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CLINICIAN SCIENTIST PROGRAM

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10 Years Clinician Scientist Program

2021

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Content

BIH Charité
(Junior) (Digital) Clinician Scientist Program Book
2021

In loving memory

Univ.-Prof. Dr. med. Duška Dragun
* 12. August 1969
† 28. December 2020

Where there was no way, Duška built one –
a visionary and passionate pioneer.

Between silent mourning and pursuing Duška's mission: Celebrating the tenth anniversary of the BIH Charité Clinician Scientist Program in honor and memory of Professor Duška Dragun

Introduction by Dr. Nathalie Huber and Dr. Iwan Meij

The date for our international symposium celebrating the tenth anniversary of the BIH Charité Clinician Scientist Program (CSP) had been in our calendars for a long time. Due to the far too early death of our program director Professor Duška Dragun in December 2020, this symposium has now taken on an entirely different and, unfortunately very sad character – namely that of a commemorative event. The same applies to the introduction of this program book[1]. Actually, we intended to write exclusively about the program's achievements of the past ten years and now this anniversary book is overshadowed by the death of Duška, which is still difficult to accept. With her tireless effort and vision, she built up the career path for a successful career in science for many physicians and acted not only as a pioneer but also as a role model for Clinician Scientists.

As a physician herself, Duška has always been committed to research: As managing senior physician and deputy to the acting director of the Department of Nephrology and Internal Intensive Care Medicine at Charité – Universitätsmedizin Berlin and head of a research group on nephrology, she made highly esteemed, internationally excellent contributions to the field of renal transplantation research. She pursued her goals with extraordinary energy and passion, impressive perseverance and clear determination. She will be remembered by us, her research group and all the program fellows as a connector of people, CSP trailblazer, outstanding physician, excellent scientist and passionate mentor.

Duška's Mission: Clinician Scientist Programs as Systemic Intervention in University Medicine

Until the end, and even from her hospital bed, Duška's untiring efforts were directed at her life's work: the CSP. The CSP is a modern career path within academic medicine that allows physicians to pursue a structured residency with time set aside for clinical and basic research. It is based on a combination of a competence oriented clinical education with a translational medicine based curriculum including clearly defined »protected time« for research. Clinician Scientists as researching physicians are not »clinicians light« or »researchers light«. Rather, they form the essential link within the competence triad of patient care, student teaching and research – the combination of these three areas is the unique selling point of clinician scientists. Patients in particular benefit from this (see Dragun et al. 2019)[2].

The cooperation with the Berlin Chamber of Physicians was a decisive component for the success of the program in order to integrate research activities into the further residency training and to avoid extending the further training period for the participants as much as possible[3]. The guidelines developed by the Berlin Chamber of Physicians and the initiators of the Clinician Scientist Program for recognition of research time as part of the training have been continuously optimized and are readjusted annually in close consultation with the Chamber. Our Junior Clinician Scientist Program, implemented in 2014 and meant as a booster program, does not include the mandatory structured training and cannot be credited as part of the residency training.

The Berlin program is not only the largest of its kind in Germany, it is also considered as a national »best-practice model« and is recognized internationally for its pioneering role. It has set nationwide standards in terms of design and quality assurance measures and has served as a model for position papers by the German Research Foundation[4] (Deutsche Forschungsgemeinschaft, DFG) and the German Science Council[5] (Wissenschaftsrat, WR). Since an increased focus on Clinician Scientist training was set as one of the science policy goals in the current coalition agreement, together with Duška we were in exchange and consultation with members of the Bundestag and science policy actors.

We participate in national and international working groups, such as the meetings of the Medizinischer Fakultätentag e.V. (Medical Faculty Association) and the Association of Academic Health Centers International (AAHCI). This has allowed us not only to be informed about national and international debates but also to be involved in setting benchmarks and quality standards for the structured training and the career pathway of Clinician Scientists. The model and success of our CSP has led to a rethinking of the biomedical research landscape in Germany and has given rise to a new generation of research-oriented clinicians who are taking on the challenges of combining research and clinical practice in order to speed up the rate at which scientific findings are translated into application and newly identified medical need feeds into new research initiatives.

1. The present version is the third edition of our Program Book. The first edition was published in 2016 on the occasion of the fifth anniversary of the BIH Charité Clinician Scientist Program and the corresponding Jubilee Symposium in June 2016. The second edition of the Program Book was published in June 2018 for the International Symposium on Translational Medicine in Berlin.

2. Dragun, Duška, Huber, Nathalie, Rösen-Wolff, Angela, Blomberg, Richard. »Clinician Scientists: Ärzte mit Kompetenz-Trias«. Dtsch Arztebl. 2019;116(50):A-2339 / B-1922 / C-865.

3. Dragun, Duška and Huber, Nathalie: »Schluss mit ›Feierabendforschung‹«. In: Berliner Ärzte, 12/2017, pp.29-31. http://www.berliner-aerzte.net/pdf/bae1712_029.pdf

4. Empfehlungen der Ständigen Senatskommission für Grundsatzfragen in der Klinischen Forschung der Deutschen Forschungsgemeinschaft: »Etablierung eines integrierten Forschungs- und Weiterbildungsprogramms für ›Clinician Scientists‹ parallel zur Facharztweiterbildung« (2015): http://www.dfg.de/download/pdf/dfg_im_profil/reden_stellungnahmen/2015/empfehlungen_clinician_scientists_0415.pdf

5. Wissenschaftsrat drs. 5663-16: »Perspektiven der Universitätsmedizin« (2016): http://www.wissenschaftsrat.de/download/archiv/5663-16.pdf

Climbing the Career Ladder Step by Step

Our target group specific structured career paths span the different career stages of the residency (cf. for this Figure 1). During clinical specialization, Junior (Digital) Clinician Scientists and (Digital) Clinician Scientists are allotted 20% or 50% of their working hours, respectively, as »protected time« to exclusively conduct research. The structured curriculum offered (including clinical, scientific, and transferable skills training) is mandatory for (D)CSP fellows and optional for J(D)CSP fellows. The appointment of clinical and scientific mentors and, in the case if the D-CSP track a digital mentor, as well as progress and feedback meetings, ensure guidance and support both for the research project itself and for the career development of the (Junior) (Digital) Clinician Scientist. New fellows are taken up into the programs twice a year following a highly competitive two-stage selection procedure.

Based on the program's fruitful experience of the last ten years, we have adapted our organizational mechanisms to ensure sustainability in a steady state recruitment of approximately 50 new fellows per year. As a general policy, we actively encourage women to apply and we have implemented flexible working options in the context of parental leave and part time-employment. Currently, 36% of our (Digital) Clinician Scientists and 37% Junior (Digital) Clinician Scientists are female.

6. DFG bietet Fördermöglichkeiten für »Clinician Scientists« in integrierten Forschungs- und Weiterbildungsprogrammen (2015): http://www.dfg.de/foerderung/info_wissenschaft/info_wissenschaft_15_25/index.html

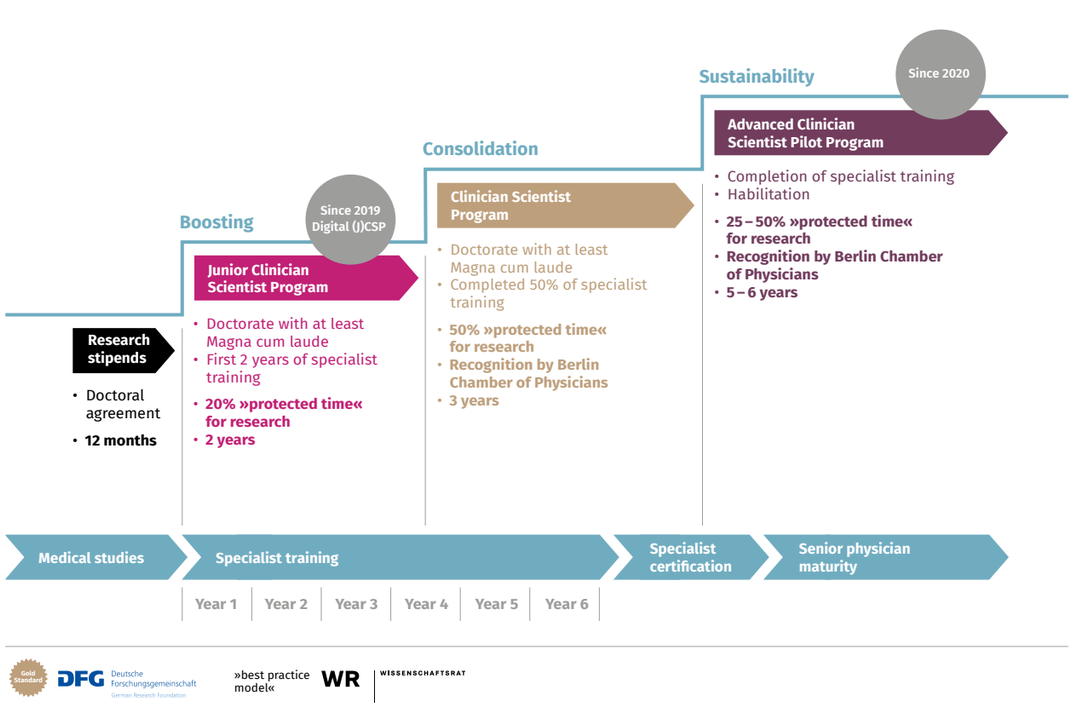

Figure 1. Structured career paths for Junior (Digital) Clinician Scientists and (Digital) Clinician Scientists spanning different stages of career beginning from medical school.

From a Pilot Project to an Institutionally Embedded Program

The CSP was preceded by the »Friedrich C. Luft« Clinical Scientist Pilot Program, which commenced in Spring 2011 through financial support of 1.4 million Euro from Stiftung Charité and Volkswagen Foundation. It has been awarded a prize from the »Deutschland – Land der Ideen« initiative in 2012. Since 2013, the program has received financial support directly from the Charité medical faculty as well as funding from Berlin Institute of Health at Charité (BIH) and through additional financial support by the Stiftung Charité via the Private Excellence Initiative Johanna Quandt. In its early years the CSP has also taken up several fellows funded through graduate schools funded within the German Federal Excellence Initiative – namely the Berlin-Brandenburg School for Regenerative Therapies (BSRT), the Berlin School of Integrative Oncology (BSIO) and the Excellence Cluster NeuroCure. In 2015, and based upon the successful cooperation with BIH, the program was integrated within the BIH Biomedical Innovation Academy (BIA), ensuring long-term structural and institutional support. Through third party funding by the German Research Foundation[6] (DFG), in 2019 the CSP could be expanded by a new »digital« branch – the »Digital Clinician Scientist Program« (D-CSP) forming an additional career track to prepare academic clinicians for the challenges of the emerging technological transformation of medicine (see below).

Keeping Abreast of the Times: Digital Clinician Scientist Program (D-CSP)

As academic medicine undergoes unprecedented technological change, many »classical« prospective Clinician Scientists are not adequately prepared for technological challenges associated with advanced computational scientific approaches. To address this, we have successfully secured additional funding from the German Research Foundation (DFG) in 2018. The DFG initially funds the project for three years with over three million euros and allows applying for a two-year extension in conjunction with a grant of two million euros. The D-CSP aims to strengthen the »classical« CSP and take it to the »next level« by integrating the new structural element of digital science training within the regular structured program. The first call for proposals for the D-CSP was published in March 2019, and funding for the first program participants, also including a Junior track, begun in August 2019.

Advanced Clinician Scientist Pilot Program (AdCSP)

In autumn 2020 we have piloted an Advanced Clinician Scientist Program (AdCSP) to close the existing gap in support for academic career paths after residency. It aims to support the so far insufficiently considered target group of scientifically active specialists who have just completed their habilitation and are developing towards becoming a senior physician or have just become a senior physician. The primary goals of the AdCSP are to create new senior physician positions with protected time for research and to strengthen the academic translational ecosystem to better meet the requirements of today´s highly specialized university medicine. Approved candidates will receive either 25% or 50% protected time for research.

CSP »Excellence Track«

Since several program participants of the (Junior) Clinician Scientist Program have applied successfully for excellent junior research group programs (such as ERC Starting Grants Program, DFG Emmy Noether Program, Freigeist Fellowships or Lichtenberg Professorship of the Volkswagen Foundation, BMBF Research Goup or Max-Eder Research Group), the idea of an »Excellence Track« was born in 2018. Fellows of the »Excellence Track« do not have to go through the official two-stage selection process of the CSP as they have already prevailed in a highly competitive external selection process. Fellows of the »Excellence Track« have the same rights and obligations as regular program participants. The only difference is that they are not financed through program funds. Currently, we have 8 members in the CSP »Excellence Track«.

Inter-Clinic Community Building

The CSP serves as an important model for building a community of early career researchers with an open mind to translational and innovative biomedical research. Fellows in the BIH Charité (Junior) (Digital) Clinician Scientist Program come from the wide variety of clinical and diagnostic disciplines creating a new translational ecosystem and nurturing transdisciplinary collaboration (see Dragun/Huber 2017). The number of participants has increased impressively from eight participants in 2011 to 141 active participants in 04/2021 (90 (Digital) Clinician Scientists and 51 Junior (Digital) Clinician Scientists). The CSP's success within Charité has steadily increased and approximately 8-10% of all senior Charité residents and 5% of all junior Charité residents receive protected time for research through the program. Figure 2 depicts a graphic representation of all program participants as distributed across disciplines.

»In my discipline of psychiatry, there is a lot of room for scientific progress. That's why I feel the urge to conduct research. The program has provided me with the protected time for research I need to do this and helped me to define myself as a Clinician Scientist.«

Dr. med. Katharina Schmack
CSP Alumna
Currently postdoctoral fellow
at Cold Spring Harbor Laboratory
(translated from (3))

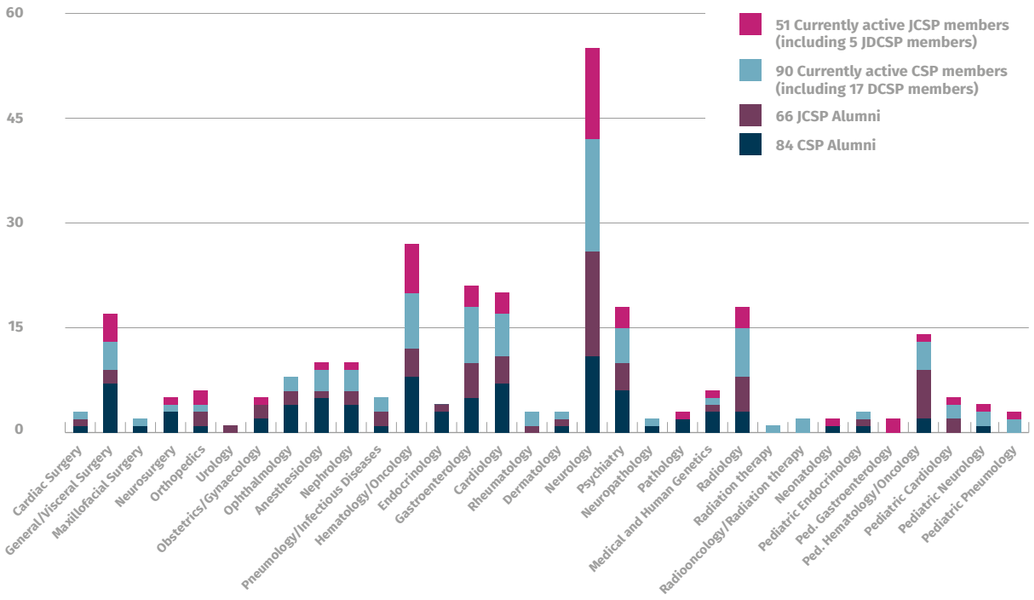

Figure 2: Broad distribution of (J)(D)CSP fellows and alumni over the clinical disciplines at Charité.

»... the CSP allowed us an intense and so far never experienced interdisciplinary scientific discussion and way of working, that still connects us today.«

PD Dr. med. Peter Bobbert
Alumnus Clinician Scientist Pilot Program
President of Berlin Chamber of Physicians
(translated from (3))

Figure 3: Foto collection of CSP Retreats at Genshagen Castle from 2016 to 2020

Interdisciplinary Networking

Interdisciplinary is not just a phrase but actually lived through different community building measurements: A monthly Jour Fixe is held for (Junior) (Digital) Clinician Scientists to present their research projects to other fellows and to the program director. Every year, a two-day retreat is held at Genshagen Castle southwest of Berlin to which all (Junior) (Digital) Clinician Scientists and their mentors and clinic directors are invited. The retreat aims at creating a communication platform for discussing both scientific and strategic topics relevant to Charité and BIH and beyond. In addition, every two years, a two-day Clinician Scientist Symposium on Translational Medicine is organized in Berlin, to which fellows can invite internationally renowned scientists as speakers. This gives (Junior) (Digital) Clinician Scientists the opportunity to discuss their project in person with leading personalities from the field of their own research and to take a big step in expanding their own scientific and professional network.

