial cells as key target of BKPyV nephropathy in kidney transplants. For the first time, we identified an evolutionarily conserved functional role of viral agnoprotein, which promotes innate immune evasion by disrupting the mitochondrial membrane potential, fragmenting the mitochondrial network, and targeting the damage mitochondria for autophagy (Manzetti et al. 2020; **Fig. 2**).

Regarding adaptive immunity, we identified more than 70 immunodominant 9mer-epitopes recognized by BPyV-specific CD8 T-cells controlling BKPyV-DNAemia. Notably, we developed a novel peptide expansion protocol of BPyV-specific CD8 T-cells *in vitro* en route to a safe peptide-based protection by adoptive T-cell transfer and vaccination (Wilhelm et al. 2020; **Fig. 3**). We also identified variant amino acid exchanges in the conserved BKPyV-early protein, which mediate escape from CD8 T-cell control (Leuzinger et al. 2020 10.3390/v12121476).

We plan to reconstitute 3-dimensional renal tubule kidney culture and organoid models for BKPyV infection and antiviral T-cell control as an animal-free surrogate

for pre-clinical models of viral immune control and to design phase I clinical vaccination studies in healthy volunteers.

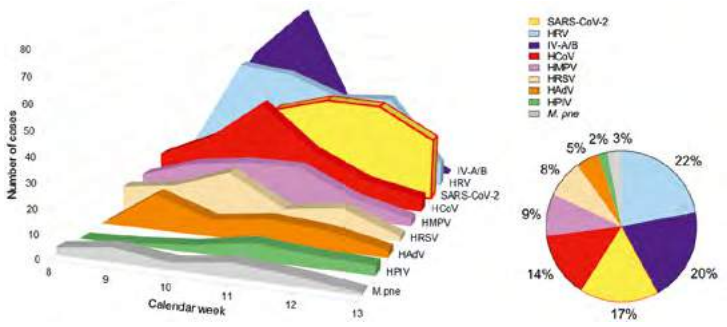

Fig. 1

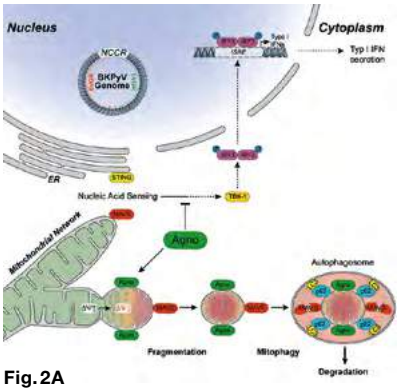

Fig. 2A

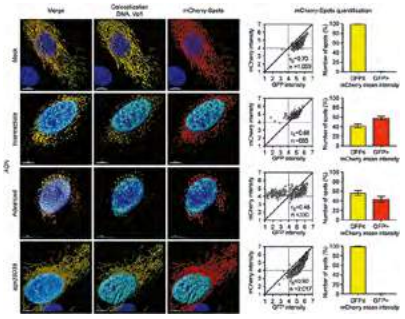

Fig. 2B

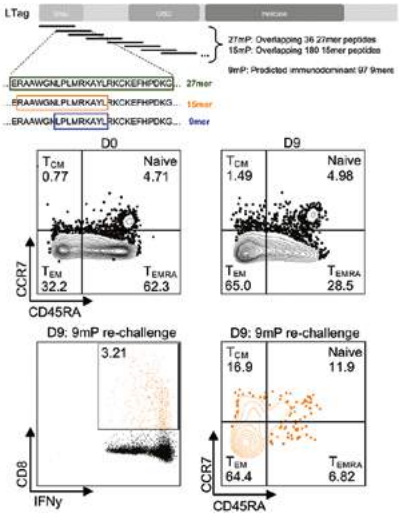

Fig. 3

Selected Publications

Ison MG and Hirsch HH (2019). Community-Acquired Respiratory Viruses in Transplant Patients: Diversity, Impact, Unmet Clinical Needs. Clin Microbiol Rev 32, e00042-00019.

Leboeuf C, Wilk S, Achermann R, Binet I, Golshayan D, Hadaya K, Hirzel C, Hoffmann M, Huynh-Do U, Koller MT et al. (2017). BK Polyomavirus-Specific 9mer CD8 T Cell Responses Correlate With Clearance of BK Viremia in Kidney Transplant Recipients: First Report From the Swiss Transplant Cohort Study. Am J Transplant 17, 2591–2600.

Leuzinger K, Roloff T, Gosert R, Sogaard K, Naegele K, Rentsch K, Bingisser R, Nickel CH, Pargger H, Bassetti S et al. (2020). Epidemiology of Severe Acute Respiratory Syndrome Coronavirus 2 Emergence Amidst Community-Acquired Respiratory Viruses. J Infect Dis 222, 1270–1279.

Manzetti J, Weissbach FH, Graf FE, Unterstab G, Wernli M, Hopfer H, Drachenberg CB, Rinaldo CH and Hirsch HH (2020). BK Polyomavirus Evades Innate Immune Sensing by Disrupting the Mitochondrial Network and Promotes Mitophagy. iScience 23, 101257.

Wilhelm M, Kaur A, Wernli M and Hirsch HH (2020). BK Polyomavirus (BKPyV)-specific CD8 T-cell expansion *in vitro* using 27mer peptide antigens for developing adoptive T-cell transfer and vaccination. J Infect Dis. doi: 10.1093/infdis/jiaa546. Online ahead of print. PMID: 32857163.

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Liaison dangereuse – Virus infection and missing immunity

"Transplantation and Clinical Virology" is interested in translational research of acute versus persistent virus infections to dissect the pathogenesis of viral diseases, to improve diagnostic tools for clinical use, and to identify strategies of prevention and treatment. Key viral threats are being addressed according to their importance as defined by frequency, severity, and available medical treatment. Thus, we are interested in

- Community-acquired respiratory virus (CARV) infections in populations without sufficient immune control including SARS-CoV-2;
- Emerging epidemics including vector-borne viral diseases (tick-borne encephalitis virus, dengue, Chikungunya, West Nile virus, Zika virus)
- Viruses affecting immunocompromised patients (HIV/AIDS; solid organ transplantation; hematopoietic cell transplantation; autoimmune diseases; primary/inherited immunodeficiency disorders).

Acute virus infections are exemplified by CARVs, while persistent virus infections are represented by human herpes- and polyomaviruses. Both, acute and chronic virus infections are naturally widespread in the general immunocompetent population, but may take a severe course in patients without functional immune memory either because of primary infection, primary immunodeficiency, acquired immunodeficiency or immunosuppression.

We aim at characterizing: 1) key determinants of virus pathology; 2) potential targets of antiviral intervention; 3) relevant innate immune mechanisms; 4) protective targets of adaptive immune memory; 5) modifiable and non-modifiable risk factors in patients to tailor and optimize interventions.

Pediatric Immunology

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Thymus Organogenesis And Function

The thymus is the anatomical site where T cells are generated and instructed to provide protective immunity against pathogens whilst ignoring the individual's own tissues. Thymic epithelial cells (TEC), an essential component of the organ's 3-dimensional scaffold, attract T cell precursor from the peripheral blood, foster their differentiation in a bespoke micro-environment, and help to select developing T cells based on their antigen specificities. Based on their distinct structural, phenotypic, and transcriptomic features, TEC are differentiated into distinct subtypes which anatomically define them as either cortical (c) or medullary (m) subpopulations (Figure 1). cTEC are instrumental in committing hematopoietic precursors to a T cell fate and in selecting cells with a T cell receptor (TCR) capable to interact with an individual's antigen presenting cells. mTEC express collectively an almost complete repertoire of an individual's protein coding genes and thus create a library of self-peptides essential for the induction of T cell self-tolerance. This unique ability is achieved by a yet incompletely understood process of promiscuous gene expression of peripheral tissue-specific antigens that is unique to a subpopulation of mTEC.

The research of the laboratory of Pediatric Immunology seeks to detail the genetic and epigenetic control of TEC development and function combining multi-parameter flow cytometry, advanced histological and molecular methods and transcriptomic analyses at both population level and single cell resolution. Recent and ongoing experiments focus on:

— The transcription factor FOXN1, a TEC master regulator. We identified *in vivo* the DNA binding motif of FOXN1, characterized the factor's molecular structure binding to that motif and ascertained the factor's molecular interactome essential for its ability to form nuclear condensates which prompt its regular transcriptional activity.

— The complexity of the TEC lineage development. Using single cell transcriptomic analysis of TEC across the life course of mice, we identified at least 9 separate TEC subtypes and demonstrated that TEC progenitor cells are the principal targets of ageing (Figure 2). Specifically, an early-life precursor cell population present in the cortex postnatally is virtually extinguished at puberty. Concomitantly, a medullary precursor cell quiesces, thereby impairing maintenance of the medullary epithelium. Hence the quiescence of TEC progenitors is a major factor underlying thymus involution and affects thymic regeneration and the preservation of central immune tolerance.

— The epigenetic control of TEC development and function. We showed that interference with DNA methylation, histone modifications or miRNA generation profoundly impairs TEC and consequently also overall thymus biology including organ size, TEC differentiation and function embracing the capacity to maintain a broad repertoire peripheral tissue-specific antigens. Interestingly, some of these changes are only apparent in adult mice thus revealing a differential dependence of perinatal and adult TEC on epigenetic regulatory mechanisms.

— The relevance of metabolism on TEC function. We found that modifications in the homeostasis of adenine nucleotides imparts significant quantitative and qualitative changes in the compartments of both cortical and medullary TEC. These alterations include changes in mitochondrial mass and superoxide production and are apparently paralleled by deviations in TEC differentiation and thymopoietic function.