Never Stand Still – Continuous Adaptation and Optimization

Start of Pilot CSP
Funding of the first 8 fellows in the »Friedrich C. Luft« Clinical Scientist Pilot Program funded by Stiftung Charité and Volkswagen Foundation

Symposium 2012
From here on, every two years an international Clinician Scientist Symposium takes place

Consolidation of the program
Funding through Charité Faculty, BIH and Stiftung Charité via the Private Excellence Initiative Johanna Quandt

Integration in BIA
Successful cooperation with BIH leads to integration of the (J)CSP into the BIH Biomedical Innovation Academy (BIA)

(J)CSP open to »returnees«
Eligibility to apply for the CS Programs is now possible for applicants returning to Germany

Prize »Deutschland Land der Ideen«

Start Junior Clinician Scientist Program (JCSP)

Participation at GAIN conference
Annual conference in USA for talent scouting

First (J)CSP Retreat
From here on, an annual retreat takes place at Genshagen castle

First award ceremony
From here on, an annual Alumni award ceremony takes place

Measures to increase family friendliness
Extensions after parental leave and part-time clinical employment possible

Hearing at Bundestag (Federal Parliament)
Invitation to answer questions about CSPs at Federal Parliament

Implementation of QUEST Criteria
With the BIH QUEST Center, selection criteria for quality, robustness and reproducibility are implemented

Start of project »structural effects of CS Programs«
Cooperation with the Institute of Medical Sociology and Rehabilitation Science (IMSR)

Implementation of semi-automatic track record analysis, extended project review and feedback in selection processes

CSP celebrates its 100th Alumnus

Integration of dental medicine

Start of Pilot Advanced CSP
Funded through the Charité Faculty, BIH and BIA, a first call for Advanced Clinician Scientists was launched

Participation in MFT »UAG Clinician Scientists«
Medizinischen Fakultätentag e.V. (Medical Faculty Association) starts Working Group on CSPs

Start of 100th Clinician Scientist Fellow

Start of CSP »Excellence Track«

Start of (Junior) Digital CSP
Funded by the German Research Foundation (DFG)

Implementation of »CSP-Button«
Quality assurence measure with the Research Time Tracking Tool to secure »protected time« for research

Start of external Program Evaluation
Cooperation with the German Centre for Higher Education Research and Science Studies (DZHW)

Death of Prof. Duska Dragun
Prof. Duska Dragun passes away at the age of 51

Publication of external Program Evaluation results

2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021

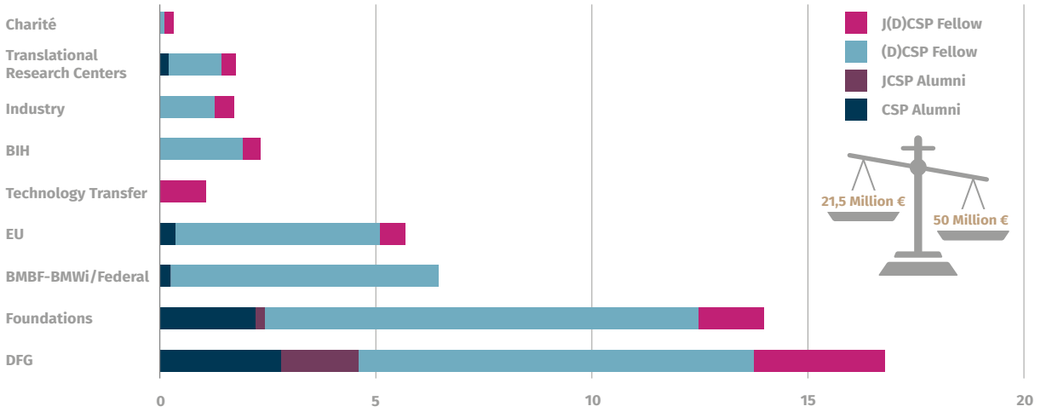

Figure 4: Estimated third-party funding raised in k€ by BIH Charité (Junior) (Digital) Clinician Scientists up to 03/2021

Outcome

An outcome analysis of our CSP alumni (04/2021) shows excellent outcomes: 94% percent have become specialists, 65% have completed their habilitation and 60% have arrived at leading positions. All alumni are not only successful Clinician Scientists by themselves, they are also raising a new generation of fellows by acting as mentors and supervisors. A significant proportion of our fellows obtain professorships – some of them already during their (J)(D)CSP funding. Overall, we currently boast 11 professors among our fellows and alumni (seven W2- and four W3-Professorships).

Another impressive statistic is the cumulative amount of third-party funding raised by alumni and (Junior) (Digital) Clinician Scientists of 50 million Euro (see figure 3). This represents roughly a two to one »return on investment« which underlines once more the effectiveness of the program and the excellence of its fellows.

Career Tracking

What started as a project to generate a reliable, unbiased, semi-automated track record analysis system to support the selection processes of the different Clinician Scientist Programs, has by now grown into the beginnings of a full-blown career tracking tool, which may be used in Meta Research analysis. With it, we hope to be able to better map typical career paths and especially the hurdles that need to be overcome by our fellows. It will allow the analysis of correlations between the careers of young academics at Charité and specifically the investigation of correlations that lead to successful careers in academic medicine. It is also possible to find out when, for example, young scientists most frequently leave the academic career path. With this in-depth understanding of the different archetypes of Clinician Scientist career pathways, on the one hand the individual tracks may be even further refined. On the other hand, we will also have a scientific basis for recommendations to politics and funding agencies for the development of innovative career support structures.

External Program Evaluation

On the occasion of the tenth anniversary of the CSP, in cooperation with the German Centre for Higher Education Research and Science Studies (DZHW), we have conducted a comprehensive and social science-based program evaluation (project duration: June 2019 -March 2021). The study uses a mixed-method approach in which qualitative and quantitative methods systematically complement each other (interviews, online survey and bibliometric analysis). Our evaluation is based on the experiences and perspectives of a total of 90 active and former (J)CSP fellows and, comparatively, a control group at Charité which is not funded by the program. The findings give multifaceted empirical insights into the program, identify opportunities and challenges and provide the basis for general recommendations for action for the development and expansion of Clinician Scientist Programs in the context of German university medicine[7].

Research Project »Structural Effects of Clinician Scientist Programs on the Biomedical Research Landscape«

How are CSPs set up at different locations and what are the similarities and differences in the context of the structural framework conditions? How can different experiences with the implementation and establishment of CSPs and the associated challenges be analytically described? In cooperation with the Institute of Medical Sociology and Rehabilitation Science (IMSR) at Charité we conducted a research project (duration: January – October 2020) to carry out a systematic review of relevant organizational framework conditions of Clinician Scientist Programs in German university medicine. Based on the empirical results, the location factors in which the CSPs are embedded can be probed for the first time, relevant strategies in dealing with differently situated challenges can be presented, and common themes and future tasks can be identified and passed on to science policy in the form of synthesized implications.

Résumé and Outlook

Within a relatively short period of time Duška has made a very significant contribution to the development of a new generation of junior medical staff – the impact of her programs will last for a long time, through promising individual careers as well as through the programmatic strengthening of patient-oriented science. Few individuals have managed to make such a positive and lasting difference to Charité and the lives of many residents there. She demanded full performance and set challenging goals. Those who made it into the one of the CSP tracks had their further development closely monitored. At the same time, she showed an almost endless commitment to the program fellows and their projects. She knew each fellow by name and their projects through the selection process, target-agreement meetings, Jour Fixes, Retreats and Symposia. We feel, thus, like a big »Clinician Scientist Family«.

We do not rest on the success of the BIH Charité Clinician Scientist Program during the last ten years. Rather we feel obligated to implement Duška's impulses, which she even set last year (like the Advanced Clinician Scientist Program or the integration of dental medicine in the (D)CSP). We will honor Duška's memory and continue her mission of training Clinical Scientists in her spirit.

7. Hendriks, Barbara; Schendzielorz, Cornelia; Heger, Christophe; Reinhart, Martin (2021): Kritische Bestandsaufnahme des BIH Charité (Junior) Clinician Scientist Programms: Untersuchungen einer integrierten Forschungs- und Facharztweiterbildung in der Universitätsmedizin. Ergebnisse der Programmevaluation 2019/20. Deutsches Zentrum für Hochschul- und Wissenschaftsforschung GmbH (DZHW). https://www.dzhw.eu/pdf/ab_folder_26/KritischeBestandsaufnahme.pdf

Junior Clinician Scientists

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› Myeloid Malignancies
› Tumor Genetics
› Vascular Biomedicine

Clinical Implications of Clonal Hematopoiesis Under Different Stress Scenarios

Ageing is strongly associated with an increasing risk of cardiovascular disease and cancer. Recently, an interesting common driver of these two age-associated diseases has been discovered: clonal hematopoiesis (CH), defined by the acquisition of somatic mutations in hematopoietic stem cells, occurs in 20-30% of individuals > 60 years and is associated with a higher overall mortality, an increased risk for cardiovascular events, and a ten-fold risk for the development of hematologic malignancies. Interestingly, a causal relation between CH and the progression of coronary heart disease driven by an altered inflammatory function of mature mutated monocytes/macrophages has been described in preclinical models. These and other recent data pinpoint towards pleiotropic effects of mutated clones in individuals with CH, not only affecting self-renewal and differentiation but also inflammatory signaling of mature blood cells, which become particularly pronounced in certain stress scenarios such as cytotoxic chemotherapy, allogeneic stem cell transplantation and inflammation. The aim of this interdisciplinary project is to investigate the clinical implications of CH in different stress scenarios. Inflammation plays a crucial role in the pathogenesis of ischemic stroke and its functional outcome after brain injury. However, despite its indisputable relevance on epidemiologic scales, the role of CH in the context of ischemic stroke remains elusive. Applying bulk and single-cell sequencing techniques to bio-banked blood samples from the Prospective Cohort with Incident Stroke Berlin (PROSCIS-B), I address the role of CH in patients suffering from ischemic stroke with respect to functional outcome and risk for recurrent vascular events. A second focus of the project is on CH in patients with non-hematologic malignancies. By integrating sequencing data with clinical data from a large phase III study of patients with metastasized colorectal cancer (FIRE-3), I aim to delineate the implications of CH on treatment outcome and analyze the clonal evolution of CH under the selective pressure of cytotoxic treatment. With the results I hope to contribute to a better understanding of this interesting new commonality between cardiovascular disease and cancer.

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› Epithelial immunology

Expression and Regulation of Interleukin-37 in Human Intestinal Epithelium During Health and Inflammatory Bowel Disease

The incidence of inflammatory bowel diseases (IBD) is markedly rising in industrialized countries, with 25% of patients being newly diagnosed in childhood and adolescence. Alterations of the epithelial barrier appear to contribute towards generating a dysbalance of the intestinal immune response in genetically susceptible individuals. Investigating the interplay of the intestinal epithelial barrier and the gut immune system in health and disease is crucial to understand the pathogenesis of IBD and to improve future treatment strategies. The epithelium is part of the intestinal immune system, producing antimicrobial peptides and interacting with immune cells through the release of immunomodulatory cytokines. Interleukin-37 (IL-37) is an anti-inflammatory member of the IL-1 cytokine family. It has been shown to protect mice from colitis and a homozygous mutation led to infantile onset IBD in a patient. The role of IL-37 has mainly been investigated in the immune cell compartment. However, our recent studies also showed IL-37 protein expression in the intestinal epithelium. We hypothesize that IL-37 contributes to the immune homoeostasis of the gut and plays a crucial role as an anti-inflammatory cytokine regulating intestinal epithelial function. The aim of this project is to understand the expression and regulation of IL-37 in the human intestinal epithelium. We investigate the expression of IL-37 and related genes using existing bulk transcriptomic datasets of children with newly diagnosed IBD and healthy controls (1). Using in vitro experiments, we explore the regulation of IL-37 expression in the human intestinal epithelium. We therefor generate patient-derived intestinal epithelial organoids as a model system (2). We then stimulate the intestinal organoids with different cytokines known to be involved in the pathogenesis of IBD (2) and investigate the time course of IL-37 mRNA expression (3). These experiments will contribute to our understanding of the expression and regulation of IL-37 in the human intestinal epithelium. Functional studies are currently performed and will further help to unravel the role of IL-37 in the pathogenesis of IBD.

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› IL6-STAT3 signalling in autoimmunity
› SUMOylation in Multiple Myeloma

Forward Genetic Screen for Functional Characterization of ASXL1-Mutated Leukemias

The epigenetic regulator Additional sex combs like 1 (ASXL1) is one of the most frequently mutated genes in hematopoietic malignancies. ASXL1 mutations (ASXL1mut) can be detected in up to 20% of patients* with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) as well as other myeloid neoplasms and are prognostically unfavorable, especially in combination with known driver mutations such as DNMT3A, JAK2, TET2 and TP53. However, the exact mechanisms of ASXL1mut-mediated malignant transformation are poorly understood and no targeted therapeutic strategy exists, thus there is great clinical need for improved molecular understanding, establishment of predictive biomarkers, and development of targeted therapeutics. Large AML sequencing studies over the past decade have cataloged gene mutations and epigenetic alterations and identified numerous prognostically relevant genes. However, identification of mutations causal for disease development and persistence and translation of these findings into clinical therapeutic strategies is currently very limited. Thus, only a few molecularly addressable mutations have been identified so far, which is why the prognosis of AML patients has hardly improved over the last decades. PiggyBac transposon mutagenesis screening is a powerful murine model system in which genome-wide in vivo screening for relevant genes in oncogenesis is feasible by random activation and inactivation of all genes and regions. PB transposons are short DNA elements that randomly integrate and de-integrate throughout the genome through PB transposase activity, resulting in a functionally relevant growth advantage in some cells via oncogene activation or tumor suppressor inactivation. Integration sites are then characterized at high resolution and classified as statistically relevant affected common integration sites. In this research project, a forward-genetics in vivo screen will identify genomic networks associated with ASXL1mut, which will be further addressed experimentally in follow-up projects. The central research question is which genes in combination with ASXL1mut are drivers of leukemogenesis and how ASXL1mut contributes to leukemogenesis through epigenetic dysregulation.

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› Cancer
› Lipidomics

Lipidomics in Anthracycline-Induced Cardiotoxicity – Identification of Novel Signaling Pathways and Drug Targets

Anthracyclines are highly potent cytostatic drugs that are widely used for the treatment of solid tumors (e.g, breast cancer or gastric cancer) as well as various leukemias and lymphomas. Unfortunately, anthracyclines are associated with severe cardiotoxic side effects resulting in dose limitation and substantial long-term complications like the development of congestive heart failure. Although there is good awareness of the potential cardiotoxicity and current guidelines recommend dose limitation in order to prevent those, cardiac damage is evident in more than 20% of patients in current clinical practice. Despite excessive research activities during the last decades, the underlying mechanisms of anthracycline-cardiotoxicity are incompletely understood, and effective strategies for prevention or treatment are currently lacking. There is evidence that anthracyclines lead to changes in cardiac lipid metabolism and that their cardiotoxicity is mediated by generation of reactive oxygen species damaging lipid membranes in cardiomyocytes. Additionally, biophysical studies indicate that anthracyclines can hamper cell function by forming complexes with lipids of the inner mitochondrial membrane. Novel mass spectrometry-based methods allow systematic investigations of the totality of lipids in cells or organs (»lipidomics«), however, data on their application in the context of anthracycline-induced cardiotoxicity is currently lacking. This project aims to characterize the lipidome changes of cardiomyocytes in response to anthracycline treatment. Based upon this, novel signaling pathways, changes in cell metabolism, and (sub-)cellular drug targets will be identified. Ultimately, potential drug candidates will be tested in vitro regarding their ability to prevent/treat anthracycline-induced cardiotoxicity.

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› Single-cell RNA sequencing
› Colorectal cancer
› Tumor heterogeneity
› Tumor microenvironment

The Impact of Transcriptional Heterogeneity for Tumor Biology, Prognosis and Therapy Response in Colorectal Cancer

Colorectal cancer is the third most common cancer and the second most frequent cause of cancer-related death worldwide. While early-stage tumors may be cured by surgical resection, patients with advanced disease benefit from systemic chemotherapy but eventually often succumb to the disease. Besides tumor stage and histological grade, individual molecular characteristics of colorectal cancer have been identified that indicate patient prognosis and response to systemic treatments, thus enabling more personalized therapeutic strategies. However, current molecular characteristics guiding clinical management completely neglect that colorectal cancers in addition to their intertumoral heterogeneity also display high degrees of intratumoral cellular heterogeneity. Tumor cell subsets may respond differently to targeted therapies and mediate endogenous therapy resistance. This indicates the need for more effective therapeutic strategies that target distinct tumor cell subsets at the same time. Furthermore, colorectal cancers harbor a complex immune- and stroma-cell rich microenvironment, which may further confound precise molecular classification when tested in bulk transcriptome assays. Recently developed single-cell RNA sequencing techniques are promising to overcome previous limitations and may allow a yet unprecedented depth in the molecular characterization of colorectal cancers. Within the Junior Clinician Scientist Program, I aim to dissect the relevance of distinct tumor cell subpopulations in primary patient-derived colorectal cancers for tumor biology, classification and therapeutic targeting by applying single-cell transcriptomics. This approach will yield a much more precise transcriptional profiling and information on functional interdependence of colorectal cancer cells, and may result in a predictive and prognostic tool that considers all relevant tumor cell subpopulations. This may eventually guide clinical decisions including choice and combination of therapeutic regimens for patients with colorectal cancer.

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Fields of Research
› Intestinal failure
› Intestinal failure-associated liver disease (IFALD)
› GLP-2 analogues
› Amyloidosis

Effect of Genetics, Trace Elements and Parenteral Nutrition on Intestinal Failure Associated Liver Disease.

Epidemiological data have shown that the incidence of chronic intestinal failure (CIF) is rising and is expected to further increase in the next decades most likely due to complications of more aggressive surgical approaches and improved perioperative management. Parenteral nutrition (PN) remains the mainstay of treatment for CIF but might be associated with potentially life-threatening complications. Intestinal failure associated liver disease (IFALD) is one of the leading long-term complications and causes of deaths in adult CIF patients receiving home parenteral nutrition. Of note, the pathophysiologic mechanisms of IFALD have not been discovered yet and seem to be of multifactorial genesis. However, promising non-invasive liver function tests and new experimental results propose a novel holistic approach to completely understand the aetiology and pathophysiology of IFALD. The aim of this study is a comprehensive analysis of the pathogenesis of hepatic damage in intestinal failure patients receiving parenteral nutrition based on the effect of genetics, serum trace elements and parenteral nutrition. This study will attribute to a greater understanding of the pathogenesis of IFALD and may lead to targeted interventions to prevent and treat the condition (e.g. individual manganese supplements, non-invasive liver assessment in clinical routine workup, development of an accurate predictive score for IFALD).

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Fields of Research
› Cerebral palsy
› Functional connectivity
› Deep brain stimulation

Functional Networks of Dyskinetic Cerebral Palsy: a Lesion-Based Study

Infantile cerebral palsy is a broad term for pre- or perinatally acquired, non-progressive, predominantly motor disorders that can affect muscle tone, strength and/or posture. The dyskinetic subtype represents 10-14% of all cases and is characterised by the presence of complex hyperkinetic movement disorders including dystonia and choreoathetosis. Current treatment is solely symptomatic and largely unsatisfactory. Dyskinetic cerebral palsy (dCP) is associated with lesions in the basal ganglia, thalamus and cerebellum. To what extent lesion characteristics such as specific location or functional connectivity are associated with clinical movement disorder patterns is still not clear. Deep brain stimulation (DBS) is an established treatment for Parkinson's disease or primary dystonia and is known to modulate abnormal motor network activity. In contrast to primary dystonia, DBS of the globus pallidus internus for patients with dCP has shown heterogeneous results. Understanding which functional networks underlie specific movement disorder patterns in dCP might facilitate patient and target selection for neuromodulatory treatments such as DBS. In this study, we hypothesise that different clinical movement disorder patterns (e.g. predominant dystonia or chorea) in dCP are related to lesions in specific nodes of larger functionally connected networks. To test this hypothesis, 30 patients with dCP will undergo a thorough clinical examination aimed at characterising the clinical movement disorder pattern. In a second step, cranial MRIs of included patients will be analysed and existing lesions delineated in order to investigate their association with the individual movement disorder. Lastly, perturbed functional networks underlying different movement disorder patterns in patients with dCP will be identified using lesion network mapping. On the long-term, these findings could be used to explore targeted treatments for dCP, taking into account individual clinical phenotypes of this heterogeneous disease entity.

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Fields of Research
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› Deep Brain Stimulation
› Neuromodulation

Towards the Clinical Implementation of Adaptive Neurostimulation: Evaluation of Chronic Electrophysiological Biomarkers

Deep brain stimulation (DBS) is an established, effective therapy for movement disorders, improving motor symptoms and restoring a better quality of life. Moreover, the possibility to record electrophysiological activity in the basal ganglia through the implanted DBS electrodes has expanded the pathophysiological understanding of movement disorders. Beta frequency band (13-35 Hz) activity in the subthalamic nucleus (STN) is characteristic for Parkinson's disease (PD) and a potential biomarker, as activity levels correlate with symptom severity and are modulated through therapy. Adaptive DBS (aDBS) is a concept aiming to provide stimulation titrated to the real-time analysis of biomarker activity. To date, most aDBS studies have been limited to short-term experimental, acute peri-operative settings, and little is known about the validity of beta-band activity as a chronic biomarker. Using the novel Percept neurostimulator (Medtronic, Minneapolis, USA), STN local field potential recordings can now be streamed from chronically implanted DBS electrodes, with the advantage of electrophysiological recordings over long time periods, in freely moving patients, and without acute peri-operative limitations. We hypothesize that beta band activity is a stable, chronic electrophysiological biomarker for long-term application in everyday-life, reflecting motor performance, affective symptoms and therapy effects. In the first study part, a cohort of chronically implanted PD patients (>3 months after DBS surgery) will participate in a monopolar review with stepwise stimulation increase and corresponding motor performance assessments, ON and OFF dopaminergic medication. This allows the evaluation of therapy effects and symptom severity in relation to biomarker activity. In a second step, long-term characteristics of biomarker peak activity will be assessed for two weeks, in relation to factors such as motor activity, mood, therapy changes or circadian rhythms documented in patient diaries and clinical scores. Overall, the results of this study will provide a better understanding of chronic biomarker dynamics. As the Percept neurostimulator also has the potential of aDBS therapy, this study lays the foundation for the implementation of neurophysiological research in therapy optimization, towards the clinical application of personalized adaptive neurostimulation.

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› Brain Development
› Oligodendroglia and Purkinje Cells
› Hyperoxia

Disturbed Interaction of Purkinje Cells and Oligodendroglia in the Postnatal Cerebellum Caused by Oxygen

Preterm birth is one of the major pediatric problems worldwide. Although advances in medical care led to increased survival, long-term neurodevelopmental disability remains an area of concern. The impact of preterm birth on psychomotor and behavioral development is reflected in diverse neurological problems such as delayed neurobehavioral development, poor cognition and academic performance. The risk of neurological sequelae after preterm birth rises with prematurity of the neonate. Recent studies of neonatal brain damage focus on the cerebellum. Brain expansion increases in the last trimester of pregnancy. The cerebellum reaches a growth rate that cannot be found in any other brain region. Human birth leads to increased oxygen tension levels in the blood even without supplemental oxygen administration. The relative hyperoxia hits the immature cerebellum of preterm infants in a phase of very dynamic growth and cellular development indicating a high vulnerability to external toxic stimuli. Our goal is to investigate the impact of oxygen toxicity on neonatal brain development in a hyperoxia rodent model. In our previous studies, we could show short- and long-term injuries of the cerebellum caused by hyperoxia. We investigated impaired neuronal and impaired oligodendroglial development, which is also seen in preterm infants. The development of oligodendroglia is highly dependent on interactions with neurons. Cerebellar development is regulated by the Purkinje cell neuron. We now aim to investigate in the impact of Purkinje cell injury on oligodendroglial development. We intend to analyze A) the influence of hyperoxia to the function and development of Purkinje cells, B) the interaction of Purkinje cells and oligodendroglia after hyperoxia exposure and c) the influence of GABA/-antagonist as a major transmitter released by Purkinje cells on the development of oligodendroglial precursor cells.

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Fields of Research
› Vascular immunology in acute coronary syndromes caused by Plaque Erosion

Characterization of the Function of T-Adaptive Immunity in Different Pathophysiologies of Acute Coronary Syndrome

Rupture of atherosclerotic plaque is the most common cause of acute coronary syndrome (ACS with ruptured fibrous cap, RFC-ACS). In about one third of ACS-events, however, the causative acute pathology is plaque erosion, characterized by coronary thrombus formation at a culprit plaque with intact fibrous cap (IFC-ACS). The pathomechanism of this important pathology is largely unknown. Within the translational OPTICO-ACS study program, we recently observed significant enrichment of cytotoxic- and helper T-cells selectively at the culprit lesion site of IFC-ACS, but phenotypical and functional details of the observed T-cell response remain unknown. In a delicate balance, the principal CD4+ T-helper (TH)-subsets (regulatory T cells (Tregs, CD127lo,CD25+), TH1- (CXCR3+), TH2-(CCR4+CCR6-), TH17- (CCR4+CCR6+), TH9- (CCR4-CCR6+) and T follicular helper (TFH, CXCR5+) cells) mediate distinct pro-inflammatory, destabilizing (e.g. TH1, TH17) or anti-inflammatory, protective (e.g. Treg, TH2) effects on coronary atherosclerosis. The aim of the current project is in depth characterization of local adaptive immune processes in IFC- and RFC-ACS, using a novel combination of OCT imaging, catheter-based sample acquisition, flow-cytometry, multiparameter proteomics and CITE-Seqeuncing.

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› Autoinflammatory diseases
› Autoinflammation
› Proteasome
› Regulation of inflammation

Identification of Novel Genetic Mutations Involved in Proteasome-Assosiated Autoinflammatory Syndrome

Monogenic autoinflammatory diseases are characterized by an unprovoked overreaction of the immune system including many organs and are characterized by high morbidity and mortality. An example of a very rare autoinflammatory disease is CANDLE syndrome (»chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature«). This is a proteasome-associated autoinflammatory syndrome (PRAAS) in which autoinflammation is triggered by a malfunction in the ubiquitin-proteasome system. The aim of my project is to study an index patient with a so far on a genetic level unexplained cause for his CANDLE syndrome as a basic model to identify further components of the ubiquitin-proteasome system that contribute to autoinflammation. Mutations known so far concern the proteasome-core complex or assembly proteins. We hypothesize that mutations in other proteasome-associated genes may also cause CANDLE syndrome. The aim is to further investigate the causes of CANDLE syndrome. This is expected to yield new insights into the regulation of the ubiquitin-proteasome system, which contributes to inflammation, and additional molecular genetic insights into the regulation of the proteasome or discovery of further proteasome system components, which can be used to develop further therapeutic options for PRAAS/CANDLE syndrome.

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› Intensive Care Unit acquired Weakness
› Translational Research
› Muscle Homeostasis

The Impact of Bioenergetic Failure on Muscular Function in Critically Ill Patients

Intensive Care Unit-acquired Weakness (ICUAW) is a clinical diagnosis defined by a reduction in maximal muscle strength, which cannot be explained by anything other than critical illness itself. It can be observed in the majority of critically ill patients and is further characterized by an early-onset, rapid muscle atrophy. Short-term as well as long-term mortality and morbidity are significantly increased in patients with ICUAW. In a previous project, we discovered that preservation of muscle mass in critically ill patients is not able to counteract development of weakness and further does not improve recovery within one year after ICU discharge. We further noticed that, while muscle strength fully recovered after ICU discharge, muscle endurance remained impaired. During commencement of our trial we performed neuromuscular electrical stimulation and noticed that patients contractile response was highly variable, declined over time and dependent on the degree of illness. An observation that had been disregarded earlier but also cannot be explained by muscle atrophy. These findings led us to the conclusion that limited muscle endurance, dissociation of muscle mass and muscle strength as well as variable contractile response to neuromuscular electrical stimulation are most likely caused by a dysfunctional energy supply. Considering mitochondria are the main energy provider for the human body and especially for muscle activity extending beyond short bursts of maximal strength, we hypothesized that impaired mitochondrial function – bioenergetic failure – could be the main culprit leading to the observed phenotype. We therefore aim in a first step to do a thorough characterization of mitochondrial function, mitochondrial biogenesis as well as related pathways and in a second step correlate our molecular findings to the clinical, metabolic and electrophysiological data in order to identify key mechanisms as possible therapeutic targets.

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› B cell receptor sequencing
› B cell reconstitution
› Bone Marrow Niche

Characterization of the Human Bone Marrow Niche and Immune Reconstitution after Allogeneic Stem Cell Transplantation

Despite the rapid advances in cancer therapies, allogeneic hematopoietic stem cell transplantation (alloHSCT) still remains an integral part of curative therapeutic strategies in the field of hematology. During alloHSCT the recipient is conditioned with high-intensity chemotherapy and/or irradiation in order to deplete residual tumor cells and to facilitate the rooting of donor's hematopoietic stem cells within the recipient's bone marrow niche. Recent studies were able to show that the interplay between non-hematopoietic bone marrow and hematopoietic cells is essential for an efficient immune reconstitution after transplantation. Several factors such as the occurrence of bone marrow graft-versus-host disease as well as irradiation have been identified to hamper the process of immune and B cell reconstitution due to niche damage, resulting in a higher risk for infections and thereby increased morbidity and mortality after alloHSCT. We are underway to conduct a full characterization of the human bone marrow niche before, during and after alloHSCT via immunofluorescence confocal microscopy as well as single-cell analyses. Our goal is to decipher the therapy-induced alterations and reconstitution of the bone marrow niche with focus on the interaction of immune and stroma cells. We will further implement flow cytometry analyses of B cell subpopulations in peripheral blood and B cell receptor sequencing at various time points before and after alloHSCT, in order to evaluate the B cell regeneration and BCR repertoire after transplantation. Pairing these findings with information on clinical features, we hope to shed some light on the pathomechanisms of bone marrow niche damage and hampered B cell reconstitution and to develop individual strategies for improving humoral immunity after allogeneic HSCT.

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› Bone Metabolism
› Joint Infection
› Osteitis
› Arthroplasty

Role of Osteitis and Osteomyelitis in Altered Bone Homeostasis in Patients with Periprosthetic Joint Infection

Despite increased use of antibiotics and improved aseptic surgical techniques, periprosthetic joint infections (PJI) still occur in 1-5% of primary total knee arthroplasties. In PJI, microorganisms form a biofilm on the implant making the infection highly resistant to antibiotic treatment. Once a biofilm forms on the implant, complete removal of the infected prosthesis and, in most cases, in a second-stage surgery, reimplantation of a new prosthesis is necessary. After PJI-dependent revision surgery, we found a drastically elevated risk for prosthesis failure: In this study, 22% of all patients suffered from long-term complication aseptic loosening and 16% from recurrent PJI; suggesting PJI significantly and lastingly alters the bone metabolism. Our research focuses on understanding the altered pathomechanisms involved in this pathology. We hypothesize that the increased risk for aseptic loosening after PJI is due to an inflammatory response in the bone and bone marrow, i.e. osteitis and osteomyelitis. In PJI, adaptive immunological processes potentially impact the regenerative function of osteoblasts and thus disturb the bone and bone marrow homeostasis, subsequently altering bone density and metabolism. Our clinical observations suggest that these changes persist despite guideline compliant anti-microbial and surgical treatment. In this respect, affected patients could benefit from treatments that restore bone homeostasis and counteract osteitis and bone loss. Additionally, profiling patient's systemic immune competence from peripheral blood samples may help identify patients especially at risk for impaired bone formation and thus consecutive prosthesis failure.

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Fields of Research
› Motor rehabilitation
› Stroke
› Optogenetics
› Deep Brain Stimulation

Neural Mechanisms of Motor Recovery After Stroke

Stroke is one of the most common diseases with acute onset. It is considered to be among the leading causes of disability worldwide, resulting mainly from remaining motor deficits. There are a lot of efforts to improve emergency care and early rehabilitation with notable improvement in the therapies for stroke patients. However, little is understood regarding the cellular mechanisms of motor recovery after stroke especially in patients who are severely disabled. Studies and previous experiments hint at the neurotransmitter serotonin to play an important role in the recovery of motor deficits. We hypothesize that an increase in serotonergic transmission in the surroundings of the brain tissue affected by stroke (penumbra) will improve the motor deficits. In our methodological approach we are using different state-of-the-art techniques to examine and modulate the serotonergic system in mice, e.g. with chemogenetic, optogenetic and electric stimulations. Furthermore, we are expecting to show improvement of motor recovery and be able to identify the critical parts of the serotonergic system using those modulations and immunohistological analyses. These experiments have to be considered as groundwork in the understanding of underlying mechanisms of longterm rehabilitation after stroke and can possibly contribute to the refinement of rehabilitation paradigms.

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› Pediatric Cardiology
› Inflammation

Cold Inducible RNA-Binding Protein (CIRBP) as a Diagnostic Marker in Pediatric Cardiac Surgery

Both inflammatory reactions and capillary leak syndrome are frequent complications after open-heart surgeries in children with congenital heart disease. Capillary leak syndrome is primarily induced by endothelial dysfunction and is characterized by intravasal volume- and protein depletion, as well as edema. Inflammatory reactions and capillary leak syndrome crucially influence postoperative morbidity as they are associated with a longer stay on the pediatric intensive care unit, prolonged mechanical ventilation and higher demands for catecholamines and sedative medication. To date, only a few risk factors have been identified for the development of inflammatory reactions and capillary leak syndrome. However, we are still lacking suitable biomarkers, which can be used to detect and treat patients at risk early on. Cold inducible RNA-binding protein (CIRBP) belongs to the family of cold-shock proteins and has been identified as a potent inflammatory mediator. So far, basic research and clinical studies indicate that CIRBP may be of both diagnostic and therapeutic use for inflammatory reactions. Furthermore, experimental studies have shown that CIRBP is involved in the pathogenesis of endothelial dysfunction. As there have been no studies analyzing CIRBP concentrations in peripheral blood after cardiac surgery in children with congenital heart disease, the present pilot study is designed to evaluate CIRBP as a potential diagnostic marker in this cohort. Therefore, patients up to the age of 18 years undergoing a corrective or palliative cardiac surgery at our center will be recruited for the study. Blood samples will be collected directly before and during the first 24 hours after operation at defined time points. In addition to analyzing CIRBP, proinflammatory cytokines, and markers for endothelial dysfunction, serum samples will be incubated with human monocytes (THP-1) and endothelial cells (HUVECs) in the experimental part of the study to analyze induced mechanisms on a cellular level.

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› Humorla Immune Response
› Autoimmunity

Evaluation of Humoral Cross-Reactivity to Viral Antigens and Central Nervous Autoantigens in Encephalitis

Encephalitis is a rare but serious disease with neurological dysfunction in the context of inflammation of the brain parenchyma, with a disease peak in infancy with 13.5 cases per 100,000. While the causal clarification remains unclear in over 30% of the cases, two main forms can be distinguished in the other cases. On the one hand, primarily infectious encephalitis occurs as a result of direct invasion of the central nervous system (CNS) by a pathogen, usually neuroinvasive viruses, most commonly herpes simplex viruses. On the other hand, auto-antibodies can cause so-called autoimmune encephalitis (AIE) as part of an aberrant immune reaction, such as anti-NMDA receptor encephalitis. AIE is more likely to be associated with viral infections, best shown for AIE after herpes simplex encephalitis (HSE), which typically occurs two months after viral infection in 27% of Anti-NMDA receptor antibodies can be detected in about two thirds of these patients a phenomenon that has been shown in a similar manner after experimental HSV infections in a mouse model.However, the mechanisms underlying AIE after HSE have so far remained largely unclear. Increased titers of serum HSV antibodies were found in patients with NMDA receptor encephalitis without clinical HSE, possibly hinting towards a molecular mimicry as a trigger of autoantibody production. But also around a third of post-HSE patients also develop auto-antibodies against other neuronal. In addition, AIEs have also been described in association with other viral infections, which suggests general trigger factors. Further studies are therefore necessary to understand the host and environmental factors that lead to the production of autoantibodies in patients after viral encephalitis.Using established methods in the recombinant generation and characterization of disease-specific antibodies from patients' CSF or blood samples this project aims to expanded understanding of antibody-mediated neurological and psychiatric diseases, thereby specifically addressing the following questions:1. Do defined pathogenic autoantibodies from AIE patients (without a history of viral encephalitis) have cross-reactivities against viral targets?2. Can monoclonal antiviral antibodies be isolated from patients with viral encephalitis or AIE after viral encephalitis? Are reactivities against central nervous autoantigens detectable for these antiviral antibodies or other antibodies from the same patient sample?

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› Neuroimaging
› Neuroinflammation

7 Tesla T2*-Weighted MRI Mapping in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are both neuroinflammatory diseases with overlapping clinical and paraclinical presentation. Despite the introduction of NMO-specific aquaporin-4-antibody (AQP4-ab) and quite recently myelin-oligodendrocyte-glycoprotein-antibody (MOG-ab) into neurological diagnostic workup, accurate differential diagnosis in patients with acute and relapsing CNS inflammation still remains difficult. As a consequence, the different disease entities are still frequently misdiagnosed and existing effective therapy is withheld from a considerable number of MS and NMOSD patients. However, overt histopathological differences between MS, AQP4-NMOSD and MOG-NMOSD with particular regards to myelin content within and outside of lesion formations have been previously described. The advent of modern T2* MRI mapping techniques allows for MRI-based quantification of myelin content within brain tissue in vivo. By use of 7 Tesla MRI at ultrahigh field strengths, we further augment image contrast and myelin quantification accuracy of T2* sequences compared to conventional routine MRI at 3 Tesla. Therefore, we attempt to explore the potential of ultrahigh field MRI-based quantification of brain myelin content to differentiate multiple sclerosis (MS) from neuromyelitis optica spectrum disorders (NMOSD) by assessing quantitative T2* parameters within inflammatory lesions and in different brain regions apart from overt lesion sites. In our clinical study, we investigate patients with MS and antibody-associated NMOSD with regards to their clinical and 7 T T2* MRI mapping features to evaluate sensitivity and specificity of T2* mapping to distinguish between MS and NMOSD. The ultimate goal is to not only visualize different myelin concentrations within brain tissue of different disease entities in vivo, but also to improve current MR differential diagnostic criteria to allow for early and accurate differential diagnosis for patients with neuroinflammatory diseases in a clinical setting.