— The role of Lin28 for TEC development and function. The RNA binding protein Lin28 regulates miRNA biogenesis and serves as a gatekeeper controlling the transition between pluripotency and committed cell lineages. Adult mice in which Lin28 overexpression was targeted to TEC failed to achieve a regular thymus size and showed defects in cTEC differentiation and consequently positive and negative thymocyte selection. Remarkably, these defects are not apparent in young mice hence demonstrating a differential susceptibility of perinatal and adult cTEC to Lin28 controlled RNA biology.

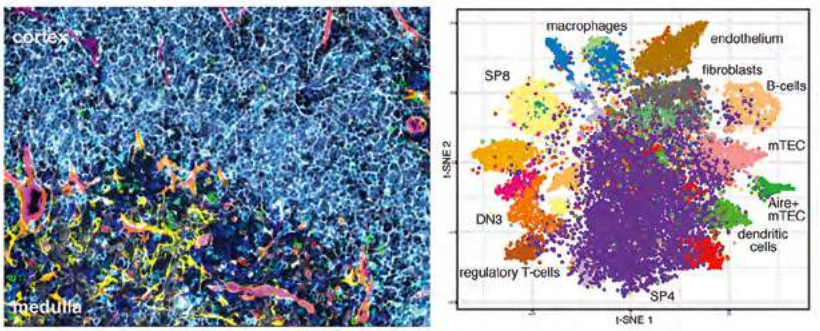

Fig. 1: Multi-parameter immunofluorescence analysis of a thymus tissue.
Left panel: shown selected markers CK8 (cytokeratin 8 identifying cTEC and mTEC) grey; CK14 (cytokeratin 14 identifying mTEC) yellow; AIRE (autoimmune regulator identifying mature mTEC) red; CD11c (identifying dendritic cells) blue; B220 (identifying B-cells) green; F4/80 (identifying macrophages) cyan; CD31 (identifying endothelium) magenta; ERTR7 (identifying fibroblasts and endothelium) brown; CD8 (identifying developing T-cells) light blue.
Right panel: t-SNE plot displaying thymic cell populations identified using staining panel simultaneously detecting 26 cellular markers. Each dot represents a single cell. Clusters are annotated based on phenotypic comparisons to known thymic cell populations largely defined by flow cytometric analysis. DN3 cells are CD4-CD8-CD44-CD25+ immature thymocytes.

Selected Publications

Baran-Gale J, Morgan MD, Maio S, Dhalla F, Calvo-Asensio I, Deadman ME, Handel AE, Maynard A, Chen S, Green F, Sit RV, Neff NF, Darmanis S, Tan W, May AP, Marioni JC, Ponting CP, Holländer GA. Ageing compromises mouse thymus function and remodels epithelial cell differentiation. Elife 9:e56221, 2020. doi: 10.7554/eLife.56221.

Dhalla F, Baran-Gale J, Maio S, Chappell L, Holländer GA, Ponting CP. Biologically indeterminate yet ordered promiscuous gene expression in single medullary thymic epithelial cells. EMBO J. 39:e101828, 2020. doi: 10.15252/embj.2019101828.

Newman JA, Aitkenhead H, Gavard AE, Rota IA, Handel AE, Hollander GA, Gileadi O. The crystal structure of human forkhead box N1 in complex with DNA reveals the structural basis for forkhead box family specificity. J Biol Chem. 295:2948-2958, 2020. doi: 10.1074/jbc.RA119.010365.

Handel AE, Shikama-Dorn N, Zhanybekova S, Maio S, Graedel AN, Zuklys S, Ponting CP, Holländer GA. Comprehensively Profiling the Chromatin Architecture of Tissue Restricted Antigen Expression in Thymic Epithelial Cells Over Development. Front Immunol. 9:2120, 2018. doi: 10.3389/fimmu.2018.02120.

Žuklys S, Handel A, Zhanybekova S, Govani F, Keller M, Maio S, Mayer CE, Teh HY, Hafen K, Gallone G, Barthlott T, Ponting CP, Holländer GA. Foxn1 regulates key target genes essential for T cell development in postnatal thymic epithelial cells. Nat Immunol. 2016 Oct;17(10):1206-1215. doi: 10.1038/ni.3537.

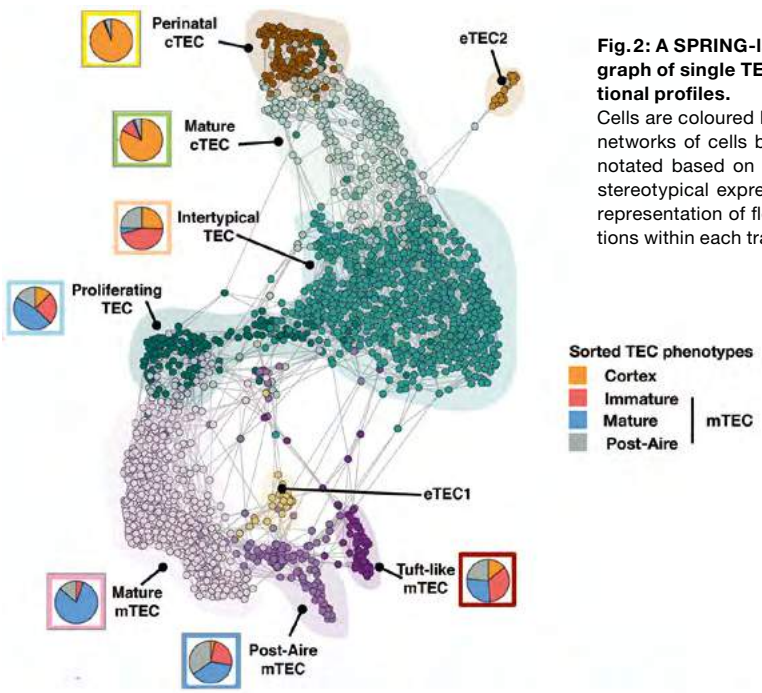

Fig. 2: A SPRING-layout of the shared nearest-neighbour graph of single TEC, derived from scRNA-seq transcriptional profiles.
Cells are coloured by a clustering that joins highly connected networks of cells based on a random walk. Clusters are annotated based on comparisons to known TEC subsets and stereotypical expression profiles. Coloured circles show the representation of flow cytometrically defined TEC subpopulations within each transcriptionally defined TEC subset.

Molecular Immune Regulation

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Exploring T cell regulation with patients in mind

The mammalian immune system is important to fight infections but immune cells are also involved in many other processes such as tolerance to the growing fetus, wound healing and eliminating tumors. To this end the immune system is composed of many cell types and soluble molecules. Many layers of regulation ensure proper functioning of the immune system as a whole since mistakes can lead to severe clinical disease.

In the past decade immunology has taken center stage in clinical medicine. Immune cells and inflammation are important in diseases affecting virtually any organ. Nevertheless, until recently, therapeutic interventions targeting the immune system were rather limited. Although vaccines are among the most effective (preventative) measures in medicine, only a limited number of vaccines were available and modulating the immune system therapeutically usually came at the cost of non-specific immune suppression. With the availability of "biologics", i.e. therapeutic antibodies or cytokines, this started to change. Cytokine blockade allows more specific intervention with specific pathways and is nowadays established in many different disciplines. In addition, antibody-mediated blockade of receptors on immune cells led to a long- awaited revolution in oncology. Since the turn of the century it was known that inflammation and cancer are closely linked. However, only in the last decade "cancer immunotherapy" has become clinical routine. Cancer can suppress immune responses by engaging inhibitory receptors on immune cells. Blocking such interactions with therapeutic antibodies can successfully "unleash" the immune system. Thus, in this approach, the therapeutic target are immune cells and only indirectly cancer cells. This broke a longstanding dogma that the cancer cells themselves are targeted in oncology. However, despite great success, not all patients respond. Therefore, we are investigating poorly studied molecules involved in immune regulation.

Our group has been studying small regulatory RNAs called microRNAs (miRNA) for over a decade. miRNAs inhibit specific messenger RNAs (mRNAs) by directly binding them. We previously demonstrated that a specific miRNA cluster (miR-17~92) is upregulated during T cell activation. When T cells recognize their target antigens they get activated. Two signals are required for this process: **a)** stimulation of the T cell receptor and **b)** a second signal called costimulation. The prototypical costimulatory signal is triggered by engagement of CD28. Based on the literature and our own work we hypothesized that miR-17~92 might mediate important signals during T cell activation. In the past reporting period we found that transgenic miR-17~92 can at least partially substitute for many of the functions that are defective in CD28-deficient T cells. We characterized the target genes that are bound and regulated by miR-17~92 and demonstrated that several pathways key for T cell activation and function are promoted by miR-17~92 (Doelz *et al.,* unpublished).

In parallel, we investigated if miRNAs that are relevant for T cell function could be targeted by small molecules. We identified small molecules that inhibit T cell function and proliferation of cancer cell lines. We are currently investigating the precise mode of action of these molecules (Matter & Jeker, unpublished).

Finally, cellular therapies are emerging as effective treatment modalities beside small molecules and biologics (Jeker, Trillium Immunologie). We have developed CRISPR/Cas9-based protocols to engineer the genome of T cells (Kornete, JI). More recently we have initiated projects involving more sophisticated engineering to explore cellular therapies for autoimmune diseases and transplantation. Thus, we are increasingly focusing on translating our research results to clinical practice.

Connection to Clinical Practice

Prof. Jürg Steiger
Nephrology and Transplantation Immunology

Our lab is associated with the clinical Transplantation Immunology & Nephrology at the USB. We are working together to prepare the infrastructure necessary to bring new multidisciplinary cellular therapies to patients at the USB.