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Fields of Research
› Ischemic stroke
› Magnetic resonance imaging (MRI)
› Contrast-enhanced MRI

Training-Induced Changes in Vascular Morphology and Cerebral Perfusion after Stroke – a Multiparametric MRI Study

Early rehabilitation is an essential part of the recommended therapy following an acute cerebrovascular event due to unequivocal evidence that regular physical activity not only mitigates risk factors (i.e. hypertension, dyslipidemia) but also has a beneficial effect on functional recovery following stroke. However the underlying mechanisms of physical activity leading to an improved outcome are poorly understood. Pre-clinical studies from our research group have demonstrated the beneficial effects of exercise on long-term stroke outcome in rodents and have attributed the observed effect to training-induced angiogenesis. Physical activity not only led to a histological increase in microvessel density but also led to visible changes in vessel morphology and ultimately resulted in enhanced cerebral flood flow and better long-term functional recovery in rodents following minor ischemic stroke. In patients, the mechanisms underlying the beneficial effects of exercise following stroke are far less explored. In 2013, our research group designed and initiated the PHYS-STROKE Trial (a Phase III randomized controlled trial [RCT]) – which was the first trial designed to assess the effect of physical activity on functional outcome following stroke. Recent developments in magnetic resonance imaging (MRI) suggest that selected sequences – such as vessel size imaging (VSI) – now allow for an in vivo assessment of cerebral microvasculature in patients. With this novel imaging technique in mind, an exploratory sub-study of the PHYS-STROKE trial was designed called BAPTISe (Biomarkers and perfusion – training induced change after stroke), in which a subgroup of patients receive multiparametric contrast-enhanced MRI before and after intervention (aerobic fitness vs. relaxation). The aim of the current project is to translate our own pre-clinical findings on the effects of exercise on cerebral perfusion and angiogenesis into clinical research with the use of multiparametric, contrast-enhanced MRI. The aim of this project is to assess whether VSI can reliably assess the cerebral microvasculature in-vivo in acute and sub-acute stroke patients. Furthermore, we aim to assess whether physical training will result in changes in MRI-derived microvascular morphology and cerebral perfusion parameters in stroke patients, corresponding to pre-clinical findings and whether these changes can predict stroke outcome.

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› Regenerative Therapies
› Gene Therapy
› Cell engeneering
› CRISPR/Cas

Neuroblastoma Tumor Microenvironment Alteration Through a Gene Therapeutic Approach to Enhance Adoptive T Cell Therapy

The gene therapeutic approach we are developing aims to modify neuroblastoma cells by CRISPR/Cas9 technology to express transgenes that encode for a T cell-attracting chemokine: CXCL10. By doing so, we aim improve CAR T cell infiltration and subsequently efficacy, even in tumors with a T cell excluding signature. To achieve transgene expression predominantly in cancer cells we will be using the sequence specificity of the CRISPR/Cas9 system. We thereby compare different genomic targets in terms of integration frequency, transgene expression and tumor specificity.

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› Neuroimaging

Towards a Computational Account of Ketamine's Antidepressant Effect

With an estimated 350 million people affected globally, depression represents one of society's most challenging and costly health burdens. Traditional pharmacotherapy of depression increases brain levels of monoaminergic neurotransmitters, such as serotonin. However, effects of monoaminergic antidepressants are often modest, and benefits emerge slowly, over a time course of weeks. Recently, an NMDA receptor antagonist, ketamine, was found to improve mood in severe, treatment-resistant depression. Unlike traditional therapy, ketamine acts rapidly, producing antidepressant effects within hours of application. Moreover, ketamine targets glutamate neurotransmission, rather than impacting brain monoamine levels. Consequently, the serendipitous discovery of this novel, rapid-acting antidepressant is hailed as one of the most important advances of modern psychiatry. However, despite ketamine's promising clinical impact, the mechanisms through which it may work remain elusive. To utilise the enormous therapeutic potential of ketamine, we require a better mechanistic, neuroscientifically grounded, understanding of its effect on brain function. In this project, I will use cognitive assessment, brain scanning and mathematical modelling, in patients undergoing ketamine treatment. Over the course of the study, patients will be repeatedly tasked on a bespoke decision-making task that I have recently validated in a similar pharmacological study (Michely et al., 2020, Nat Commun). This gamified computer task enables a precise assessment of how patients learn from, and emotionally respond to, rewarding experience. Additionally, I will use non-invasive, functional magnetic resonance imaging (fMRI), allowing me to probe activation of brain circuits involved in human reward processing. Building on a computational psychiatry approach, I aim to decipher the cognitive mechanisms that give rise to ketamine's antidepressant effect, and identify neurocomputational markers for a clinical response to intervention. Informed by a deeper understanding of the neurobiology of depression and its treatment, my goal is to improve tailoring of currently available, and development of novel antidepressant therapies in the future.

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› Liver Transplantation
› Extended Criteria Donor Organs
› Proteomics
› Aging

Extracorporeal Evaluation of Liver Grafts from Older Donors

Liver transplantation is the treatment of choice for patients with advanced liver cirrhosis, hepatocellular carcinoma within Milan-criteria, and severe metabolic or autoimmune hepatic disorders. However, the number of patients waiting for liver transplantation exceeds the number of available organs. Notably, in Germany, the success of liver transplantation has been limited by a dramatic decline in organ donation over the last decade. To alleviate the supply and demand imbalance, an increasing proportion of grafts meeting so called extended donor criteria (i.e. high donor age or macrovesicular steatosis hepatis) are accepted for transplantation. These extended criteria donor organs are usually discarded due to a higher susceptibility for ischemia reperfusion injury (IRI), which associated with an increased rate of primary non-function and early allograft dysfunction. IRI is initiated during warm reperfusion of livers in situ after static cold storage, which remains the current standard of care. A recent alternative to static cold storage is normothermic ex vivo liver machine perfusion (NEVLP): livers are perfused with an oxygenated medium to achieve an almost physiological milieu prior to transplantation. NEVLP enables 1) reduced IR, 2) organ evaluation and characterization prior to transplantation, 3) optimized transplantation logistics, 4) potential for metabolic conditioning during perfusion. Ex vivo machine perfusion therefore has the potential to increase the pool of available organs for transplantation. Currently, around 15% of potential liver grafts are declined in Germany due to donor age or morbidity. Indeed, this problem exists worldwide with similarly high decline rates in the United States with 13%. However, it still remains unclear why some organs from older age donors perform better after transplantation than others. The aim of the project EvALT (Extracorporeal Evaluation of Liver Grafts from older Donors) is therefore to characterize older donor organs during NEVLP using a previously developed small animal model for NEVLP and possibly identifying therapeutic targets for future graft optimization prior to transplantation.

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› Pancreatic cancer
› Organoid cultures
› Personalised therapies

Potential of Organoid Cultures to Predict the Therapeutic Response in Patients.

Pancreatic cancer is a highly malignant tumor with a dismal prognosis. Non-specific symptoms, rapid progress, a high rate of metastasis and very little progress in treatment options result in a five-year survival rate of less than 10% with the only curative treatment to be the surgical resection of the tumor. Pancreatic cancer is expected to be the second deadliest cancer by 2030. Once metastasised the treatment is purely palliative. Only very few chemotherapeutic regimes can be administered. None of them taking into account the specific metastatic patterns patients present. Previous results of the CONKO-01 and -05 study group, however, were able to show a significantly prolonged overall survival of isolated pulmonary metastasis after initial surgical resection compared to isolated hepatic metastasis (30,4 vs. 18,1 months) representing a differential physiology of the tumor. Consequently, possible subgroups of the metastatic stage might benefit from more personalised treatment options. By establishing and analysing patient derived organoid models not only from the primary tumor but also from the different metastatic sides, the tumor physiology as a whole can be understood more thoroughly. The aim of this project is to expose patient derived tumor organoids of the primary and metastatic sides to various targeted and well-known chemotherapies and to use proteomics to classify subgroups and identify potential biomarkers of the tumor. By correlating the in-vitro data to the clinical response rate of these patients, the organoid model can be evaluated as to whether more personalised therapeutic approaches can become future clinical practice.

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› Thermoablation
› CT-Thermography
› Dual-energy computed tomography
› Sepsis

CT-Thermography for Intraprocedural Ablation Zone Monitoring

Using density data routinely acquired by computed tomography but neglected so far, it is now possible to provide an estimate on tissue temperature during thermoablation for operator feedback. Previous experiments in ex vivo porcine liver tissue indicated that heat ablation yields more accurate temperature estimates than cryoablation. Current challenges include the optimized coregistration of images in order to reduce breathing artifacts in the living animal. We are working on CT-Thermography to improve the quality of thermoablation especially in renal cell carcinoma and thereby fight local recurrence.

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› Autoimmune encephalitis
› Neuronal surface antibodies
› CRISPR Cas technology

Identification of New Antibody Targets in Autoimmune Encephalitis

Autoimmune encephalitis caused by antibodies targeting neuronal surface antigens is an only recently explored neurological disease that leads to psychiatric and mnestic deficits as well as epileptic seizures and focal neurological signs. New disease-causing antibodies are frequently being detected. Yet in clinical routine, we see many patients with unclear antibody findings, with the pathogenicity being unknown. Precise description of the antigen could not only work as proof of pathogenicity but also justify advanced immunotherapy in patients. It thus represents an immediate medical need. Today detection of an autoantibody using immunohistochemical methods is relatively easy and well established. The exact identification, however, of the antigen targeted by the antibody is still challenging. Even advanced methods using mass spectrometry or phage display fail to identify the complex membrane-expressed native receptor proteins. The proposed project therefore aims at identifying the surface receptors targeted by anti-neuronal autoantibodies by applying a new genome-wide screening method using the CRISPR/Cas9 activation technology. The CRISPR/Cas system is originally known from bacteria where exposition to viral DNA leads to integration in the bacterial genome by inducing double strand-breaks and thus providing a vaccination against future viral invasion. In our project we use a mutated, catalytically inactive (dead) nuclease dCas9 which is still able to bind DNA with high precision. If the dCas9 is led to the promoter region of its target gene by a so-called single guide RNA (sgRNA), it can act as a transcriptional regulator, amplify gene expression, and thereby promote expression of receptor subunits or whole receptors to the cell surface. The use of a genome-wide library of guide RNAs, containing all possible antibody targets, allows for inducing the overproduction of each single antigen in the respective cells. If a patient-derived antibody now binds to one of these cells, we can stain this antibody-labelled cell, sort it by flow cytometry, and select the positive cells. Cells can then be analysed by next-generation sequencing. Identification of the antigens would allow to better judge the autoimmune findings, guide therapeutic options, and facilitate development of target-selective immunotherapy in the future.

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› Molecular MR Imaging
› Hepatocellular Carcinoma
› Tumor Microenvironment

Novel Molecular Imaging Biomarkers of Liver Tumor Adaptation to Hypoxia and Immune Evasion

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related deaths worldwide with the majority of cases being diagnosed at intermediate or advanced stages. In these patients, transarterial chemoembolization (TACE) is a guideline-approved therapy based on the synergistic effects of chemotherapy and ischemia-induced cell death. However, efficacy of TACE remains limited by high rates of local tumor recurrence. Postulated underlying factors are associated with tumor hypoxia. Inter alia, it promotes the upregulation of various growth factors, which propagate the expression of immune-checkpoints and promote regulatory T-cell activation, both of which contribute to immune evasion and dismal prognosis.Along with tissue destruction and a possibly favorable exposure of tumor-associated antigens to the immune system, TACE-induced ischemia is known to exacerbate tumor hypoxia and thus affect the local immune response. Therefore, exposure to sublethal ischemia is hypothesized to promote tumoral adaptation mechanisms that facilitate the creation of an immuno-compromised, pro-tumorigenic niche, where cancer cells can survive and regrow. However, TACE-induced tumor adaptation mechanisms are highly variable among patients resulting in heterogenous susceptibility, which may cause a substantial barrier to clinical efficacy of TACE applied alone or with immunotherapies. Thus, an unmet clinical need exists for novel methodologies to non-invasively characterize the hypoxic and immune phenotype of the tumor and monitor TACE-triggered alterations in order to ultimately design strategies to mitigate its immuno-inhibitory effects. Therefore, the goal of our translational research project is to develop and establish novel MR-based molecular imaging probes for the quantitative monitoring of tumor adaptation to TACE-induced hypoxia and interactions with the local immune response in liver cancer. To ensure clinical translatability of the newly developed imaging techniques, we will use a stepwise experimental design including 3D organotypic cell cultures and an orthotopic rabbit tumor model for TACE in liver cancer. Such imaging techniques will help exploit TACE as a conditioning tool for the tumor microenvironment and develop targeted approaches to disrupt resistance mechanisms. This is envisioned to transform TACE into a personalized and systematic »one-stop-shop« treatment that ultimately improves the clinical outcome in liver cancer patients.

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› Intestinal Microbiome

Effect of Allogeneic Stem Cell Transplantation and Cyclophosphamide (PTCy) on Intestinal Microbiome in Mice

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for many hematological, malignant diseases and as well as for primary immune deficiencies. The major causes of mortality after HSCT are relapse, graft-versus-host disease (GVHD), and infections. Research has recently highlighted the importance of the composition of the gut bacteria (intestinal microbiome) for the outcomes of patients after HSCT as well as in development of graft-versus-host disease (GVHD). There are limited data available on how the conditioning regimens change the intestinal microbiome and how intestinal microbiome itself can influence the long term outcome in patients after HSCT. Moreover, post-transplant cyclophosphamide (PTCy) treatment is widely used and has been proven to be highly effective at preventing severe acute and chronic GVHD after hematopoietic cell transplantation by inducing allo-reactive T-cell dysfunction and promoting preferential regulatory T-cell reconstitution. However, effector T-cell function may be influenced by the gut microbiota, which recently has been demonstrated to be associated with the severity of GVHD and overall survival after HSCT. In this project we use an MHC-haploidentical mouse model of allogeneic bone marrow transplantation to investigate the microbiome changes occurring with the bone marrow transplantation and post-transplant treatment with PTCy. We specifically study the effects of letal radiation, followed by bone marrow cell transplantation, and later PTCy and antibiotic treatment. After collection of serial fecal samples, DNA is extracted from the stool samples, sequenced for the genomic 16S V1-V9 regions and then analyzed. The primary objective of this murine study is to evaluate the dynamic changes of the microbial composition of murine fecal samples taken at different time points before and after HSCT in order to determine the effects of the individual treatment steps, which are widely used in human conditioning regimens. Specifically we seek to determine how lethal radiation trauma, PTCy and antibiotic treatments modulate the microbial community and how the start of immunological reconstitution of graft transplantation influences the bacterial composition of the intestinal microbiome.

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› Stem cell technologies
› Disease modeling

Induced Pluripotent Stem Cell Derived Sensory Neurons as a Patient-Specific Model of Chemotherapy-Induced Neuropathy

Chemotherapy-induced neuropathy (CIN) is a frequent, potentially irreversible adverse effect of cytotoxic chemotherapy often leading to treatment reduction or discontinuation which directly affects patients' prognosis. There is significant heterogeneity between patients regarding development and severity of CIN and susceptibility to different neurotoxic compounds. While the majority of patients develops CIN to variable extent, some patients are spared from these neurotoxic side effects. To date, however, neither predictive biomarkers nor preventive treatments for CIN are available, which is partially due to a lack of suitable experimental models. We therefore aim to evaluate whether sensory neurons derived from induced pluripotent stem cells (iPSC-DSN) of genetically distinct donors can serve as human disease model system for CIN. This could open new avenues for personalized medicine with individual risk prediction, choice of chemotherapeutic compounds and preventive treatments.

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› Deep Brain Stimulation
› Synaptic Mechanisms
› Human Single Cell Research

Synaptic Mechanisms to Retune Inhibitory Control of the Subthalamic Nucleus in Patients with Parkinson's Disease

Deep brain stimulation (DBS) of the Subthalamic Nucleus (STN) is an effective treatment for Parkinson's Disease symptoms. However, DBS only provides transient relief of symptoms, which rapidly return when stimulation is discontinued. To advance DBS therapy, a more thorough understanding of fundamental mechanisms is needed. Evidence from rodent studies has shown the potential of microcircuit interventions to induce long-lasting recovery of movement. Specifically, selective stimulation of inhibitory projections to the STN have been implicated in these effects. In humans, there is exciting new evidence that deep brain stimulation may serve to retune inhibitory synaptic control of basal ganglia structures. At present, however, inhibitory synaptic plasticity in basal ganglia structures has exclusively been studied in STN output structures in humans. In the rat, we have previously shown that the input of inhibitory projections is sustained at high stimulation frequencies in contrast to rapidly depressed excitatory input. Capitalizing on the unique opportunities of intraoperative microelectrode and human single-neuron recordings, this study aims to elucidate effects of the activation of inhibitory projections to STN by DBS in humans. Understanding the underlying physiological mechanisms of this aspect of DBS may be critical in optimizing DBS stimulation paradigms.