Selected Publications

Doelz M, Gagnon JD, Kornete M, Marone R, Bantug G, Kageyama R, Hess C, Ansel KM, Seyres D, Roux J and Jeker LT (2020). The non-coding RNA miR-17-92 is a central mediator of T cell activation. https://www.biorxiv.org/content/10.1101/2020.10.13.336537v1.

Doelz M, Marone R and Jeker LT. Plasmid- or Ribonucleoprotein-mediated CRISPR/Cas Gene Editing in Primary Murine T Cells. Meth Mol Biol, in press.

Kornete JI, Kornete M, Marone R and Jeker LT. (2018). Highly Efficient and Versatile Plasmid-Based Gene Editing in Primary T Cells. J Immunol 200, 2489–2501.

Jeker LT. (2018). T Zellen nach Mass. Trillium Immunologie; 2(2).

Pua HH, Steiner DF, Patel S, Gonzalez JR, Ortiz-Carpena JF, Kageyama R, Chiou NT, Gallman A, de Kouchkovsky D, Jeker LT *et al.* (2016). MicroRNAs 24 and 27 Suppress Allergic Inflammation and Target a Network of Regulators of T Helper 2 Cell-Associated Cytokine Production. Immunity 44, 821–832.

Infection Biology

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New strategies to combat bacterial and viral infections

Infectious diseases remain a leading cause of death worldwide. Modern procedures including complex surgeries, cancer treatment and transplantation are associated with high risk of infections. Emerging resistance of pathogens are serious threats increasingly limiting the effectiveness of the antimicrobials in use today. Our research group explores host- and pathogen-specific aspects of infectious diseases in a strong translational setting – with the overarching goal to identify new treatment strategies.

New treatment strategies for staphylococci

Health care associated/nosocomial infections – the fourth leading cause of disease in industrialized countries – are a major health issue. Together with Gram-negative microorganisms, Staphylococcus aureus is one of the major causative agents.
Staphylococcal strains are highly virulent and are increasingly becoming resistant to every clinically available antibiotic. One particularly important unmet medical need for anti-S. aureus therapies is to treat biofilm-associated infections. Novel approaches to combat staphylococcal biofilm infections are therefore urgently needed. Together with our collaborators from the Department of Biosystems Science and Engineering (D-BSSE, ETH Zürich) we demonstrated that engineered designer cells containing a synthetic genetic circuit expressing lysostaphin under the regulation of human Toll-like receptor (TLR) 2, TLR1, TLR6, and CD14 can effectively sense methicillin-resistant Staphylococcus aureus (MRSA) implant-associated infections by detection of blood reporter proteins and prevent as well as cure infections in our tissue cage infection mouse model. This novel mammalian cell-based anti-infective approach was superior to conventional antibiotics (Fig. 1/2). (www.cell.com/action /doSearch?searchType=quick&searchText=immunomimetic+cells&searchScope=fullSite& occurrences=all&code=cellsite&contentType=video&startPage=).

Translation to clinics

Adoptive transfer of pathogen-specific donor-derived T cells is to date the most promising and feasible immunotherapeutic strategy in transplant recipients restoring the lacking T-cell function. Its potential as prophylactic or therapeutic treatment for viral infections after transplantation has been demonstrated.
We have pioneered virus-specific T-cell therapies in Switzerland. In a phase I/II study, in which we assess the feasibility of directly isolated virus-specific T cells using the cytokine capture assay, we test their safety in patients with treatment-refractory adenovirus, cytomegalovirus or Epstein-Barr virus infections after allogeneic hematopoietic cell transplantation (Clin Trials ID NCTO2007356). Currently, ten patients of which five patients each received CMV or EBV virus- specific T cells have been included. We are currently working on an improved cell expansion protocol for clinical use (Fig. 2).
In December 2019, the University of Basel has received the grant to establish the National Center of Competence (NCCR) in Research “AntiResist”, directed by the Biozentrum. Together with researchers at the Biozentrum, and the D-BSSE we will establish a unique interdisciplinary center for the development of new strategies in the fight against antibiotic-resistant pathogens (https://nccr-antiresist.ch/).

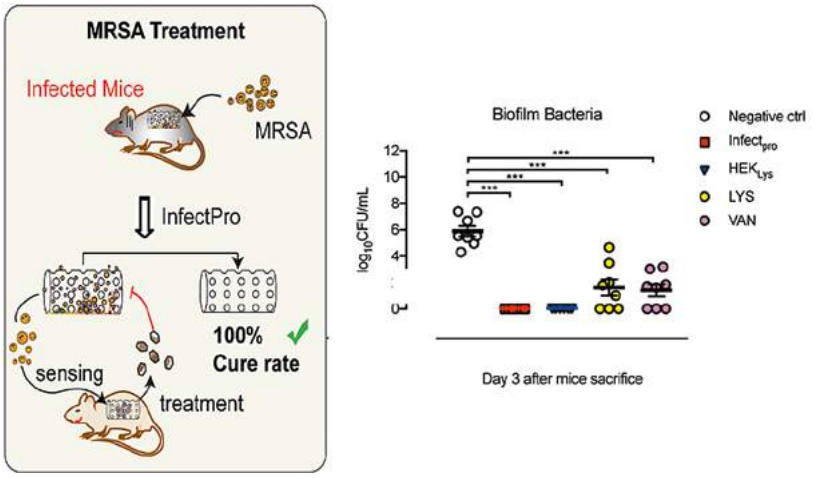

Fig. 1: Curing acute MRSA infection in Mice. To evaluate Infectpro's potential for the treatment of acute MRSA foreign-body infections, infected mice were treated with microencapsulated pYL25/pYL30/ pYL3-transgenic HEK293 cells (negative ctrl), HEKLys, Infectpro, recombinant lysostaphin (LYS, 5 mg/kg, once), or vancomycin (VAN, 200 mg/kg, every 12 hr). After 3 days, adherent MRSA in tissue cage biofilms of treated mice were evaluated.

Selected Publications

Wüthrich D, Cuénod A, Hinic V, Morgenstern M, Khanna N, Egli A, Kuehl R (2019). Genomic characterization of inpatient evolution of MRSA resistant to daptomycin, vancomycin and ceftaroline. J Antimicrob Chemother, 74(5):1452–1454.

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Schürmann N, Forrer P, Casse O, Li J, Felmy B, Burgener AV, Ehrenfeuchter N, Hardt WD, Recher M, Hess C, Tschan-Plessl A, Khanna N, Bumann D (2017). Myeloperoxidase targets oxidative host attacks to Salmonella and prevents collateral tissue damage. Nat Microbiol., 2:16268.

Stuehler C, Bernardini C, Elzi L, Stoeckle M, Zimmerli S, Furrer HJ, Gunthard H, Leibundgut- Landmann S, Battegay M and Khanna N (2016). Immune recovery in HIV-infected patients after Candida esophagitis is impaired despite long-term antiretroviral therapy. AIDS, 30(12):1923–33.

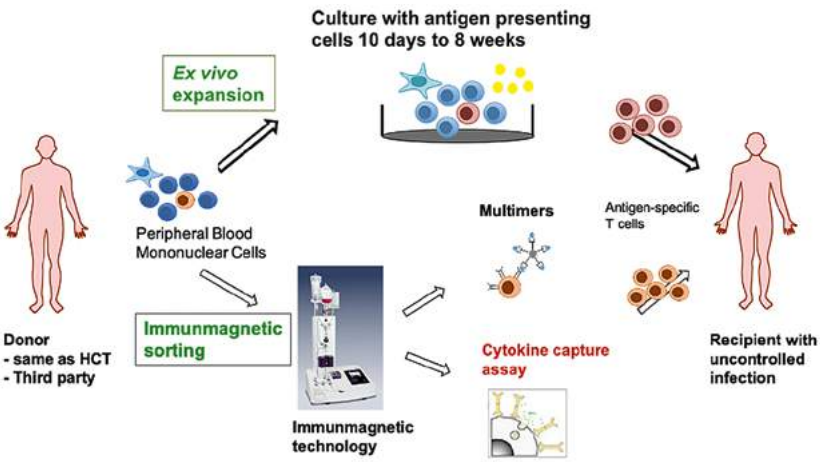

Fig. 2: Virus-specific T-cell therapies – current strategies. Virus-specific T cells for T-cell therapy (derived from the original stem cell donor or from a matched third party donor) can be obtained either by *ex vivo* expansion (top) or direct isolation via immunomagnetic sorting (bottom). For *ex vivo* expansion peripheral blood mononuclear cells are stimulated with antigen in the presence of cytokines for 10 days to several weeks to expand and enrich antigen-specific T cells. For immunomagnetic sorting antigen-specific T cells are directly isolated from peripheral blood by multimer technology or Cytokine capture assay (Miltenyi Biotech) within 1 to 2 days.

Immune Cell Biology

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CD4 memory T cells in health and disease

Our lab investigates CD4 memory T cells with a specific focus on CD4 T cells that support antibody production by B cells. Using a combination of single cell and systems immunology approaches we are addressing the biology and therapeutic potential of mucosal immunity to combat globally relevant pathogens including influenza and tuberculosis.

T follicular helper memory cells: a new target for vaccination: Much of the research on CD4 T cell memory is focused on T central memory (TCM) cells, which due to their persistence and multipotency are considered an optimal target for vaccination. In contrast, T follicular helper (TFH) cells, specialized to support antibody production by B cells, are thought to disappear within one to two months after viral clearance. We recently reported that TFH cells are exquisitely sensitive to NAD induced cell death. By inhibiting NAD-induced cell death we found that TFH cells comprise a robust portion of the memory cell compartment, are metabolically fit, and survive to at least 400 days after infection. Surprisingly, TCM cells were absent at this very late time point. Using single-cell RNA sequencing (scRNAseq) we determined that long-lived TFH cells are transcriptionally distinct from TCM cells, maintain stemness and self-renewal gene expression, and a high degree of differentiation plasticity. We also demonstrated that long-lived TFH cells actively support antibody production by splenic plasma cells, making a key contribution to systemic antibody titers at very late time points after infection when the immune response has supposedly died down. Taken together, these data highlight memory TFH cells as an attractive target for vaccination.

Tissue resident CD4 memory T cells: division of labor in the lung: Using an influenza model of infection we characterized the dynamics and transcriptional regulation of lung resident and lymphoid CD4 T cells; our analyses led to the definition of a “universal” residency signature which is agnostic to Th cell subset. We further identified a population of T resident helper (TRH) cells that require intrinsic Bcl6 expression as well as B cells for their differentiation, but arise independently from TFH effector cells in the lymph node. Using quantitative histology, we determined that TRH cells co-localize with B cells in tertiary lymphoid structures known as inducible Bronchus Associated Lymphoid Tissue (iBALT). Strikingly, late deletion of Bcl6 in CD4 T cells led to their exit from iBALT and impaired mucosal antibody production following heterologous challenge. These data indicate that CD4 T cell mediated protection involves the coordination of heterogeneous and specialized Th cell subsets. These findings also suggest that specific targeting of TRH cells will bolster mucosal immunity, and have additional implications for reinvigorating or dampening T cell responses in tissue or tumors where tertiary lymphoid structures are present.

T cell receptor signal strength and chronic infection: There is an ongoing debate about whether the strength of T cell receptor (TCR) signals alone can independently instruct one Th cell fate over another. Importantly, although cumulative TCR signal strength is influenced by the cellular microenvironment, whether or not TCR signal strength plays a primary role in CD4 T cell fate decisions occurring within distinct infectious contexts is unknown. To address this, we generated a panel of variant viruses by introducing mutations into the immunodominant peptide of both acute and chronic strains of lymphocytic choriomeningitis virus. By characterizing the response of adoptively transferred TCR transgenic T cells we discovered that the impact of TCR signal strength is not uniformly maintained between resolving and persistent viral infections. Particularly interesting is that weak TCR signals during chronic infection support the accumulation of Th1 effectors. Since loss of the Th1 cell compartment correlates with CD8 T cell dysfunction/exhaustion during chronic infection, our findings suggest that targeting low affinity CD4 T cell expansion may be a strategy to improve viral control.

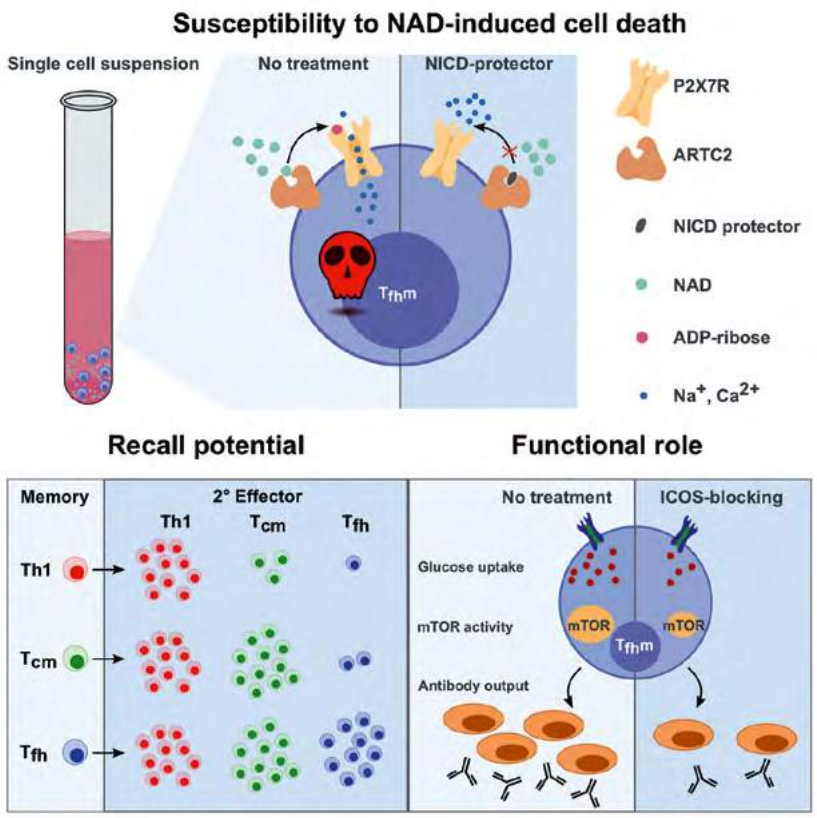

Fig. 1: TFH cells are long-lived, plastic and contribute to splenic antibody production.

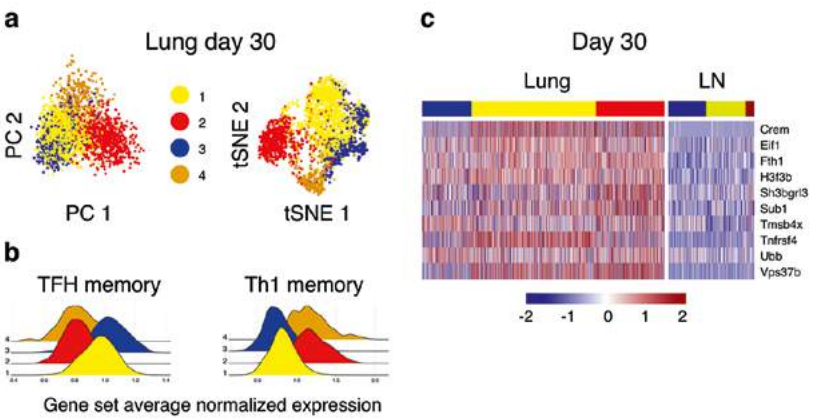

Fig. 2: (a) Unsupervised hierarchical clustering of lung CD4 T cells post influenza infection
(b) Log-normalized average expression of TFH and Th1 memory signatures.
(c) Heatmap of scaled, single cell expression showing conserved genes for lung and lymphoid tissue. Adjusted P value < 0.05.

Connection to Clinical Practice

We collaborate with pulmonary clinicians in Cape Town South Africa.

Although several groups have reported transcriptional signatures that discriminate individuals with various disease comorbidities, it is difficult to investigate the mechanistic basis of these pathways in humans. Similarly, despite the deeper mechanistic insight that can be gained by animal studies, not all findings can be translated to humans. We are bridging this divide by conducting in-depth, systems biology analyses of immune cells from humans and mice, focusing on pathways that are shared across the species. Our goal is to uncover biomarkers in the periphery that can be used to predict immune status in the tissue and, by proxy, disease status. We are complementing these studies by developing novel mouse models to induce cell intrinsic gene deletion in a tissue restricted manner. Manipulation of species conserved pathways in mice will allow us to unravel the immunological basis of disease comorbidity.

Selected Publications

Swarnalekha N, Schreiner D, Litzler LC, Iftikhar S, Kirchmeier D, Künzli M, Son YM, Sun J, Moreira EA, King CG (2020). T resident helper cells promote humoral responses in the lung. In press Sci Immunol.

Kunzli M, Schreiner D, Pereboom TC, Swarnalekha N, Litzler LC, Lotscher J, Ertuna YI, Roux J, Geier F, Jakob RP, et al (2020). Long-lived T follicular helper cells retain plasticity and help sustain humoral immunity. Sci Immunol 5.

Künzli M and King CG (2020). Resident Memory T Cells Escape "Home Quarantine." Trends Immunol 41, 454–456

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Molecular Virology

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HIV Reservoirs and Identification of Obstacles to a Cure

HIV-1 reservoir formation, stability and dynamics during early therapy *(Fabian Otte)*

Our research strategy focuses on viral properties of HIV-1 that change over the course of infection, even during suppressive therapy. We have shown that the viral tropism for CXCR4-expressing cells but also that of silently infected cells, correlates with poorer outcome in therapy-naïve individuals. We hypothesized that this might trigger superior HIV control during effective treatment. We aimed at characterizing HIV inside key T-cell populations in early therapy periods to identify cell populations driving this selective virus elimination to understand the preservation or re-establishment of crucial immune functions. Recent studies suggest that only few PBMCs harbor integrated HIV-1 genomes, mostly defective, in most assays counted as part of the "latent HIV-1 reservoir". We developed a new, highly sensitive method, 'GERDA' (Gag and Envelope Reactivation Detection Assay) to identify cell populations in peripheral blood that contribute to viral replication and to understand viral dynamics during therapy (Fig. 1). To dissect the contribution of specific cell reservoirs, we assessed viral activity on DNA, RNA and protein level, showing that viral activity quickly declines during therapy. Cells with lymphoid homing properties maintained the highest viral activity, which was overall very low. Our data strongly suggest that main contributors to viral persistence reside outside the periphery, likely in lymph nodes and gut. Next steps of our work will focus on biopsy material from these compartments.