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› Stroke

Brain Morphometry and Resting State Functional Connectivity to Study Heart and Brain Interaction

Severe cardiac complications occur in 15-20% of patients during the first few days after acute ischemic stroke. Myocardial injury (i.e. elevated cardiac troponin levels) is one of the most common and relevant post-stroke cardiac complications. Patients with myocardial injury during the first days after an ischemic stroke are at increased risk of unfavorable outcomes. Until now, the underlying mechanisms are not well understood. There is evidence that stroke-induced functional and structural interference in the central autonomic network may contribute to the occurrence of myocardial injury after stroke. In a previous voxel-based lesion-symptom mapping (cerebral MRI), it has been shown that stroke lesions in the right anterior insular cortex are associated with the extent of acute myocardial injury. The right insular cortex is an important region of the central autonomic network (CAN) and involved in the autonomic cardiac control. In this project, we hypothesize that structural or functional alterations within the CAN promote the occurrence of acute myocardial injury (individual vulnerability). By using different morphometric and functional MR-imaging analyses, we aim to identify MR-biomarkers associated with myocardial injury after stroke. In a prospective observational cohort of stroke patients (BeLOVE), we will conduct an analysis of structural imaging data (surface-based morphometry (SBM) and voxel-based morphometry (VBM)) as well as a functional-connectivity analysis in resting state fMRI to compare anatomical differences and connectivity pattern of regions within the CAN between stroke patients with and without acute myocardial injury. This project represents a new approach in investigating the role of the autonomic nervous system in stroke-associated myocardial injury and would be an important step towards a better understanding of the mechanisms of cardiac complications after stroke.

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Fields of Research
› Visceral surgery
› Oncology
› Patient-reported quality of life

NOTE – Necessity of Protective Ileostomy in Rectal Resection?

Low anterior rectal resection for rectal cancer goes along with the creation of a protective ileostomy in most of the cases. A protective ileostomy can cause an immense deterioration of the patients' quality of life. Furthermore, postoperative complications such as excoration of the peristomal skin, peristomal abscesses, prolapse of the ileostomy or renal failure because of high fluid losses occur in nearly 15%. Ileostomy reversal requires surgery once again with inherent hospital stay, healthcare costs and possible complications. But the patient's safety in rectal resection must be mentioned as well. There are data that a protective ileostomy can lower septic complications caused by insufficiency of the rectal anastomosis. To further evaluate the necessity of protective ileostomy in low anterior rectal resection we conduct the NOTE trial which is a multicentric, prospective, randomised-controlled trial comparing patients with and without protective ileostomy undergoing rectal resection because of rectal cancer. Primary hypothesis says that patients without protective ileostomy have a better quality of life one year after rectal resection than patients with protective ileostomy measured by the mean score of the category »physical function« of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). There will be 224 patients overall, 112 each group, when a dropout rate of 10% is assumed. After randomisation of 25 patients in each group a safety analysis regarding operative revision because of insufficiency of rectal anastomosis will be conducted. All, inclusion criteria, surgical technique and perioperative management will be standardized. Three year follow-up of the patients includes both clinical examination and questionnaires as well as oncological outcome.

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Fields of Research
› Gastrointestinal Barrier, Regeneration and Carcinogenesis
› Tissue Microbiology
› Stem Cell Biology

Inflammatory Mechanisms of Gastric Stem Cells Upon Infection

Mechanisms by which mucosal surfaces discriminate between harmless bacteria and pathogens are not well understood. Helicobacter pylori colonizes the stomach of about 50% of the world´s population and is the main risk factor for gastric cancer. A subpopulation of gland-associated bacteria, in contrast to bacteria found on the surface, induces an inflammatory response, which leads to chronic gastritis as well as gland hyperplasia and metaplasia, which are precursor lesions for gastric cancer. To maintain gland homeostasis, a close interplay between epithelial and stromal cells builds a molecular signaling network that controls epithelial turnover and differentiation. The gastric gland base contains gastric stem cells that are characterized by high Wnt signaling and expression of stem cell markers such as Axin2 and Lgr5. This cell population relies on stromal-derived R-spondin. Using in vivo mouse models, in which the stem cell compartment can be altered, and the organoid culture system, we will demonstrate that gland base stem cells function as important sensors and effectors of bacterial infections and establish a novel link between stem cell signaling and mucosal immunity. Mechanistically, the interplay between R-spondin and NF-κB signaling and their impact on epithelial homeostasis, inflammation and infection will be explored.

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Fields of Research
› Schizophrenia
› Negative symptoms
› Empathy
› Electroconvulsive therapy

The Contextual Influence of the Oxytocin System on Empathy in Patients with Schizophrenia.

In previous studies the neuropeptide oxytocin has been in particular associated with social enhancing and anxiety relieving effects. The purpose of this study is to investigate the effect of oxytocin on empathy in patients with schizophrenia. On a neurobiological level, social effects mediated by oxytocin are based on oxytocin`s influence on the complexly regulated mesocorticolimbic dopamine system. Preliminary studies have already shown that oxytocin increases neuronal connections between social reward expectancy networks and networks for socioemotional processes in the brain. On a behavioral level this leads to increased social activation, motivation, and also improved social perception.Furthermore, an increase in empathy modulated by the amygdala has been shown in healthy individuals following oxytocin administration. In particular, primary psychotic disorders, such as schizophrenia, are associated with deficits in the domain of social cognition, including empathy. The degree of negative symptoms is expected to play an important mediating role here. Another study demonstrated a significantly lower expression of empathy as well as significantly lower oxytocin levels in patients with schizophrenia compared to healthy subjects. According to the theory of social salience, which describes an increased importance of certain social stimuli, the effect of oxytocin varies depending on specific contexts and individual variables of the perceiving person. One of the individual variables is the degree of negative symptoms in schizophrenic patients. Therefore, based on such preliminary findings, the research project will explore an effect of oxytocin, given by nasal spray, on empathy within a positively experienced and controlled context, especially in patients with schizophrenia regarding their negative symptoms.

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Fields of Research
› Preeclampsia
› Oocyte-donation pregnancies
› Perinatal Medicine
› Obstetrics

Immunological and Cardiovascular Inbalance in Oocyte-Donation Pregnancies

Our main research area is preeclampsia (PE), the sudden onset of hypertension (blood pressure > 140/90 mmHg) after the 20th week of pregnancy accompanied by proteinuria of >0,3g in 24 hours. Severe PE causes intrauterine growth restriction (IUGR) of the fetus, preterm delivery or even stillbirth. If PE is not detected and treated at an early stage, it leads to eclampsia, a tonic-clonic seizure, and a hypertensive crisis. During the seizure, the fetus might die within the uterus and the mother might suffer permanent cerebral damage if emergency Caesarean section is not performed immediately. Thus, PE is the leading cause of maternal and fetal morbidity and mortality, causing 20-25% of overall perinatal mortality and 16% of overall maternal mortality. The underlying pathomechanism of PE and the reliable prediction of the onset of the disorder are still unknown. However, it is evident that the placenta plays a major role in the development of this disease. In our clinical experience in one of the largest obstetric care units in Berlin (Charité), the number of pregnancies resulting from oocyte donation (OD) - performed abroad due to legal restrictions in Germany - rise continuously. Several studies conducted in OD pregnancies support the hypothesis that abnormal placentation owing to an immunological response of the mother to the fetus appears to be the cause of the high rate of PE in OD pregnancies. To investigate the pathway leading to preeclampsia we currently enroll pregnant women in prospective clinical trials, the »Berlin Brandenburg Pregnancy Cohort« and the »oocyte-donation pregnancy cohort« due to the high risk of preeclampsia in oocyte-donation pregnancies. During the visits, pregnant women are assessed using detailed cardiovascular and immunological phenotyping at three time points during the pregnancy, at delivery and 2-5 years after pregnancy (to further reveal the cardiovascular long term consequence of PE). The aim of this study is to develop a profound understanding of the immune cells playing a pivotal role at the fetal-maternal interface and their role in the development of preeclampsia in oocyte-donation pregnancies via single-nucleus RNA sequencing (sNuc-Seq) using samples from healthy controls and preeclamptic pregnancies resulting from Berlin and Oslo cohorts. Furthermore, we plan to process a subset of samples for spatial transcriptomics.

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Fields of Research
› Neuroblastoma
› Signal transduction pathways

Pharmacological Reactivation of the P53 Pathway by DS3032b in Neuroblastoma

Neuroblastoma is the most common extracranial childhood tumor. Despite aggressive multimodal therapy, survival of patients with high-risk neuroblastoma, which represent the majority of neuroblastoma patients, is <40% and the outcome of patients with relapsed neuroblastoma is almost always fatal. In addition, side effects of current multimodal therapeutic regimens for the treatment of neuroblastoma are high, often resulting in lifelong sequelae in survivors. Therefore, the development of targeted approaches with fewer adverse effects is of major importance for patients with primary high risk or relapsed neuroblastoma, who are in urgent need of additional effective therapies. The tumor suppressor gene TP53 is involved in the formation of different malignancies. Inactivating mutations in the TP53 gene are rare in neuroblastoma, but overexpression of MDM2 resulting in functional p53 inactivation is commonly detected. Specific antitumor activity of compounds targeting the p53-MDM2 axis has been demonstrated. Treatment with MDM2 inhibitors reduced cell viability in vitro and in vivo by re-activating p53 function. On the basis of the existing data, functional reactivation of p53 and/or inhibition of the p53/MDM2 axis in neuroblastoma are therefore promising therapeutic options. A prerequisite to clinical testing of DS3032b in patients with neuroblastoma is the comprehensive preclinical evaluation of the antitumor effect of this compound against neuroblastoma cells in vitro and in vivo. As a basis for clinical testing of DS3032b in neuroblastoma patients, we will analyze the effect of these compounds on cell lines in vitro and in subcutaneous xenograft models in vivo. In a first step, we plan to analyze the antitumor activity of DS3032b using cell growth, proliferation, senescence and apoptosis assays, flow cytometer, Western blotting and reverse transcription-quantitative PCR (RT-qPCR) analysis of p53 target genes. The specificity of the effect of DS3032b treatment should be detected by »rescue« experiments. In addition, we want to examine the activity of DS3032b in a subcutaneous xenograft mouse model.

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› Patient-Derived Xenografts
› Lymphomagenesis
› Personalized Medicine
› Diffuse Large B-Cell Lymphoma
› Personalized Medicine

Establishment of Diffuse Large B-Cell Lymphoma PDX-Models for Functional Lymphoma Pathogenesis and Personalized Medicine

Experimental studies in animal models, particularly in transgenic mice models, led to a fundamental understanding of the functional role of activated oncogenes and inactivated tumor suppressor genes as well as of stress-response-programs as apoptosis or cellular senescence in human diffuse large B-cell lymphoma (DLBCL). However, due to species differences, these models can only recapitulate parts of the temporospatial genetic complexity of human lymphoma pathogenesis. In order to recapitulate human biological systems more closely, sophisticated small-animal models are acutely required. Systemic-orthotope propagation of primary patient-derived tumor-material in immunodeficient mice (so-called »Patient-derived Xenografts [PDX]«) is one solution. These DLBCL cases comprise our in-house patients who received standard therapy (R CHO[E]P) as well as patients enrolled in our active recruiting investigator-initiated trial »ImbruVeRCHOP« (PI/LKP: Clemens A. Schmitt). In this multi-center first-line trial, high-risk elderly DLBCL patients receive two additional small compounds (the BTK inhibitor Ibrutinib and the proteasome blocker Bortezomib) as an extension to the R-CHOP backbone, intended to double-target the pivotal B-cell receptor (BCR)/NF-B axis, at both proximal (BTK) and distal (IB [an endogenous NF-B inhibitor]-degrading proteasome) ends. Comparable patients, but not fitting the »ImbruVeRCHOP« trial criteria are recruited into our local Charité ›Match point‹ clinical registry as control cohort receiving standard therapy. To test whether our PDX-DLBCL models recapitulate treatment response and long-term outcome of individual DLBCL cases observed in the clinic, the same chemotherapy received by the patient is administered to the corresponding PDX model. Individual components of the »ImbruVeRCHOP« protocol are applied as a single-agent or multi-drug-combined therapies to unveil the unique dynamic and outcome attributed to each drug. Tumor materials have been collected as tumor chunk before treatment, as intra-vital punch biopsies 24 hours after treatment exposure to assess acute drug responses, and at relapse. The samples will then be subjected to targeted re-sequencing to investigate therapy-driven clonal evolution and development of resistance. A long-term aim of this clinical-translational project is to use this PDX-DLBCL-models for prediction of individual therapy response to one or a combination of new targeted-therapies, biologicals and antibodies.

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Fields of Research
› Musician's Dystonia
› Electrical Cerebellar Stimulation

Characterization of Cerebellar Function in Musician's Dystonia Patients and its Electrical Modulation Capability

Musician's dystonia (MD) is a task-specific form of focal dystonia that manifests itself as a loss of voluntary motor control when playing an instrument. Up to 1-2% of professional musicians are affected, and in many cases, the disorder terminates the professional career. The underlying pathophysiology is not fully understood. However, recent findings suggest a cerebellar contribution to the disease. For instance, cerebellar activity is reduced in other forms of isolated dystonia like cervical dystonia leading to an abnormal excitability of the cortex. Therefore, the study aims at investigating the cerebellar influence to the pathomechanism of MD. We hypothesize that reinforcement of the cerebellar output will lead to a clinical improvement of symptoms. In order to modulate the cerebellar activity, we will apply oscillating transcranial direct current (o-tDCS), alternating current (tACS) and placebo stimulation to the cerebellum on three different days. A cohort of 15 pianists with focal hand dystonia will be compared to a control group of 15 healthy pianists to take in to account sensorimotor adaptation due to prior musical training. Electroencephalographical measurements before and after the intervention will help to explore the stimulations' effect on different frequency bands of the cortex. Clinical outcome will be measured via MIDI recordings of the piano playing, scoring parameters like the variability of inter-onset intervals, velocity and error rate. The findings of this study may have considerable consequences for the therapeutic treatment of MD patients.

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Fields of Research
› Complement system
› Age-related macular degeneration
› Retinal pigment epithelium

Influence of AMD Patients' Sera on ARPE-19 Cells

Being responsible for more than 40 % of all cases, age-related macular degeneration is the leading cause for blindness in industrial countries. AMD is a neurodegenerative disease, caused by environmental factors, such as age, smoking or obesity as well as individual genetic risk factors. A strong association was found for polymorphism on the complement factor H (CFH)- gene and age- related maculopathy susceptibility 2 (ARMS2)- gene. Several studies already revealed the involvement of the complement system in the local AMD pathogenesis and progression, mainly regarding the retinal pigment epithelium (RPE). It is already known that AMD patients' sera are characterized by an altered serum complement level. However, it is still unknown how far this elevated levels of serum complement and increased activity of the alternative complement pathway influence the RPE. Genewsky et al. revealed that active complement components don't induce a direct cell lysis in the RPE but a deficient regulation of cell functions. This study aims to gain new insights into the involvement of the complement system in the cellular pathophysiological processes of the RPE in the context of AMD using Ca2+ imaging and gene expression analysis. As a source for active complement components sera of AMD patients with known genotype of CFH and ARMS-2 are used.

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› Borderline Personality Disorder
› Posttraumatic stress disorder
› Social cognition
› Oxytocin

Impact of the Oxytocin System on Intrusive Symptoms after Analog Trauma: A Model to Study Posttraumatic Stress Disorder

Intrusive symptoms, i.e. aversive, unwanted memories of trauma, are core symptoms of post-traumatic stress disorder (PTSD). Yet, little is known about biological factors leading to the formation of these intrusive symptoms. Oxytocin seems to play a key role in the onset of PTSD. Previous studies point to anxiolytic effects of oxytocin, e.g. via the hypothalamus-pituitary-adrenal axis. Recent studies postulate a social salience hypothesis, which states that the oxytocin effect is dependent on context and person variables. In our previous study, the administration of intranasal oxytocin imminently before an analogue trauma lead to an increase in intrusive symptoms in healthy women. This raises the question how oxytocin may influence intrusive symptoms in a non-negative context, and whether the timing (acquisition vs. consolidation of a memory) of oxytocin administration influences its effect on intrusive symptoms. In this experimental, randomized, double-blind, placebo-controlled trial, 220 healthy women aged 18-45 years will either receive 24 I.U. intranasal oxytocin or placebo right after watching a film sequence showing physical and sexual violence, which has been frequently used as a trauma film paradigm in previous studies. Primary outcome is hereby the number of intrusive symptoms in the following 4 days.

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› Retinal Degeneration
› Neuroinflammation
› Radiation Retinopathy

The Fractalkine Receptor CX3CR1 and its Role in the Pathogenesis of Choroidal Neovascularizations and Radiation-Induced Retinopathy

Vascular disorders of the retina with choroidal neovascularisations are one of the most common causes of blindness. The aim of this project is to investigate the role of inflammation in the pathogenesis of CNV and to identify a link between vascular proliferation and neuroretinal degeneration, which allows a treatment optimization of vascular diseases of the retina. Our hypothesis is that a local or systemic cellular immune response precedes the development of a CNV. To test this hypothesis we examine the Migration of Leukocytes and development of a CNV in the fractalkine receptor (CX3CR1) mouse as the receptor is involved in the migration of immune cells.

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› Tumor Immunology
› Translational Medicine

Targeting the SUMO Pathway as a Novel Tumor Therapy – Effects on Hematopoiesis and the Immune System

Covalent ligation of the small ubiquitin-like modifier (SUMO1, SUMO2 or SUMO3) moiety to target proteins (SUMOylation) belongs to the group of post-translational protein modifications that control the localization, stability and activity of target proteins. Importantly, various components of the SUMO core machinery are upregulated in cancer. Augmented SUMOylation is associated with overexpression of the onocogene MYC and both hyperSUMOylation and MYC expression are linked to aggressive cancer phenotypes and thus to poor prognosis. Addressing possibilities of taking advantage of MYC-induced cancer cell vulnerabilities like SUMOylation could be exploited for future clinical use. We here report that pharmacological SUMO inhibition leads to a complete eradication of the tumor cell population in a MYC-induced lymphoma model in vivo, concluding that hyperSUMOylation is crucial for proliferation of MYC-induced lymphoma and therefore presents a therapeutic vulnerability in B cell lymphoma treatment. Surprised by the massive tumor killing efficacy of SUMOi we want to focus on associated mechanisms how hyperSUMOylation leads to a survival advantage in tumor cells. RNA expression profiling linked the hyper-SUMOylated state to a downregulation of the antigen presenting machinery in B cell lymphoma. In this project we aim at deepening the understanding about the role of SUMOylation in the tumor's immune evasion strategy to depict SUMO inhibition as a potential therapeutic option to overcome the immune escape phenomenon in lymphomas.