Improve coreceptor prediction for HIV-1 subtype CRF01_AE isolates, common to South-East Asia *(Nina Marty)*

The algorithm Geno2pheno[coreceptor] (G2P) is a widely used genotyping tool for predicting co-receptor usage (=viral tropism) of HIV-1 isolates, critically important when using a coreceptor-antagonist for therapy. Especially for HIV-1 subtype CRF01_AE, a massive overcalling of X4-tropic isolates was observed with standard G2P settings. Aim of this study were the phenotypic validation and experimental proof of algorithm adaptations to better predict the tropism of clinical HIV-1 CRF01_AE isolates. For this, V3 env-sequences of 20 clinical HIV-1 subtype AE samples were sequenced and analyzed by G2Pco. In parallel, coreceptor usage was determined by phenotyping in human cells applying specific X4- or R5-inhibitors. When exchanging only the CRF01_AE V3 region in a subtype B cassette no replication-competent viral progeny could be produced, necessitating a full genome-replacement strategy to obtain an infectious CRF01_AE cassette (gag and pol sequences of AE were crucial). Replicative phenotyping confirmed the suspected overcalling of X4-tropism for CRF01_AE with the current G2P version. By lowering the False positive rate cut-off from 10 % to 2.5 % minimized this X4-overcalling yet permitting a predictive value for administrating the coreceptor-drug maraviroc (Fig. 2). Our study shows the complementing power of phenotyping and genotyping for validating new bioinformatics tools.

Transdominance of premature Rev expression *(Yuepeng Zhang)*

HIV replication requires the viral Tat protein to initiate its gene expression. It remains unclear, how the expression of other proteins is regulated. Viral Rev *e. g.* is needed for late expression (Env and Gag). We used specific mutations in our molecular HIV-1 clone and an LTR-lacZ reporter cell for studying these kinetic aspects. Wild type produces extended and blue Env-mediated syncytia, and high levels of released (= particle-associated) RT activity. Fusion of the AUG codon of tat to the gene body of rev led to a perplexing result: Large syncytia formed (like wild type), but without any blue X-gal stain. This demonstrated that late gene expression events (syncytia) are possible even in the absence of Tat (no blue). It is

known that Rev function requires its accumulation of large amounts that will then prevent RNA splicing. Only then late genes, i.e. env and gag, can be expressed. Our studies reveal a modulating role of Rev in the 'kinetic crosstalk' of events early in viral infection. Moreover, we observed that an "artificial, premature Rev expression" creates a dominant negative phenotype, interfering with the wild type virus production (Fig. 3). Our finding of a non-complementable negative impact of Rev when expressed prior to HIV infection or before Tat expression shows that i) functions of Tat and Rev can be uncoupled (Env expression without Tat) and ii) a strict kinetic dependence is critical for a productive HIV infection *in vitro*. We now analyze, if this property can be exploited for HIV control *in vivo* and towards new drugs.

Selected Publications

Amstutz A, Nsakala BL, Vanobberghen F, Muhairwe J, Glass TR, Namane T, Mpholo T, Battegay M, Klimkait T, Labhardt ND (2020). Switch to second-line versus continued first-line antiretroviral therapy for patients with low-level HIV-1 viremia: An open-label randomized controlled trial in Lesotho. PLoS Med. 17(9):e1003325.

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Bachmann N, von Siebenthal C, Vongrad V, Turk T, Neumann K, Beerenwinkel N, Bogojeska J, Fellay J, Roth V, Kok YL, Thorball CW, Borghesi A, Parbhoo S, Wieser M, Böni J, Perreau M, Klimkait T, Yerly S, Battegay M, Rauch A, Hoffmann M, Bernasconi E, Cavassini M, Kouyos RD, Günthard HF, Metzner KJ; Swiss HIV Cohort Study (2019). Determinants of HIV-1 reservoir size and long-term dynamics during suppressive ART. Nat Commun. 2019 Jul 19;10(1): 3193.

Kouyos RD, Rusert P, Kadelka C, Huber M, Marzel A, Ebner H, Schanz M, Liechti T, Friedrich N, Braun DL, Scherrer AU, Weber J, Uhr T, Baumann NS, Leemann C, Kuster H, Chave JP, Cavassini M, Bernasconi E, Hoffmann M, Calmy A, Battegay M, Rauch A, Yerly S, Aubert V, Klimkait T, Böni J, Metzner KJ, Günthard HF, Trkola A; Swiss HIV Cohort Study (2018). Tracing HIV-1 strains that imprint broadly neutralizing antibody responses. Nature 561(7723):406–410.

Labhardt ND, Ringera I, Lejone TI, Cheleboi M, Wagner S, Muhairwe J, Klimkait T (2017). When patients fail UNAIDS' last 90 – the "failure cascade" beyond 90-90-90 in rural Lesotho, Southern Africa: a prospective cohort study. J Int AIDS Soc. Jul 19;20(1): 21803.

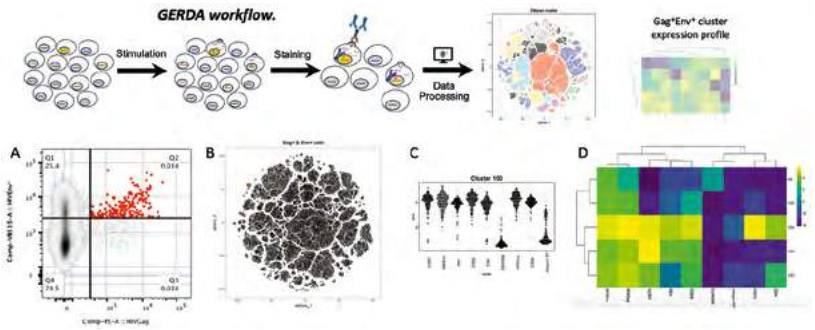

Fig. 1: GERDA workflow: Preselected CD4+ PBMCs are stained for immunological markers, HIV Env, and HIV Gag protein. Dimensional reduction and cluster analysis are performed using tSNE and DBSCAN, highlighting key clusters. Gag+Env+ events are marked in the plot and mean marker expression of each identified cluster is summarized in a heatmap. **A:** Gag vs Env expression in a recently diagnosed ART naïve individual. Gag+Env+ stained cells (in red). **B:** tSNE plot, each dot representing one cell as data point (1.41mio cells). Gag+ (green) and Gag+Env+ (red) populations are highlighted. **C:** Cell marker expression profiles of a representative Gag+Env+ cell cluster. **D:** Marker expression heatmap of all identified biologically relevant clusters.

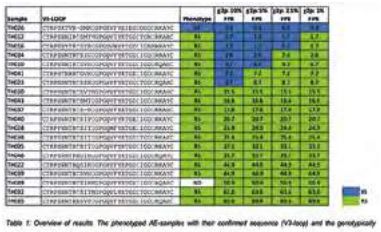

Fig. 2: Tropism prediction for clinical HIV-1 subtype CRF01_AE samples using different Geno2pheno settings (False-Positive-Rate cutoff, FPR) in comparison with phenotyping of the same samples. Blue = X4-tropic, green = R5-tropic, ND = not determined

Connection to Clinical Practice

Niklaus Labhardt

Research Group Leader, University Hospital Basel; Scientist at STPH, Basel

HIV-1 Viremia in Infected Children/ Adolescents on HIV Therapy: An Open-Label Randomised Clinical Trial

Jennifer Brown (as joint PhD student with N. Labhardt)

Background for our 'GIVE MOVE' resistance study in HIV-Infected children and adolescents is that this study group is the most vulnerable patient group and experiences high rates of treatment failure. Unnecessary switching to a second-line ART regimen can increase pill burden, side-effects, and cost and will limit future therapy options, whereas maintaining a regimen during emerging resistance increases the risk of progression to AIDS and mortality. In many African countries, access to resistance tests is extremely limited.

Our trial assesses the clinical impact and cost-effectiveness of resistance testing (GRT) in children and adolescents with HIV with therapy failure. This open-label, parallel-group randomised clinical trial recruited so far 276 children and adolescents living with HIV in 7 sites in Lesotho and Tanzania. The study compares standard of care with an intervention arm (GRT to inform onward treatment). Endpoint is the occurrence of i) death due to any cause ii) disease-related hospital admission, iii) clinical exacerbation, and iv) no documentation of viral suppression.

With increasing availability of GRT for African countries, and while rates of pre-treatment drug resistance rise, the clinical impact and feasibility of broader implementation must be explored, especially among children and adolescents. Currently, enrollment is ongoing, with 56 participants enrolled by December 8, 2020.

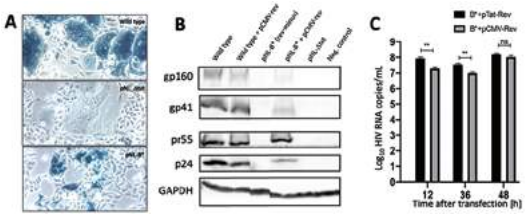

Fig. 3: Impact of redirecting HIV-Rev expression to the start of the Tat gene. **A:** Phenotype of infection in reporter cells (blue = HIV-1 infected); 'Wild type' expresses blue (viral Tat) and fuses cells (Env); 'NL-Δtat' expresses only Env (no blue); NL-B* lacks the fusion phenotype (no fusion). **B:** Immunoblot for HIV protein expression in transfected cells: Env (gp160, gp41); Gag (pr55, p24); GAPDH as cell control. **C:** Virus release (copies/mL) from transfected cells, showing delayed complementation when Rev is supplied too early in infection (CMV-Rev).

Experimental Rheumatology

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Prof. Dr. med. Ulrich Walker
(Project Leader)

The role of innate immune mechanisms in the pathogenesis of chronic inflammatory rheumatic diseases

The research of the Experimental Rheumatology (ER) group is focused on the pathogenetic mechanisms of inflammatory rheumatic diseases including chronic arthropathies such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA), connective tissue diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS) and systemic sclerosis (SSc), autoimmune vasculitides (AAV) as well as the crystal arthropathies gout and calcium pyrophosphate deposition disease. In several research projects, including collaborations with academia and pharma/biotech industry, we investigate the immunopathogenesis of some of these diseases with special focus on mechanisms of the innate immunity.

The research topics include
- the regulation of inflammatory pathways during macrophage differentiation and polarization.
- immune-modulation by extracellular vesicles and the identification of their functional load in rheumatoid arthritis.
- the screening of novel inhibitors targeted against inflammatory pathways and autoimmune disease- relevant factors
- the role of neutrophil extracellular traps and cell-free mitochondrial DNA in the pathogenesis of various rheumatic diseases.

We follow a translational approach, using patient materials such as blood and synovial fluid. *In vitro* cell cultures with primary cells are set up and phenotypic and functional analyses are performed *in vitro*.

In our recent work one of the main topics was the analysis of microRNA (miR) as epigenetic regulators of inflammatory signaling pathways (Figure 1). In a search for microRNA expressed by *in vitro* differentiated macrophages stimulated via TLR ligands we have identified miR-221-3p as a driver of a polarization of macrophages towards a proinflammatory M1 phenotype. We found that overexpression of miR-221-3p in anti-inflammatory M2-macrophages is repressing JAK3/STAT3 signaling that governs anti-inflammatory IL-10 secretion in these cells. In addition, miR-221-3p overexpression or pharmacological inhibition of JAK3 not only suppressed IL-10 secretion but also imposed a pro-inflammatory cytokine profile in M2- macrophages, including an increased secretion of IL-12 and IL-6. We hypothesize that this mechanism may contribute to chronic inflammation and destruction in rheumatoid arthritis (RA). Our results add to existing evidence suggesting microRNAs as tarpeutic targets. Currently we are involved in an Innosuisse funded collaborative project searching for small molecular inhibitors of microRNA.

Another focus is the role of neutrophil extracellular traps and cell-free mitochondrial DNA in the pathogenesis of various rheumatic diseases. Activated neutrophils have been implicated in the pathogenesis of Systemic Lupus Erythematosus (SLE) and the ANCA-associated vasculitides (AAV). Recent data suggests that subjects with SLE are characterized by impaired NET degradation, disseminating the availability of extracellular DNA as a pro-inflammatory stimulus to the innate immune system. NETs may also contain mitochondrial DNA (mtDNA), a dsDNA molecule which is phylogenetically evolved from bacteria and rich in hypomethylated CpG sequences, thus especially suited to trigger TLR9 signaling and disease flares. The main goal of the particular study is to analyse the extent and nature of circulating extracellular DNA species (mtDNA vs. nDNA) in SLE and AAV and determine if mtDNA plasma concentrations can serve as a marker for diagnosis and disease

activity. Overall we aspire to contribute to a better understanding of the contribution of innate immune mechanisms to the pathogenesis of rheumatic diseases.

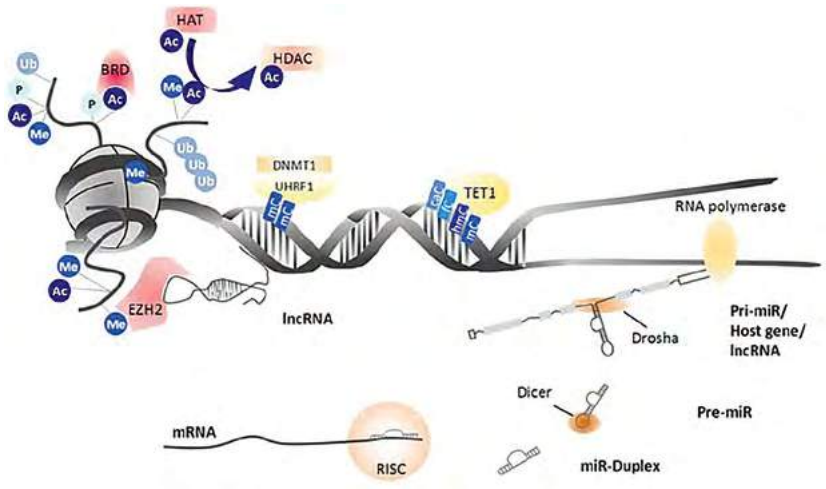

Fig. 1: Epigenetic modifications and microRNA biogenesis.
MicroRNAs are transcribed as primary transcripts (pri-miR) that can be embedded in host genes or lncRNA. Drosha processes the pri-miR and Dicer cleaves the resulting precursor miR (pre-miR). The miR-Duplex is loaded onto the RNA induced silencing complex (RISC) where the separated strands bind their target mRNA.

Ac = acetylation, Me = methylation, P = phosphorylation, Ub = ubiquitination

Modified from: Kyburz, Karouzakis and Ospelt, Best Pract Res Clin Rheumatol (28) 2014: 577–587

Connection to Clinical Practice

Prof. Diego Kyburz, Prof. Ulrich Walker
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Biomarker analysis in autoimmune inflammatory diseases

We are conducting clinical studies on patients treated in the Department of rheumatology to identify biomarkers that are associated with the diagnosis and/or the activity of diseases such as rheumatoid arthritis or systemic lupus erythematosus. By combining analysis of clinical and imaging data with biomarker analysis in peripheral blood, urine and synovial fluid we aim at defining markers for prediction of disease outcomes and response to therapy.

Selected Publications

Streese L, Khan AW, Deiseroth A, Hussain S, Suades R, Tiaden A, Kyburz D, Cosentino F and Hanssen H (2020). High-intensity interval training modulates retinal microvascular phenotype and DNA methylation of p66Shc gene: a randomized controlled trial (EXAMIN AGE). Eur Heart J 41, 1514–1519.

Quero L, Tiaden AN, Hanser E, Roux J, Laski A, Hall J and Kyburz D (2019). miR-221-3p Drives the Shift of M2-Macrophages to a Pro-Inflammatory Function by Suppressing JAK3/STAT3 Activation. Front Immunol 10, 3087.

Hargreaves P, Daoudlarian D, Theron M, Kolb FA, Manchester Young M, Reis B, Tiaden A, Bannert B, Kyburz D and Manigold T (2019). Differential effects of specific cathepsin S inhibition in biocompartments from patients with primary Sjogren syndrome. Arthritis Res Ther 21, 175.

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Quero L, Hanser E, Manigold T, Tiaden AN and Kyburz D (2017). TLR2 stimulation impairs anti-inflammatory activity of M2-like macrophages, generating a chimeric M1/M2 phenotype. Arthritis Res Ther 19, 245.

Translational Neuro-immunology

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Chemokines, atypical chemokine receptors and chemotaxis in multiple sclerosis

Migration of immune cells plays an important role in protective immunity but also in the pathogenesis of multiple sclerosis. Directed migration of immune cells is governed by chemokine gradients acting as extracellular guidance cues. During the last years we have developed various microfluidic devices to study migration properties of primary immune cells on a single cell level. These devices allow to generate precisely controllable stable diffusion-based and/or immobilized chemokine gradients of various shapes. This allows studying basic aspects of signal integration of migrating cells, including the question how cells sense the direction of chemokine gradients and what sustains migration along potentially irregular gradients in non-inflamed and inflamed tissues.
Consensus exists that chemokine gradients offer the main guidance cues for migrating immune cells. Only limited data is available regarding how such gradients are generated and maintained. Atypical chemokine receptors (ACKRs) are able to scavenge chemokines, hereby shaping the distribution of chemokines locally. The expression of chemokine-scavenging ACKRs in inflamed multiple sclerosis lesions suggests that ACKRs also play an important role in shaping chemokine distribution –and hence immune cell recruitment to sites of inflammation. We aim to understand, how expression of ACKRs on glial cells impacts on the distribution of chemokines in inflamed CNS tissue.

Vaccinations, immunosenescence and multiple sclerosis
Vaccinations are important measures of global health, not only since the Coronavirus pandemic. Consensus exists that all persons with MS should be immunized according to the local vaccine standards.
Physicians and other healthcare providers caring for persons with MS are often faced with questions concerning vaccinations, particularly in patients receiving disease modifying therapies (DMTs). We aim at understanding how DMTs and also how treatment histories impact on vaccine responses. We further link these data to the degree of immunosenescence in individual patients, since immunotherapies can result in accelerated aging of the immune system.

Connection to Clinical Practice

Our group is closely connected to the MS Centre and Outpatient Clinic of the Department of Neurology, University Hospital Basel that provides care for more than 1300 MS patients per year. Particularly, collaboration with the Swiss Multiple Sclerosis Cohort (SMSC, coordinated by Prof. Kuhle, Neurology Department of the University Hospital Basel) provides an internationally unique long-term follow-up of over 1200 Swiss MS patients with clinical and MRI data and serum samples for vaccine research. Prospective vaccination studies are organized in collaboration with the Vaccine Service of the Medical Outpatient Clinic, University Hospital Basel (coordinated by PD Dr. Ch. Berger).

Selected Publications

Amstad A, Coray M, Frick C, Barro C, Oechte-ring J, Amann M, Wischhusen J, Kappos L, Naegelin Y, Kuhle J, Mehling M. Growth differentiation factor 15 is increased in stable MS. Neurol Neuroimmunol Neuroinflamm. 2020 Feb 5;7(2):e675.

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Gastro-enterology

Macrophages and microbial metabolites in intestinal diseases

Humans with inflammatory bowel disease, such as Crohn's disease or eosinophilic esophagitis have an altered gut microbiome. Emerging evidence indicates that microbial metabolites and not only the microorganisms and their structural components modulate mucosal immune responses and metabolism. These microbial metabolites may influence the development of inflammatory bowel disease and eosinophilic esophagitis. Our research group aims to unravel some of the mechanisms how microbial metabolites are recognised by the host in the context of inflammatory bowel disease. We focus on studies, in which we genetically delete metabolite sensing receptors in macrophages and intestinal epithelial cells. Our studies suggest the possibility that microbial metabolites will fuel inflammatory bowel disease and eosinophilic esophagitis.