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› Acute coronary syndrome
› Atherosclerosis
› Immunology

The Role of Neutrophil Granulocytes and Neutrophil Extracellular Traps in Distinct Pathophysiological Mechanisms of Acute Coronary Syndrome

One of the most important acute manifestations of Cardiovascular Disease (CVD) is acute coronary syndrome (ACS). Recent studies brought about the understanding of plaque rupture (PR) and plaque erosion (PE) as two distinct pathophysiological processes triggering thrombotic vascular occlusion. It was demonstrated that in cases of PR a preexisting thin-capped fibroatheroma (TCFA) ruptures, exposing an underlying necrotic core and lipid-rich, thrombogenic material to the blood stream, thus leading way to thrombus formation and arterial occlusion. On the other hand, PE is categorized as endothelial deterioration leading to thrombus formation, but with a thick fibrous cap, reinforced with smooth muscle cells underneath. Indeed, investigators now support the idea that these two processes might have different underlying mechanisms. Numerous studies demonstrated that inflammation plays an important role in CVD with promotion and resolution of innate and adaptive immune responses in a delicate balance. However, novel pathways and mechanisms in the ischemic damaged heart remain to be discovered. Interestingly, neutrophil granulocytes seem to play a key role in the inflammatory component of plaque formation and acute complications of atherosclerosis. In recent past a distinct ability of neutrophil granulocytes was discovered: by formation of neutrophil extracellular traps (NETs) these cells release a variety of intracellular components including proteins from azurophilic granules and chromatin, thereby forming extracellular matrices that not only serve as physical barriers, entrapping pathogens, but also have antimicrobial properties. Our study will define for the first time the role of neutrophil granulocytes and neutrophil extracellular traps (NETs) for different pathophysiological mechanisms in acute coronary syndrome. Hence, we will provide deeper mechanistic insight into inflammatory processes triggering acute myocardial infarction and determine the relevance of NET formation as a potential therapeutic target for human ACS patients.

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› Pancreas adenocarcinoma (PDAC)
› Genomics
› Gene editing (CRISPR/Cas9)
› Carcinogenesis

Derivation of Normal Pancreatic Duct Cells from Human Primary Tissue and Their Genetic Modification in Vitro

Pancreatic adenocarcinoma (PDAC) is an aggressive disease with overall poor survival rates. PDAC growth and dissemination is preceded by specific driver gene alterations present already in pancreatic precursor lesions. Current view suggests, that early oncogenic activation of KRAS is followed by inactivation of tumor suppressors (CDKN2A, TP53, SMAD4) in higher grade lesions. The central aim of this study is to model carcinogenesis in vitro and derive novel immortalized pancreatic duct cell lines with well-defined genetic alterations. This should improve future experimental investigation of pancreatic precursor lesions in vitro and will guide us to better understand the specific roles of pancreatic driver genes. Curative treatment options for pancreatic adenocarcinoma rely on the combination of surgery and (neo-)adjuvant chemoradiation. Relatively low efficiency of chemotherapeutics warrants efforts to find molecular targets in terms of precision medicine. To date, all main driver genes have not been shown druggable. As such, we need to understand when and how dysplastic cells manifest traits of uncontrolled proliferation, invasion, metastasis and other hallmark functions, to define biologically relevant targets. Suitable human in vitro models together with modern genome engineering techniques may generate new strategies for targeted therapies.

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› Interventional Oncology
› Quantitative MR Imaging
› Machine Learning

Development of Multipurpose Polymer-Microspheres for the Use of Catheter-Based Embolization

»... the vascular catheter can be more than a tool for passive means for diagnostic observations: used with imagination, it can become an important surgical instrument.« Dr. Charles T. Dotter Catheter-based embolizations form a key treatment pillar in the field of interventional radiology. The broad range of clinical indications reaches from active arterial bleedings to state-of-the-art tumor therapies. Generally, an embolic agent is administered into the target vessel via a previously placed catheter, hence occluding the vessel. In this context, the treatment of primary and metastatic liver tumors take a special role. Transarterial Chemoembolization (TACE) is a minimally invasive procedure performed to restrict a tumor's blood supply while simultaneously locally treating the tumor with high doses of chemotherapeutic drugs. To date, the targeted tumor-feeding arteries are embolized permanently making it impossible to use for re-interventions, while also triggering tumor-neoangiogenesis. This leads to a therapeutic dilemma. By developing multi-purpose microspheres that (i) can be used for intra-arterial embolization, (ii) can be loaded with chemotherapeutics and (iii) are degradable, hence offering the option of temporary embolization, we aim to solve this problem. In extensive in-vitro tests, we believe to have identified two materials deriving from gelatine and PMMA, that meet the above-mentioned requirements for an ideal embolization material. Within the next two years we will in-vivo test both newly developed embolization materials in several embolization- and tumor-models and hope to add to the development of new and advanced clinical treatment options.

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Fields of Research
› Dementia due to Alzheimers Disease
› Mild Cognitive Impairment
› MRI-Imaging

High Resolution MR-Elastography of the Hippocampus in Patients with Alzheimer's Disease

Alzheimer's disease (AD), the most common cause of dementia, is marked by progressive neurodegenerative changes of brain tissue. One of the regions to be affected early in the course of the disease is the hippocampus. Current diagnostic methods (structural MRI, PET-imaging, and analysis of cerebrospinal fluid) are either invasive or detect changes only late in the course of the disease. The search for non-invasive methods for early diagnosis of the AD is ongoing. MR elastography is a non-invasive technique that measures the elasticity of brain tissue. It has been hypothesized that tissue elasticity is a surrogate parameter for microstructural architecture and therefore an interesting parameter to investigate structural changes of brain tissue in the course of neurodegenerative diseases such as the AD. Whole brain MR elastography has been demonstrated to detect decreased overall brain stiffness in AD compared to healthy controls. In this project, we investigate whether multifrequency MR elastography (MMRE) can detect differences in the elasticity of the hippocampus between patients with clinical diagnosis of the AD and healthy controls. This is a pilot study including patients with clinical diagnosis of AD and age- and sex-matched healthy controls. To quantify memory performance, all study participants undergo standardized neuropsychological test batteries (MMSE and CERAD). Further, all study participants undergo a structural MRI-Scan (including T1-, T2- and DTI-sequence) and the MMRE (single-shot EPI-based MRE sequence). The elasticity parameters of the Hippocampus region and a reference region are extracted from the images and compared between the two groups. We hypothesize that patients with AD have lower elasticity measures in the hippocampal region compared to healthy controls. If these hypotheses can be confirmed, the detection of decreased hippocampal stiffness may become a biomarker for early diagnosis and progression monitoring in the AD.

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Fields of Research
› Complement activation
› Acute coronary syndrome

Complement Activation in Acute Coronary Syndrome

In this project, mechanisms and effects of activated complement system in acute coronary syndrome (ACS) will be investigated. It is assumed that intracoronary complement activation is partly responsible for post-ischemic damage of endothelium and myocardium in ACS. In the first phase of this project intracoronary blood from ACS patients will be obtained and compared to healthy control groups in terms of included complement proteins, analphylatoxins as well as further proinflammatory cytokines. Thus, an encompassed knowledge about relevant key proteins of intracoronary complement activation will be achieved. In the second phase cell culture conditions will provide endothelial cell responses under hypoxia after ACS patient plasma stimulation. Cell vitality, changes in expression of cell adhesion proteins and membrane associated complement regulators will be explored. The third phase will determine the effects of pharmacological complement inhibition by use of cell cultures. In line with the second phase, experiments will be performed again. However, a C1 esterase inhibitor will be applied and mutually compared. Finally, this study will investigate which anaphylatoxins accumulate due to ACS and which complement inhibiting properties can be acquired by coronary endothelial cells. Effects of pharmacological complement inhibition on endothelial cells in ACS will be determined.

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Fields of Research
› Fracture Healing and Traumatic Brain Injury
› Polytrauma

Clinical Study on the Phenomenon of Improved Fracture Healing After Traumatic Brain Injury

Although the development of modern osteosynthesis techniques within the last 20 years has vastly improved the operative outcome after fracture treatment, we can still observe fracture non-unions in up to 10%. Non-unions have a tremendously negative effect on the quality of life of patients and generate exuberant health-economic costs. Previous approaches aimed at improving bone healing biologically were only of mediocre success. This is surprising because bone is one of only two organs in humans that can regenerate itself without scar-tissue formation. Patients with long-bone fractures can demonstrate with improved fracture healing and significantly increased callus formation if they suffer from an additional traumatic brain injury (TBI). This is remarkable because increasing degrees of trauma severity can negatively influence bone regeneration. Although the phenomenon of increased callus formation after TBI has long been known to the clinician since the 19th century, the pathological pathways which are triggered after traumatic damage to the brain and accelerate bone healing could not be identified yet. Our research group could already establish a highly standardized and reproducible combined trauma model for mice in which we could reproduce this phenomenon. Furthermore, we could demonstrate that the osteoinductive effect after TBI is dependent on intact leptin signaling. On the basis of the results from our screening studies on mice we hypothesize that changes in energy homeostasis and immunological cellular (CD4/CD8) and humoral (IL-1, IL-6, TNF α) responses after TBI are responsible for the improved fracture healing. In our clinical study, we include patients who are admitted to the emergency room of our trauma department and demonstrate with an isolated long-bone shaft fracture, an isolated TBI or the combination of both injuries. Blood samples and X-rays are taken from the patients in a specific timely manner in order to confirm the results from our studies on mice.

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Fields of Research
› Lymphovascular Medicine
› Genetics
› Imaging
› Histopathology

Lightsheet Microscopy-Based 3D-Histology of Human Tissue Samples

Over the last years, there was a lot of progress in identifying genes, which cause primary lymphedema in humans, but how genetic abnormalities cause lymphedema at the cellular level is still unknown. This lack of mechanistic insight is associated with the absence of suitable microscopic imaging techniques for the visualization of the vasculature as classical 2-dimensional histology is not sufficient to understand the complex lymphatic vessel architecture. This has been one of the major contributing factors to the lack of detailed knowledge of the pathogenesis of lymphedema. To understand the underlying vascular alteration causing lymphedema in more detail and to overcome the limitations of classical histology, we have developed innovative and optimized immunofluorescence staining protocols for entire tissue biopsies from patients suffering from lymphedema. Following immunofluorescence staining, we apply VIPAR (volume information-based histopathological analysis by 3D-reconstruction and data extraction), a novel diagnostic tool for vascular diseases, on tissue biopsies from lymphedema patients. ViPAR, a lightsheet microscopy-based approach for optical of entire tissue biopsies, is based on digital 3-dimensional reconstruction and allows the visualization of the entire vascular network. Using automated data extraction and analysis algorithms, the underlying histology is described and quantified in 3-dimensional space. This knowledge on the underlying pathology and alterations associated with the disease is a prerequisite for future pharmacological interventions as it supports clinicians' decision-making by improved patient stratification. In summary, this approach for 3D-histology allows 3-dimensional visualization of the entire blood and lymphatic vasculature in lymphedema patients and therefore facilitate a deep-phenotyping of patients' tissue, which is not possible by using classical methods, e.g. 2D-histology. By using state-of-the-art imaging techniques, this study will expand our current knowledge on primary lymphedema significantly and will set the basis for new treatment regimens.

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Fields of Research
› Leukemogenesis
› Acute Myeloid Leukemia
› Single-Cell Analysis

From Clonal Hematopoiesis to Relapsing Leukemia: Tracing the Roots of AML on Single Cell Level

Acute Myeloid Leukemia (AML) – the most common type of acute leukemia in adults – remains a demanding challenge for researchers and physicians all over the world with a 5-year survival rate of less than 30%. It originates from early pre-leukemic hematopoietic stem cells which gain additional leukemia-defining mutations over time. In some patients, these pre-leukemic lesions persist in remission after intensive chemotherapy. Recent studies have shown that the persistence of pre-leukemic lesions in these patients associates with a higher risk of disease relapse. Managing disease recurrence embodies a major therapeutic challenge as relapsed AML is accompanied by the high prevalence of therapy resistance. From a molecular point of view, this can be explained by a significant genetic evolution of the tumor genome. In the past few years, multiple next-generation sequencing (NGS) studies have already paved the way for the revelation of the genetic heterogeneity of AML. However, by using bulk DNA, the obtained findings by NGS methods display only an average molecular image of a diverse cell population. In contrast, single-cell DNA genotyping now allows for the revelation of the clonal evolution of the tumor genome and a more precise detection of intercellular variety. Using a combination of whole-exome sequencing (WES) and single-cell DNA genotyping, I aim to unravel the phylogeny of AML and trace the clonal evolution from diagnosis to relapse. Therefore, I will analyze bone marrow and peripheral blood samples from a target cohort of 30 AML patients. WES will be applied to identify tumor-specific genetic target alterations. For Fluidigm-based targeted single-cell genotyping defined flow-sorted stem cell fractions will be used. By means of bioinformatic and statistical analysis, an individual phylogenetic tree will be created for each patient. Hereby, I aim to identify novel therapeutic targets and thus improve the therapeutic management of AML.

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› Postoperative Ileus
› Small Bowel Obstruction

Effect of Preoperative Selective Decontamination of the Digestive Tract (SDD) and Mechanical Bowel Preparation (MBP) on Postoperative Ileus in Mice

The phenomenon of postoperative ileus (POI) frequently occurs after abdominal surgical interventions. Consequences of POI are delayed ingestion, prolonged enteral nutrition, pain and sustained hospitalization. In single cases, POI-associated vomiting, followed by aspiration can lead to life-threatening situations. Consequently, the incidence of POI is highly expensive, due to prolonged treatment and patient's inability to work. Although several aspects of POI pathophysiology are described, intervention procedures or therapies are not effective enough to prevent or inhibit POI completely, so far. Especially, in case of an advanced state, therapeutically intervention is difficult. Therefore, an early intervention during the initial phase seems more promising. In the 1970´s the combination of mechanical bowel preparation (MBP) and selective decontamination of the digestive tract (SDD) has been routine practice in colorectal surgery. After research indicating that MBP may be harmful, it has been completely abandoned. Since this decade the discussion came to a renaissance. In 2015 a large retrospective study showed that the combination of MBP with SDD reduces POI in patients. Up to this point, there is a lack of experimental data concerning this matter, especially regarding POI. We induce postoperative ileus in mice after laparotomy and systemic manipulation of the intestine. Afterward, the intestinal barrier dysfunction is being tested in Ussing-chambers and by immunohistochemistry. Therefore the aim of our work is to determine whether intestinal permeability and leukocyte infiltration of the intestinal wall decrease during SDD and/or MBP in POI in mice.

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› Regenerative Medicine/Oncology

Decellularized Human Liver Slices as a Three-Dimensional Platform to Generate In Vitro Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (iCCA) is the second most common tumor entity of the liver. The only curative treatment options for patients suffering from an iCCA is surgical resection. iCCA show a high rate of intrahepatic recurrence, which was found to be up to 60 %. For patients with recurrence, primary metastatic cancer, lymph node metastasis or R1 resection, chemotherapy or local ablative therapies are the remaining treatment options. Unfortunately, these therapeutic concepts have poor response rates. Considering this there is the need to explore new therapeutic options: In vitro models are essential tools to investigate tumor biology and the effect of certain pharmaceuticals. Despite iCCA cell lines and 2D primary cell cultures gave insights into the biology of these tumors, they have some important drawbacks like the poor translational value due to the artificial culture conditions. New approaches for in vitro studies are the formation of 3D spheroids and organoids. Nevertheless, these approaches have also shown a selection of tumor cells and tumor-organoids still showed differences in mutations-patterns in comparison to native tumor tissue. In a recently published study, the value of decellularized rat lung and liver tissue on the in vitro formation of colorectal metastasis has been described. We hypothesize that decellularized human liver tissue will promote the in vitro tumor formation of iCCA tumors with a better preservation of tumor microenvironment, genetic mutation pattern and therefore will reflect a better clinical correlation for adjuvant treatments in comparison to 2D primary culture and tumor organoids.

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Fields of Research
› GPCR biology
› Intracellular signaling
› Glomerular disease of the kidney

Involvement of Functional Antibodies Targeting GPCRs in Glomerular Disease of Native and Transplant Kidneys

Our group has pioneered the concept that functional antibodies targeting G-protein coupled receptors (GPCRs) including the angiotensin type 1 receptor (AT1R) and endothelin type A receptor (ETAR) induce severe pathologies in autoimmune disease and organ transplants independent of HLA recognition mechanisms (Dragun D et al., N Engl J Med. 2005). My project focuses on transplant glomerulopathy as a leading chronic lesion in kidney transplants responsible for chronic dysfunction and late graft loss. The mechanisms involved in development of transplant glomerulopathy remain largely unknown. Significant phenotypic overlap in pathohistological description with native kidney disease entities such as membranoproliferative glomerulonephritis, thrombotic microangiopathy, focal segmental glomerulosclerosis, and lupus nephritis make the diagnosis difficult, yet may suggest common pathophysiologic mechanisms. We expect to link epitope recognition with signaling and effector functions of two important GPCRs mediating severe pathologies of transplant and native kidneys. This combined epidemiologic and experimental approach should help to provide the template for future analysis of novel antibody candidates. Moreover, a yeast model, modified to express human AT1- or ETA-receptors, where growth is linked to receptor activation, may well serve for screening of mimotopes aiming to attenuate antibody mediated actions. Aim is to finalize screening of independent cohorts with glomerular disease of native kidneys and transplants with our assays detecting antibodies targeting AT1- and ETA-receptors. Functionality of antibody binding will be studied in the yeast model using native or mutated receptors. Differences and similarities of antibody-receptor interaction should help to identify various conformational epitopes and help explain disease heterogeneity.

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Fields of Research
› Computed Tomography
› Magnetic Resonance Imaging

Iterative Reconstruction – Dose and Quality Optimized Computed Tomography

Various novel technical solutions are subsumed under the term of iterative reconstruction (IR). Its goal is the efficient reduction of image noise and radiation dose in computed tomography (CT). The objective of this project is to investigate whether iterative reconstruction allows for an effective reduction of dose without having to accept a significant loss of image quality. The use of first-generation iterative image reconstruction techniques (ASIR) allows for a dose reduction of about one third compared to conventional filtered back projection (FBP) image reconstruction while maintaining image quality. Particularly young patients who often receive multiple follow-up CT exams may benefit from this reduction. To define more individualized and dose optimized CT examination protocols, additional patient populations need to be studied. In a next step, the previous research on radiation dose reduction and image optimization is to be continued and expanded in studies at the institute's own research CT. It would be a milestone in CT diagnostic imaging if the expected dose values in the sub-millisievert range together with a corresponding good image quality turn out to be realistic.