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Anna Steinert* (PhD Student)
Dr. Philipp Wuggenig* (PhD Student)

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Selected Publications

Herrema H, and Niess JH (2020). Intestinal microbial metabolites in human metabolism and type 2 diabetes. Diabetologia.

Kaya B, Donas C, Wuggenig P, Diaz OE, Morales RA, Melhem H, Swiss, I.B.D.C.I., Hernandez PP, Kaymak T, Das S, *et al.* (2020). Lysophosphatidic Acid-Mediated GPR35 Signaling in CX3CR1(+) Macrophages Regulates Intestinal Homeostasis. Cell Rep 32, 107979.

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Radulovic K, Ayata CK, Mak'Anyengo R, Lechner K, Wuggenig P, Kaya B, Hruz P, Gomez de Aguero M, Broz P, Weigmann B and Niess JH (2019). NLRP6 Deficiency in CD4 T Cells Decreases T Cell Survival Associated with Increased Cell Death. J Immunol 203, 544–556.

Steinert A, Linas I, Kaya B, Ibrahim M, Schlitzer A, Hruz P, Radulovic K, Terracciano L, Macpherson AJ and Niess JH (2017). The Stimulation of Macrophages with TLR Ligands Supports Increased IL-19 Expression in Inflammatory Bowel Disease Patients and in Colitis Models. J Immunol 199, 2570–2584.

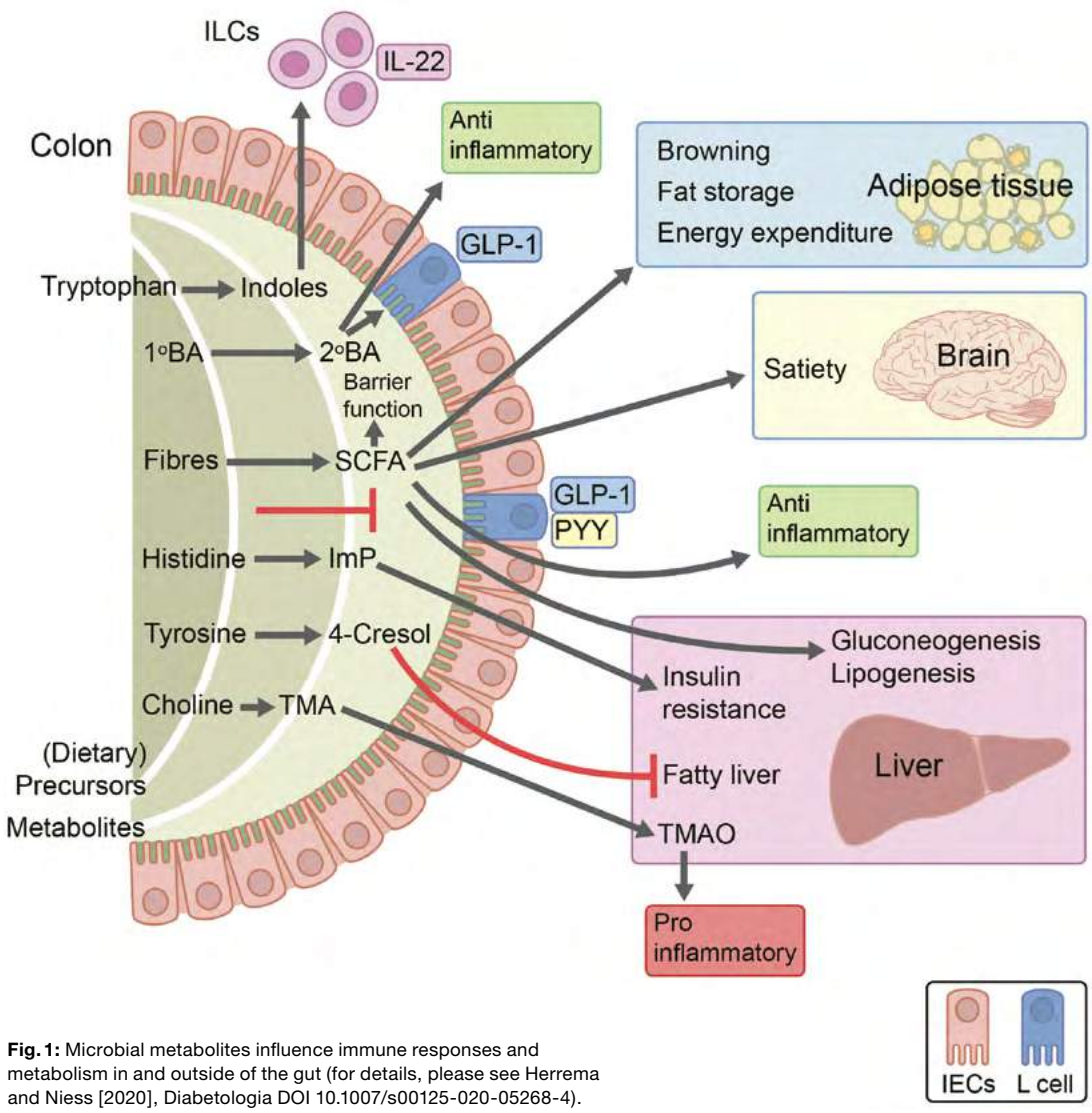

Fig. 1: Microbial metabolites influence immune responses and metabolism in and outside of the gut (for details, please see Herrema and Niess [2020], Diabetologia DOI 10.1007/s00125-020-05268-4).

Immuno-deficiency

Primary Immunodeficiency

Primary immunodeficiencies (PID), also known as inborn errors of immunity (IEI), are a rapidly evolving group of genetically determined human diseases associated with susceptibility to infection, autoimmunity/autoinflammation and/or lymphoproliferation. To date more than 450 different PID entities have been elucidated.
The main current basic immunology focus of the research lab is to characterise the role of a yet poorly studied transcription factor in the generation and maintenance of human memory T lymphocytes. This is done by analysing functional consequences of T cell intrinsic over- expression vs. knock-out of the transcription factor complemented by a detailed clinical immunology assessment of patients carrying homozygous loss of function mutations in the gene encoding the transcription factor.
The aim is to molecularly define a non-redundant role for this transcription factor in the generation of human T cell memory and to characterise drugable targets to potentially restore immunity in patients carrying loss of function mutations in the gene encoding this transcription factor.

Mike Recher

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Dominique Tschopp
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Selected Publications

Légeret C, Meyer BJ, Rovina A, Deigendesch N, Berger CT, Daikeler T, Heijnen I, Burstein E, Köhler H and Recher M (2020). JAK inhibition in a patient with X-linked reticulate pigmentary disorder J Clin Immunol. in press.

Delmonte OM, Baldin F, Ovchinsky N, Marquardsen F, Recher M, Notarangelo LD, and Kosinski SM (2020). Novel Missense Mutation in SP110 Associated with Combined Immunodeficiency and Advanced Liver Disease Without VOD. J Clin Immunol 40, 236–239.

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Connection to Clinical Practice

Mike Recher; Christoph Hess
Immunodeficiency Clinic, Medical Outpatient Unit,
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Molecular dissection and personalised treatment of patients with primary immunodeficiency

Patients with suspected immunodeficiency or immune dysregulation are clinically evaluated in the Immunodeficiency Clinic of the Medical Outpatient Unit of the Basel University Hospital. Patients are treated with immunoglobulin supplementation and, if available, specific immuno-active compounds.

Since 2015, patients with the diagnosis of primary (genetically determined) immunodeficiency are included into a prospective research cohort. Following informed consent, a standardised documentation of the physical status of the patient is combined with analysis of clinically validated and/or research based immunological lab data and next generation immune-gene sequencing. This allows us to prospectively study the disease course but also to determine the molecular mechanism of disease and at best to treat the patients in a targeted, personalised manner.

Currently, more than 225 patients have been included into the prospective cohort and selected patients are further molecularly characterised in the research lab. Novel disease causing immune gene variants have been identified in CTLA-4, SP110, SDHA, SAMHD1, Ligase 4 and many others. Novel targeted personalised treatment strategies have been or are currently clinically evaluated in patients with disease causing mutations in CTLA-4, SDHA, POLA1, SAMHD1 and others.

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Complement-dependent pathogenic mechanisms in systemic autoimmunity

Systemic Lupus Erythematosus (SLE) is the archetype of an autoimmune disease and can involve any organ system eventually leading to comorbidities that can also be observed independently of underlying SLE. The complex pathogenic mechanisms leading to and being involved in this autoimmune-inflammatory syndrome are not well understood. However, complement C1q, the first component of the classical pathway, seems to play a central role. By analysing the role of C1q as well as it's interaction with autoantibodies targeting C1q (anti-C1q) in SLE, we aimed at elucidating 1) mechanisms being involved in the initiation of autoimmunity, 2) mechanisms of secondary acceleration of inflammation, and 3) processes being associated with atherosclerosis and thromboembolism.

With regard to mechanisms being involved in the initiation of SLE, homozygous C1q deficiency is the strongest genetic risk factor for the development of SLE. Vice versa, in SLE patients without primary C1q deficiency, C1q is consumed during disease flares, deposited in affected tissues and becoming a target of autoantibodies (anti-C1q). The identification of a major linear epitope of C1q targeted by anti-C1q having a striking sequence homology with an antigenic site of Epstein Barr Virus (EBV) suggests cross-reactivity between anti-C1q and anti-EBV antibodies through molecular mimicry. This was an important observation since EBV infection is considered to be an essential step in the development of SLE. We now could demonstrate that EBV-derived antigenic peptides indeed can induce antibodies cross-reacting with complement C1q *in vivo*.

Secondly, C1q mediates and modulates the uptake of apoptotic cells, a mechanism that is defective in SLE patients. In the context of a defective clearance, dying cells can become antigenic and trigger the autoimmune response. In previous studies I could show that anti-C1q specifically recognize C1q when being bound to apoptotic cells and that anti-C1q induce a proinflammatory phenotype in macrophages being associated with reduced phagocytic capacity. We are currently exploring these mechanisms of secondary inflammation, in particular how C1q and anti-C1q affect macrophage-mediated T-cell activation.

Thirdly, our previous analyses of bone marrow-derived human anti-C1q identified sequence homologies with von Willebrand Factor (vWF). In striking analogy to anti-C1q, vWF also binds to C1q leading to consecutive platelet rolling and adhesion, and the lack of C1q is associated with increased bleeding *in vivo*, thus establishing a novel link between C1q and primary hemostasis. In addition, binding of vWF to C1q on cholesterol crystals substantially affects phagocytosing macrophages. This is of importance since both, C1q and vWF, have been shown to be implicated in atherosclerosis and thromboembolism, both being typical comorbidities in SLE patients.

Taken together, our projects elucidate the role of complement C1q and anti-C1q in interaction with EBV infection, macrophages, the clearance of apoptotic cells and primary hemostasis, all having been implicated in the pathogenesis of SLE. Our data improve the understanding of immune-mediated pathology occurring related to but also independently of autoimmunity.

Connection to Clinical Practice

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The role of complement in human disease

In clinical studies we were and still are analysing the role of anti-C1q as a biomarker in SLE patients and it's relation to previous Epstein Barr Virus infection. In addition and thanks to the participation in the Swiss SLE Cohort Study (SSCS) we are also studying the role of other autoantibodies and serum cytokines in SLE.

Independent from anti-C1q studies, we are studying the role of complement split products (i.e. activation parameters) and complement mannan-binding lectin (MBL) in clinical settings. MBL is strongly related to C1q and has been shown to play an important role in the defense against infectious agents. More recent studies suggest that MBL also binds to apoptotic cells and plays a pro-inflammatory role in experimental settings of ischemia-reperfusion injury. The high frequency of functional MBL deficiency in the general population (about 25 %) predestines MBL for clinical studies investigating its role in human disease.

Selected Publications

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Immune Regulation

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Dendritic cell development

Dendritic cells (DCs) are a specialized immune subset dedicated to the sensing of pathogens and the induction of the appropriate immune response. Under steady state conditions DCs can be subdivided into conventional DCs (cDCs) and plasmacytoid DCs (pDCs). cDCs are specialized in antigen uptake and presentation to naïve T cells and can be further subdivided into IRF8- and IRF4-expressing cDC1 and cDC2, respectively. pDCs are a distinct lineage dedicated to the production of high amounts of type I IFNs in response to viral infections. Development of DCs occurs in the bone marrow (BM) and requires a complex transcriptional network, where progressive lineage specification gradually limits and excludes alternative fates. A common DC progenitor (CDP) able to give rise to both cDCs and pDCs, had been identified in the BM. However, while cDCs arise in the periphery, mature pDCs are present in BM suggesting that their development is accomplished before entering the circulation.

Furthermore, the evidence that CDPs can generate pDCs and cDCs at a clonal level is conceivable with a pre-determined and cell-intrinsic transcriptional induction of lineage specification, already at the CDP stage. In recent years precursors of cDC1 and cDC2 were identified, as several TFs involved in their commitment. However, the molecular mechanisms leading to DC-lineage specifications are still unclear. Moreover, the evidence that both hematopoietic branches, namely the lymphoid via CLP and the myeloid via CMPs, can both give rise to DCs has further complicated our understanding of their ontogeny. In order to characterize the developmental pathway of DCs and in particular of pDC we searched for a committed precursor. The expression of the E protein Transcription factor 4 (TCF4), also referred as E2-2 was shown to be essential for pDC development and identity, however the exact stage at which this TF is expressed is unclear. The requirement for this TF for pDC development appears shared across species as in humans haploinsufficiency, referred as Pitt-Hopkins syndrome, results in impaired pDC besides mental retardation and cranio-facial dysmorphia. It was hypothesized that development of pDCs and cDC1 is regulated by the expression and mutual inhibition of TCF4 on pDCs and the inhibitor of DNA binding 2 (ID2) on cDC1, respectively. Further, the zinc finger E box–binding homeobox 2 (Zeb2) was recently identified as key regulator of early DC development as Zeb2 deficient mice have reduced pDCs, and increased cDC1. The proposed mechanism of action suggested repression of ID2 by ZEB2.

However, while this molecular regulation is compatible with the pDC phenotype observed in Zeb2 deficient mice, it does not explain Zeb2 transgenic mice, which have unaltered pDCs and reduced cDC1s. Collectively, these results suggest a dual origin of pDCs, where the requirement for TCF4 and ZEB2 is lineage as well as stage specific. A CDP independent origin for pDCs is further supported by the evidence that the pool is only partially reduced in Itgax-cre but totally absent in Mx1-cre conditional deficient mice. Given the complexity of the transcriptional interactions happening at different stages during DC commitment, and the possible developmental convergence into one phenotypically unique lineage, we decided to explore in depth the paths leading to pDC and cDC development. Contrary as previously hypothesized, we could recently show that pDCs mostly develop from CLPs and not CDPs. Within the BM we were able to dissect the progressive stages that lead to the formation of mature pDCs. The expression of SiglecH and Ly6D identifies on IL7Rexpressing bone marrow precursors pre-pDCs. At this stage high expression of IRF8 appears to be essential to promote pDC lineage specification through the induction of TCF4, while we hypothesize that within the immediate upstream progenitor expression of EBF1 leads to the induction of TCF3 along the B cell pathway (Figure 1). Single cell analysis of mature pDCs within BM and Spleen

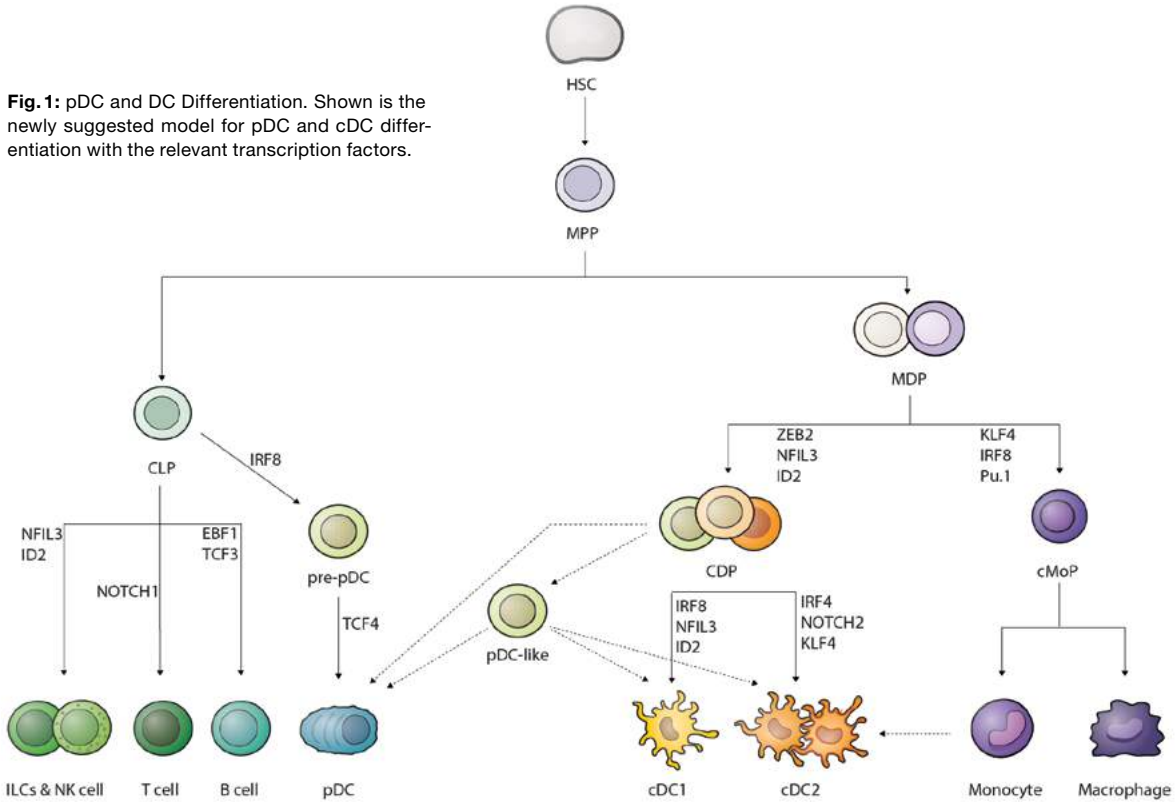

Fig. 1: pDC and DC Differentiation. Shown is the newly suggested model for pDC and cDC differentiation with the relevant transcription factors.

also highlighted heterogeneity within the pDC compartment leading to the identification of a new subset referred as pDC-like cells. This subset is present as a small fraction of cells that fall within the pDC gate but appears to share hallmark features not only with pDCs but also cDCs. Recent evidence has shown the presence of this subset also within the peripheral circulation of healthy donors. It appears that pDC-like cells are an immature cDC-progenitor subset capable of differentiating upon activation in efficient cDCs. The functional properties of pDC-like cells as well as their differentiation capacity remain to be investigated.

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