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› Neurology
› Radiology
› Cerebrovascular disease

Validation of a Non-Invasive, Automated Perfusion MRI Method in Stroke Patients

Cerebrovascular diseases and stroke are some of the leading causes of morbidity and mortality worldwide. Understanding which pathophysiological mechanisms are responsible for perpetuating tissue damage in individual patients can help clinicians make better decisions about how to treat these patients. Much of this information is, however, unavailable to clinicians in routine practice because the methods used to assess these pathophysiological phenomena are inconvenient, unreliable, or inaccessible. As a result, more than two-thirds of stroke patients are not eligible for crucial treatments in the very early stages of the disease, where the benefit of these treatments is highest. My research focuses on developing and validating neuroimaging techniques that are easier for clinicians to access, use, and interpret. The aim is to use these techniques to provide clinicians with individualized and readily interpretable information on stroke pathophysiology using efficient and convenient methods, which could potentially improve how, and how many, strokes are treated.

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Fields of Research
› Parkinson's Disease
› Deep Brain Stimulation
› Motor Control

Network Modulation of Motor Inhibition in Parkinson's Disease

Subthalamic deep brain stimulation (DBS) is a well-established and effective treatment option for patients with Parkinson's disease (PD) leading to better motor performance and quality of life. A common side effect of dopaminergic medication consists in involuntary movements, so-called dyskinesia. Dyskinesia can also be evoked by high stimulation intensities and lesioning of the subthalamic nucleus (STN). Taken together, these observations suggest a major role of the STN in motor inhibition, with special emphasis on control of involuntary movements. In this study, we will investigate the neuronal network of motor inhibition in PD patients and its modulation by subthalamic DBS. We hypothesize that subthalamic DBS facilitates the initiation of voluntary movements while impeding their termination. This may rely on the modulation of an inhibitory network between the STN and other brain regions that depends on the exact connectivity profile at the DBS-electrode position. With the help of a behavioural paradigm that a cohort of PD patients with subthalamic DBS will perform ON and OFF stimulation, the differential effect of DBS on movement termination will be quantified across patients. In a second step, the patient-specific connectivity profile of DBS-electrode localization will be reconstructed and related to the DBS-related effect on movement termination. The results of this study can be integrated in a broader goal of developing a personalized DBS with optimal efficacy / side effects profile. With a similar approach, a previous study of our group was able to predict a »sweet spot« for DBS with best clinical outcome. The localization of an important motor side effect of DBS would further refine this optimal stimulation spot. Given that new types of DBS electrodes allow a precise and directional current steering, this may lead to a direct clinical benefit for patients with subthalamic DBS.

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Fields of Research
› Intravital Microscopy and Fluorescence Lifetime Microscopy
› Neuromuscular Diseases

Oxidative Stress in Muscle Diseases

Oxidative stress is a major factor in the progression of muscle diseases, proving to affect cellular signaling pathways, enzyme expression, membrane stability and cellular regeneration. Conclusions about the origin of oxidative stress are currently drawn indirectly on the presence of free radicals, their oxidation products and expression subunits of the enzymes involved. With the establishment of NAD(P)H-fluorescence lifetime microscopy in chronic neuroinflammation we were able to for the first time monitor the genesis of oxidative stress intravitally, in real time and without influencing the system through staining or fixation by measuring the activity of NADPH-oxidase, the main source of reactive oxygen species (Mossakowski et al, Acta Neuropathologica 2015). Instituting NAD(P)H-fluorescence lifetime microscopy in muscle tissue will complement the hitherto existing means of diagnostics and pathophysiological research in neuromuscular disease, adding a new metabolic monitoring system that, in the long run, might be used to diagnose oxidative shifts in muscle tissue even before the appearance of histopathological changes. The method can potentially be used to monitor disease-modifying therapies by directly detecting the dynamics and impact of antioxidants on the ROS production in muscle tissue. The aim of this work is thus to establish NAD(P)H-fluorescence lifetime microscopy, previously used in other tissues and cell types, in muscle tissue and to ensure a valid transfer between intravital and ex vivo measurements. We use a custom-built multiphoton laser microscope with a time-correlated single photon counter as part of the intravital microscopy network JIMI (German Rheumatism Research Center, Max Delbrück Center and Hans Knoell Institute) and cooperate with Dr. rer. nat. Raluca Niesner, group leader of Biophysical Analytics at the German Rheumatism Research Center.

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› Stem Cell Transplantation
› Graft-Versus-Host Disease
› Extracellular Vesicles

Preclinical Evaluation of Mesenchymal Stromal Cell-Derived Exosomes for GvHD-Therapy

Hematopoietic stem cell transplantation (HSCT) is currently the only therapeutic option for a number of malignant and nonmalignant diseases. Graft-versus-host disease (GvHD) is the most common complication, mainly mediated by donor T lymphocytes attacking host cells and causing multiorgan damage especially affecting the skin, liver and intestines. A severe GvHD is associated with 90% patient mortality. Steroids are the standard first-line therapy. Cell-based second-line therapy with MSCs is standard treatment for steroid-refractory GvHD cases since ten years, and administering MSCs stimulates a response and improves 2-year survival in ~50% of these patients. In the last years it was demonstrated that MSCs do not engraft in the patients, what lead tot he speculation that soluble factors secreted by the administered MSCs may be driving patient response. This was supported by a recent case report of one patient with steroid-refractory GvHD that showed substantial improvement after administration of exosome-enriched MSC supernatant. Exosomes are 70-140 nm microvesicles secreted by cells that contain a variety of biomolecules, and are thought to function as intercellular messengers. This project will establish a patient-derived exosome characterization pipeline that assesses biomolecular content via RNA sequencing (RNA-Seq) and allows functional in vitro testing via T-cell proliferation assays to qualitatively and quantitatively explore the immunemodulatory potential. Furthermore, exosomes from different donors will be compared, and exosomes from patients will be associated with their clinical course in terms of GvHD occurrence to predict associations with specific exosome contents.

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› Osteology

Evaluation of the Validity of New Methods for the Assessment of Bone Quality Using Vertebral Biopsies

In osteroporosis, changes in bone composition and structure result in reduced bone stability. In orthopedic surgery, such a »weak« bony bearing represents a significant challenge intraoperatively and can have serious consequences for affected patients due to resulting implant failure. To avoid such complications, preoperative diagnostics are necessary to allow the timely initiation of adequate therapeutic measures (e.g., cement augmentation). However, reliable methods that allow preoperative prediction of intraoperative findings are still lacking. The current clinical standard for the assessment of bone quality is Dual Energy X-ray Absorptiometry (DXA), which measures the mineralization density of bone using 2D X-ray projections. In a previous study, we demonstrated that DXA is unsuitable for assessing bone quality at the lumbar spine. In this research project, we therefore want to examine whether the alternative methods Trabecular Bone Score (TBS) or Bone Material Strength index (BMSi) reflect the actual bone quality at the lumbar spine determined on the basis of vertebral body biopsies and whether they are suitable for assessing the risk of material loosening after spinal surgery.

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› Hematologic malignancies, tumor immunology, single cell sequencing, clonal evolution

Immunologic Biomarkers and Therapeutic Targets in Rectal Cancer

Early disease and relapse detection are critical for colorectal cancer prognosis. However, the reliable identification of relapse can be challenging, especially if the suspected tumorous lesions are small in size and/or not easily accessible, underlining the need for highly specific and sensitive biomarkers. Most of the established tumor markers are not cancer-specific and show poor sensitivity for relapse detection varying between 15 and 70%. There is increasing evidence that tumor-infiltrating (immune) cells are critical for disease development, spreading, and patient survival and frequencies of tumor-infiltrating lymphocytes (TILs) correlate with the clinical outcome regardless of the tumor stage. Our group could show that colorectal cancer is infiltrated with T lymphocytes of a highly specialized T cell receptor (TCR) repertoire and distinct functions suggesting a tumor-driven T cell reaction. Therefore, technologies for cancer (-relapse) detection could significantly benefit from the inclusion of disease-associated immune measurements. This study will result in a phenotypic, functional, and molecular immunology approach to the human immune system in rectal cancer. Emerging technologies including cytometry by time-of-flight (CyTOF) and single cell next-generation sequencing (NGS) will help to detect cancer-associated immune responses as a highly specific and sensitive immune-biomarker. We hypothesize that unique rectal cancer-associated, clonally related T lymphocytes are detectable in the tumor tissue and peripheral blood of patients and that their frequencies correlate with disease burden which makes them useful as immune biomarkers for early relapse detection. Selectively expanded T cell clones and phenotypes can be quantified and possibly used as highly sensitive and specific cancer-associated markers for therapy monitoring and early relapse detection.

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› Innate Immunity
› Helicobacter Pylori
› Signal Transduction

Characterization of a Pro-Inflammatory Pathway Triggered by Bacterial Sugar Molecule

Activation of the transcription factor NF-κB is a linchpin in the initiation of an inflammatory process in cells of the adaptive and innate immune response. Chronic or inadequate activation can lead to deleterious outcomes like the development of cancer. In 2015, a bacterial sugar, D-glycero-beta-D-manno-heptose 1,7-bisphosphate (HBP), an intermediate metabolite of LPS synthesis, was identified as novel Pathogen Associated Molecular Pattern (PAMP) inducing NF-κB activation in epithelial cells. In a Helicobacter pylori (H. pylori) infection model we have recently identified a HBP triggered NF-κb activating signaling axis. We demonstrated that HBP is delivered via H. pylori's Type 4 Secretion System to the host cell. Here ALPK1 and TIFA act as indispensable host cell factors for the early activation of NF-κB. This renders ALPK1 a central infection specific actor in activating a pro-inflammatory signaling pathway. The general importance of this pathway is underlined by the fact that HBP has already been identified as a pro-inflammatory factor in a row of infections with gramnegative bacteria making this a likely candidate for induction of a pro-inflammatory response in a multitude of infectious settings. Yet the exact function of the ALPK1 in the activation of this pathway is not yet understood. Aim of this project is to get a deeper insight in this novel-signaling axis, understanding the way of induction and the regulatory mechanisms it induces and additionally deciphering how HBP is sensed in infected cells. Finally, with this project we want to understand the impact of ALPK1 on the outcome of an infection in vivo.

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› Migraine
› Sex hormones

Plasma CGRP Levels in Patients with Migraine and Endometriosis

Migraine and endometriosis are two of the most prevalent disorders in women with a significant burden of disease, high socioeconomic costs, and a relevant impairment of quality of life. Epidemiological studies report a solid comorbidity between migraine and endometriosis. From adolescence onwards, women with endometriosis have a two- to threefold higher risk of suffering from migraine compared to the general female population, and vice versa, patients with migraine have a twice higher probability to develop endometriosis. Fluctuations in ovarian sex hormones modulate the course of both diseases and severe pain attacks occur often during the perimenstrual period. Previous research pointed to a possible common etiological background for migraine and endometriosis. Shared pathophysiological mechanisms include impaired regulation of inflammatory signaling pathways and neurotransmitters such as Calcitonin Gene-Related Peptide (CGRP). While acute migraine is clearly linked to CGRP release from trigeminal afferent neurons during attacks, the evidence for a role of CGRP in endometriosis pain is limited. The release of CGRP seems to have an impact on the neurogenic inflammatory reaction in this endometriosis tissue and might be also involved in proliferation and growth of endometriotic cells. Despite these findings, CGRP and CGRP-related mechanisms have not been studied to date in vivo in women with endometriosis.In the current project, we aim to analyze CGRP plasma concentrations in patients with migraine and endometriosis, compared to patients with migraine only, endometriosis only, and healthy controls. For each group, we will compare CGRP concentrations during menstruation and in the intermenstrual period. It is our hypothesis that CGRP levels increase during menstruation with most pronounced changes in women with the comorbidity of migraine and endometriosis.

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› Renal Cell Carcinoma

Prediction of Primary Resistance to First-Line Treatment with the Tyrosine Kinase Inhibitor Sunitinib in Renal Cell Carcinoma Specimens by MiRNA Profiles

The introduction of targeted therapy agents has significantly improved the overall survival (OS) of patients with metastatic renal cell carcinoma (mRCC). The VEGF-inhibitor sunitinib (sun) is considered the standard of care for the first-line treatment of these patients, however, the tumor response to this drug at first evaluation is crucial. Patients with a primary resistance inherit a poor overall survival. A reliable prediction of the primary resistance to sun therapy could be helpful to avoid useless treatment trials of patients with extremely expensive drugs and to save time to select other therapeutic options. So far, there has been no approved biomarker in form of a companion diagnostic test to correctly predict the response to targeted therapy in these patients. In this regard, microRNAs (miRNAs, miRs) as small, non-protein coding transcripts could be considered as suitable biomarkers because of their important role as posttranscriptional regu-lators in all network processes of carcinogenesis and metastasis. So, the aims of this study were (a) to identify typical microRNA profiles in nephrectomy specimens from the two groups of mRCC patients under sunitinib treatment, (b) to explore under high statistical power the most discriminative microRNAs between the two patient groups as predictive biomarkers of primary resistance and (c) to validate the data quantified by reverse transcription quantitative polymerase chain reaction (RT-qPCR) additionally through sophisticated digital PCR technique and decision curve analysis in comparison to conventional clinicopathological variables.

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Fields of Research
› Hypoplastic Left Heart Syndrome
› Genetics of Congenital Heart Disease

Genetic Analysis and Risk for Cardiac Malformations in Families with Hypoplastic Left Heart Syndrome

The Hypoplastic Left Heart Syndrome (HLHS) is a rarecongenital heart defect, where the structures of the left heart and the aortic arch are severely hypoplastic. Without surgical treatment, term infants die within the first days of life. With a three-stage palliative surgical procedure creating a circulatory system with a single ventricle, newborns with HLHS can survive today. Nevertheless, long-term prognosis for patients with HLHS is disappointing, only 50%-70% of newborns surive to age 5 years and survival is associated with significant long-term morbidity. Several observations support a genetic cause for HLHS, as it occurs in children with chromosomal abnormalitis and syndromal diseases and seems to have a strong familiar clustering with an increased prevalence of CHD in families with HLHS. The identification of specific genetic variants has been difficult because of the complex inheritance and the low prevalence of HLHS. With new technological and analytical approaches and the establishment of a Family-Screening Programm, where children with HLHS and their relatives are phenotypically and genetically characterized, we hope to identify new genetic variants and recapitulate cardiac maldevelopment of HLHS. We expect that the identification of genetic underpinnings will result in better understanding of HLHS and lead to new approaches in the care of HLHS patients and their families.

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Fields of Research
› Lymphoma
› Host-Microbiota Interactions
› Flow Cytometry

Analysis of the Interdependence Between the Intestinal Microbiota, Lymphoma Disease and Therapeutic Immunochemotherapy

Constant crosstalk between immune cells and the intestinal microbiota at the level of the gut allows for a symbiotic tolerance, modulates local immunity and impacts innate and adaptive immune response. While the immune system has long been recognized as a major factor in cancer control, there is recent mounting evidence supporting the influence of the microbiota on both carcinogenesis and on the response to immunochemotherapy across various forms of malignant disease. Vice versa, immunochemotherapy is known to disrupt microbial homeostasis and thereby contribute to therapy-related complications such as bloodstream infections. Malignant lymphoma is innately linked to the immune system: it arises from lymphoid cells and its progression is characterized by numerous mechanisms of immune escape. The close physical contact of circulating lymphoid cells and the microbiota within the intestinal immune system and their bidirectional relationship is highly suggestive of a complex and thus far insufficiently examined interdependence. We plan to address the possible link between lymphoma disease and the intestinal microbiota by analysing the microbial composition of healthy subjects and lymphoma patients at the point of diagnosis and longitudinally during immunochemotherapy. To do so, we will establish a flow cytometric-based approach for human samples, perform segregated analyses of cell abundances in microbial subcommunities and examine their dynamic changes. To validate our findings, we will also employ the gold standard for microbiota profiling, 16s ribosomal DNA sequencing. The analyses are embedded in a comprehensive immune monitoring algorithm, allowing us to integrate various patient and tumor parameters. Correlations with clinical and laboratory parameters (e.g. incidence, duration and type of infections, treatment response, blood counts) will be performed to determine the impact of the microbiota on the clinical outcome of lymphoma patients.

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Fields of Research
› Long-read sequencing
› Genomics
› Hematologic Malignancies
› Molecular Diagnostics

Improved Molecular AML Diagnostics-Prerequisite for Individualized Patient Management

Genetics and cytogenetics play a pivotal role in diagnosis and treatment of acute myeloid leukemia (AML) but also other malignancies such as Lung Cancer and Multiple Myeloma. Improvements in AML genetic diagnostics are a prerequisite for individualized patient management. Yet, current second generation sequencing methods are hard to implement into daily clinical routine with regard to the application of rapid cytogenetics and methylation profiling. To address these clinical needs in AML and other malignancies we will use third generation long-read (Nanopore) sequencing that allows to directly read information from the nucleic acid strand enabling rapid high-resolution karyotyping and access to DNA and RNA modification information that was out-of-reach in molecular diagnostics. Access to this new dimension of molecular information will lead to a better understanding of disease biology and improve treatment approaches.

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› Neuroblastoma
› MicroRNAs in Tumor Biology
› Targeted Cancer Therapy/Survivin

Targeting Survivin in Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for approximately 20% of all childhood cancer deaths. The relapse rate of high-risk neuroblastoma exceeds >50% despite most intensive multimodal treatment, and relapsed neuroblastoma is almost always fatal. Therefore, new treatment strategies for high-risk neuroblastoma are an urgent, but still unmet medical need. The most common genomic alterations in high-risk neuroblastoma comprise amplification of the MYCN oncogene (in approx. 40% of all cases) and gain of chromosome 17q (in >60% of all cases). The oncogene BIRC5 (encoding the protein Survivin) is located on chromosome 17q, upregulated by MYCN, and was found to be strongly overexpressed in high-risk neuroblastoma. Survivin is involved in suppression of apoptosis, mitosis, cell cycle, metabolism, invasion and several other key cellular functions. Knock-down of Survivin in neuroblastoma cell lines resulted in cell death. Treatment of neuroblastoma cell lines or mice with neuroblastoma xenografts with the Survivin inhibitor YM-155 resulted in cell death and tumor regression. However, more recent studies revealed YM-155 treatment to result in unspecific DNA damage and other unspecific effects rather than specific inhibition of Survivin. In the current project we (a) analyze the contribution of Survivin to neuroblastoma pathogenesis and metastasis, (b) assess the specific functions of Survivin in neuroblastoma, and (c) model specific strategies to inhibit Survivin.

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Fields of Research
› Gastrointestinal inflammation
› Epithelial barrier
› Intestinal pathogens

Epithelial Polarity and Intestinal Inflammation

Phosphatidylinositol phopsphates (PtdInsP) sum up for just a small percentage of the lipids in the plasma membrane in epithelial cells. Yet, as a source important second messengers they are key substrates in multiple membrane functions, e.g. endocytosis, exocytosis, enzyme activation and actin skeleton organization, to name but a few. Their asymmetric distribution on the inner leaflet of the plasma membrane is crucial for cell homeostasis and differentiation. An essential enzyme in the PtdInsP metabolism is Phosphatase and Tensin homolog (PTEN). It dephosphorylates PtdIns(3,4,5)P3, thereby suppressing Akt/PKB activation. PTEN localizes in the apical membrane during epithelial morphogenesis and polarization and leads to apical enrichment of PtdIns(4,5)P2. In our study we developed a transfection model of intestinal Caco2 cells with a GFP-linked PtdIns(4,5)P2-binding domain (PLC-delta-PH-GFP). Thereby we are able display the PtdIns(4,5)P2- distribution among the cells with a focal laser scanning microscope. Using life cell imaging technique, changes in PtdIns(4,5)P2-distribution could be observed in the course of cell infection with bacterial pathogens. In a screening with various intestinal pathogens we identified an Escherichia coli exotoxin that induces a delocalization of the PtdIns(4,5)P2-signal from the plasma membrane. Barrier analyses on confluent polarized PLC-delta-PH-GFP-transfected Caco2-monolayers revealed simultaneously occurring barrier defects of the epithelium. Our goal is to gain further insight into the underlying mechanisms and depict the cellular structures which are involved in the toxin-induced perturbation of the epithelial barrier.

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› Maternity care for migrant women in Berlin – perceptions of health care professionals and patients
› Public health
› Migrant care
› Infectious diseases
› Violence against staff

Maternity Care for Migrant Women in Berlin – Perceptions of Health Care Professionals and Patients

Berlin is a multicultural city and recently migration numbers are further increasing. Studies in Berlin have shown that communication problems are the principal source of doctor's dissatisfaction in doctor-patient encounters in emergency departments (Babitsch et al. 2008). Low German-proficiency correlates with less frequent use of antenatal care (Brenne et al. 2015) and dissatisfaction with inpatient hospital care on the side of migrant women (Borde et al. 2002). Migrant women have higher rates of overweight (Reiss et al. 2015) and anemia, less frequently receive peridural anesthesia during birth (David et al. 2006) and their crash cesarean section rates are higher (David et al. 2015). Migrant women in Australia have a less satisfying birth experience (Small et al. 2002). Migrant women from third world countries in Sweden have higher levels of stress in the first year after birth (Fabian et al. 2008). Causative factors for these disparities need to be identified in order to design targeted interventions. This study aims at exploring the perceptions and experiences of medical personnel and migrant women especially in the context of limited German-proficiency during labor to inform policy and clinical practice. A quantitative survey and a qualitative design using grounded theory methodology are currently in progress. In a second step, an intervention study is planned to improve the obstetric care for migrant women with the targeted use of modern communication technology.

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› TGF-Beta Superfamily Signaling
› Pancreatitis
› Gastrointestinal Cancer

Activin as Novel Risk Stratifying Marker in Acute Pancreatitis

Acute pancreatitis, the sterile inflammation of the pancreas, is one of the most common gastroenterological causes for hospitalization today. Currently clinical management is restricted to pain medication, intravenous rehydration and initial bowel rest. In about 15 percent of cases, severe acute pancreatitis with persistent organ failure develops, which is accompanied with considerable morbidity and mortality. To date, no treatment besides aggressive early hydration therapy has been shown to reduce pancreatitis-induced mortality, and clinical markers to stratify patients for their risk of developing severe acute pancreatitis are missing. We are investigating novel biomarkers and therapeutic possibilities for this clinical challenge. Previously, we were investigating the role of activin, a central immune modulatory cytokine and TGF-beta superfamily member. We were able to demonstrate that in vivo, activin serum levels are specifically elevated in acute severe pancreatitis but not mild acute pancreatitis, and furthermore that the inhibition of activin reduced mortality significantly (Staudacher et al. Scientific Reports 2017). We are now investigating activin in a prospective clinical cohort of acute pancreatitis and evaluating its potential as a clinical marker. Additionally, to delineate activin's mechanism of action in acute pancreatitis, we are examining its function on immune cells, namely neutrophils and macrophages, the dominant inflammatory cells in acute pancreatitis.

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› Schizophrenia
› Dopamine
› Functional MRI

The Role of Dopamine in Psychosis-Related Perceptual Aberrations

Paranoid schizophrenia is a serious mental illness with poorly understood etiology. Although acoustic hallucinations are the classic leading symptom of schizophrenia, changes in visual perception are also typically found, the potential of which as a diagnostic marker could be underestimated. It is believed that these symptoms are associated (among other things) with excessive dopaminergic neurotransmission. A cognitive mechanism that has been related to the development of hallucinations is an increased willingness to perceive significant structures in noisy sensory signals. The background to this consideration is the knowledge of perception research that the subjectively experienced clear perception is the result of a calculation process that uses probabilities, context information and signals from other sensory modalities in order to generate reliable statements about the environment from an extremely noisy sensory signal. A constant challenge in this calculation process is the distinction between really significant signals and pure sensory noise. Hence, a reduced ability to differentiate between signal and noise and an increased tendency to interpret noise as a meaningful signal can result in a tendency to hallucinations. A number of empirical studies confirm, especially in the domain of acoustic perception, an increased perception of signal in noise in people with psychosis, psychosis proneness or isolated hallucinosis. The neurophysiological aberrations leading to such an increased perception of meaning in noise are largely unexplained. This concerns both the aspect of the involved neurotransmitter systems as well as the functionally affected brain areas. The present study aims to contribute to closing this gap by firstly examining the specific effect of a dopamine-enhancing drug modulation compared with placebo in healthy volunteers and secondly the involvement of specific brain areas through functional MRI during an face detection task.

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› Endoscopic Lung Volume Reduction
› Quantitative CT Scan Analysis

Evaluation and Optimisation of Endoscopic Lung Volume Reduction Therapy in Patients with Pulmonary Emphysema by Means of Quantitative Lung Parenchyma Analysis

Chronic obstructive pulmonary disease (COPD), which is often accompanied by emphysema in its final stages, is one of the leading causes of death worldwide. Air trapping in the alveoli causes permanent enlargement of the airspaces distal to the terminal bronchioles thereby decreasing the surface area for gas exchange. Overall increased lung volume, in turn, leads to impaired breathing mechanics furthering the problem. A more recent therapeutic approach to severe COPD with emphysema is endoscopic lung volume reduction (ELVR) therapy. ELVR works by inducing atelectasis in one lobe thereby allowing the rest of the lung to expand and breathing mechanics to be somewhat restored. The aim of this project is to improve the understanding of pulmonary emphysema and to evaluate and optimize ELVR therapy. To this end, we will make use of the software MeVisPULMO 3D (Fraunhofer MEVIS, Bremen, Germany), which allows quantification of emphysematous lung parenchyma and semi-automatic lung lobe segmentation of CT scans of the lung. Factors that influence the outcome of ELVR are sought after as well as selection criteria for the targeted lobe. Already established factors that have an impact on the outcome of ELVR are emphysema heterogeneity and collateral ventilation of the targeted lobe. How to determine these factors in the best possible way in clinical routine will also be part of this research project.

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› Longterm Survival with Ovarian Cancer
› Polypharmacy in Ovarian Cancer
› Supportive Care in Ovarian Cancer

Caroline Meets HANNA – Holistic Analysis of Longterm-Survivors with Ovarian Cancer

Ovarian cancer is the leading cause of mortality of all gynecological cancers. Despite radical surgery followed by adjuvant platinum-based chemotherapy 75-80% of patients relapse within the first years after chemotherapy and die from the disease. However, there is a rare patient group who survives longer than eight years after initial diagnosis, sometimes even despite several recurrences of the disease. Typical prognostic factors such as age, FIGO stage, and tumor residuals after cytoreductive surgery cannot completely explain this phenomenon. The aim of this study is to identify factors that are unique in longterm-survivors regarding tumor biology, immunological features, resilience and clinical factors such as comedication, polypharmacy, and comorbidities. Furthermore, we are investigating lifestyle factors such as nutrition, physical activity, and sleep quality. Our results shall have an impact on survival of our ovarian cancer patients – also by factors that patients can modify by themselves. The project name is based on the patrons of this study: Mrs. Caroline Masur, who was diagnosed with ovarian carcinoma more than ten years ago and still experienced no relapse. As well as on Hanna, a Catholic nun, who survived the disease despite a relapse for more than eight years. More information can be found at: www.carolinmeetshanna.com

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Fields of Research
› Neuroblastoma
› Immunooncology
› Bispecific Trifunctional Antibodies

Functional and Therapeutic Evaluation of a Trifunctional Bispecific Antibody Against Neuroblastoma

Neuroblastoma is the most common solid tumor of childhood. Approximately 50% of all children initially present with a high-risk disease, for which therapeutic options are extremely aggressive and have limited cure rates. Of the high-risk patients treated in Germany between 1990 and 2007, 56% relapsed. Only very limited therapeutic options exist for relapsed neuroblastoma, and 5-year survival is < 10% in patients. New therapeutic options are needed to improve cure rates for patients with refractory or relapsed neuroblastoma. Immunotherapies with monoclonal antibodies are gaining more importance for oncology. Treatment with the ch14.18 antibody was recently reported to improve 2-year survival in patients with high-risk neuroblastoma by 20%. Trifunctional bispecific antibodies destroy tumor cells and prevent relapse by combining direct tumor lysis via simultaneous tumor and effector cell binding with a long-term vaccination. A trifunctional bispecific antibody has shown promising preclinical results in mouse models for malignant melanoma. Tumor cells can circumvent the host immune system by expressing surface proteins that interact with T cells, which immune checkpoint inhibitors block, to avert this escape mechanism. Through combining trifunctional bispecific antibodies with checkpoint inhibitors, we aim to both enhance the direct cytotoxic effect and achieve tumor vaccination. The proposed project will preclinically evaluate (i) the efficacy of trifunctional bispecific antibodies directed against the neuroblastoma-specific marker, GD2, in vitro and in vivo and (ii) the effectiveness of combining this type of immunotherapy with checkpoint inhibitors. These necessary preclinical data will help develop a trial protocol for patients with refractory or relapsed neuroblastoma. Our long-term aim is to improve survival of children diagnosed with high-risk neuroblastoma.

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Fields of Research
› Experimental research
› Molecular imaging
› Quantitative MR imaging
› Deep learning with focus on radiology

MR-Based Assessment of Aortic Aneurysms with Molecular Probes Targeted at the Extracellular Matrix

Rupture of an abdominal aortic aneurysm (AAA) is one of the most common causes of sudden death and is associated with a high mortality. Currently, there are only invasive treatment options with substantial peri-procedural risks. It is therefore desirable to reduce the number of unnecessary procedures, but to date there are no established biomarkers available, which would allow for a differentiation between rupture-prone and stable AAA. As an AAA results from a weakness of the aortic wall, investigating the extracellular matrix as the major structural component of the aortic wall is a promising approach to identify early biomarkers of rupture-prone AAA. There are two main causes for weakness of the aortic wall: First, the degradation of extracellular matrix proteins, such as elastin or collagen, which provide tensile strength to the wall, enabling it to resist intraluminal hemodynamic forces. And second, proinflammatory cells (e.g. macrophages), which play an important role in the initiation of AAA and the degradation of extracellular matrix proteins. Since these molecular changes can be visualized by in vivo magnetic resonance imaging, we investigated several multi-target approaches, including a combination of collagen type I-specific probes with very small iron oxide particles to assess rupture risk in a longitudinal setup in a murine model of AAA. Here, we found that combining the information from collagen-related ECM remodeling and inflammatory activity was the most accurate predictor for AAA rupture (sensitivity 80%, specificity 100%, area under the curve 0.85), being superior to information from the individual probes alone. Based on a fully synthetic method, we are currently designing a new novel small-molecular-weight peptide targeted against the metalloprotease ADAMTS-4, which was found to be strongly upregulated in unstable AAA. Consequently, our novel ADAMTS-4-specific probe might enable a non-invasive differentiation between rupture-prone and stable AAA. The future goal for clinical implementation is that clinicians will be able to monitor individual AAA development with targeted molecular probes to reliably assess rupture risk and provide personalized treatment.

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Fields of Research
› Heart Failure
› Hemodynamics
› Nanotechnologies

Inhalable Nanoparticle Formulations Targeting the Heart

Heart failure is defined as the inability of the left ventricle to meet body's demand at physiological filling pressures. Approximately 15 million Europeans and 6 million Americans suffer from HF, with annual direct and indirect costs in the billions. The prevalence of HF is about 1-2% in the adult population in western countries, and, given the aging of the population, epidemiologists already in the early 90s predicted an exponential increase of HF incidence and prevalence in the upcoming decades. However, in spite of all medical efforts, the 5-year mortality of heart failure was decreased significantly less than that of malignant diseases. In fact, the day-to- day management of individual end-stage patients is still challenging with only short-term benefits, and heart transplantation is available only to a minority of patients. Altogether, this situation highlights the urgent need to overcome the difficulties associated with the use of conventional pharmacological therapies (i.e. drug instability, hampered efficacy and collateral side effects due to unspecific tissue targeting, invasive drug administration in end-stage disease) by developing novel groundbreaking therapeutic strategies that go far beyond any current conventional medical approach. Aim of this study is to provide a preclinical proof-of-concept for a non-invasive (via inhalation) nanoparticle-based delivery of therapeutic biomolecules to the diseased heart.

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Fields of Research
› Multimodal liver imaging
› Interventional therapy of liver tumors
› MR imaging of glioma

MRI Morphologic Noninvasive Subclassification of Hepatocellular Carcinomas – The »HepCasT«-Study

Hepatocellular carcinomas (HCCs) are a heterogeneous group of tumor subtypes with a different response behavior and prognosis. As a reaction, the World Health Organization (WHO) in its 5th version (updated in 2019) classifies no more two but eight subtypes, each with a different tumor biology and outcome. The new classification may serve as a key factor optimizing a more personalized therapeutic approach and therefore, especially diagnostic disciplines have to implement these new subtypes as soon as possible into their daily clinical routine algorithms. Imaging does play a key role in this situation. Newer and advanced MRI techniques allow a precise tissue characterization. Furthermore, with the help of latest generation hepatobiliary contrast agents it is possible to quantify and measure the organ function and specific uptake behavior of focal liver lesions. Another approach that hold promise for advancing the characterization of HCCs heterogeneity is the use and development of artificial intelligence (AI)-based image post-processing algorithms including radiomics analysis. To date there aren't any established imaging features correlating with any of the new WHO HCC-subtypes. The goal of our project is to identify imaging biomarkers correlating with the new HCC-subtypes, helping to classify them noninvasively. As a next step with the help of our collaborators we will facilitate a radiological-pathological reference database. In a third step and with the help of the data we curated we will try to identify morphologic imaging characteristics by the use of AI-based post-processing algorithms to classify the subtypes noninvasively and to predict / estimate patients individual therapy response and prognosis. The last challenge will be to implement these algorithms into daily clinical routine, we therefore have to identify interface dilemmas and present smart solutions to solve them. We are convinced that by implementing the updated WHO-criteria into clinical workflows current believes and guidelines in the diagnosis and therapy of HCC will change. The results of our project may provide the knowledge to represent as a cornerstone in imaging and therapy assessment of HCC to improve a personalized therapy approach.

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› Fertility Impairment
› Quality of Life
› Risk factors

FeCt Hematology, Fertility in Patients with Hematologic Diseases

Diseases causing chronic anaemia require constant monitoring and treatment to avoid potentially life-threatening complications. Improvements in medical treatment in recent years has notably raised patient prognosis. Therefore, long-term consequences of the underlying disease and/or the necessary treatments as well as quality of life of those affected are of increasing relevance. A key aspect of high quality of life is successful family planning. However, patients with different anaemia may suffer from fertility impairment. FeCt-HAEMATOLOGY aims to identify prevalences, disease and therapy-related risk factors and dynamics of fertility impairment in adolescents and adults with different anaemia as well as the psycho-social relevance of successful family planning for those affected. The study will be conducted as a multicentre retro- and prospective study in cooperation with disease-specific registries and working groups in centres for paediatric and internal medicine in Germany, Austria and Switzerland. The psycho-social relevance of successful family planning, patient education and utilization of fertility preservation will be assessed with the help of a patient questionnaire. Medical data, such as patient core data (sex, date of birth, diagnosis and date of diagnosis) and data on pubertal development, pregnancies and births as well as clinical and laboratory findings, results of fertility testing and therapy data will be collected from patient files/ data bases for data analyses. Findings will be distributed to the disease- and treatment-specific registries and working groups. Project output will help to (1) improve therapeutic strategies to reduce adverse late effects, (2) assist therapists and patients in optimizing family planning and (3) determine timing and choice of fertility-preserving measures and/ or reproductive therapies.

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› Neuroimmunology
› Neuroimaging

Longitudinal Structural Brain MRI Analysis and Cognitive Outcome in Anti-NMDA-Receptor Encephalitis

Anti-NMDA receptor encephalitis (NMDARE) is the most common form of autoimmune encephalitis, a group of recently identified autoantibody-associated inflammatory brain disorders. It mainly affects young women and children but can occur at any age. The clinical course is usually monophasic with severe neurological and neuropsychiatric symptoms. Most patients have a good outcome based on physical disability after 24 months. However, recent studies and observations from clinical practice show considerable cognitive deficits after the acute phase. The long-term outcome and course of these cognitive deficits as well as the underlying mechanisms are still unknown and have not been systematically investigated. Interestingly, structural brain damage visualized on routine cerebral magnetic resonance imaging (MRI) has only been identified in around 50% of patients, despite a severe clinical course in most cases. Previous studies indicate that the presence of MRI changes correlates with a worse outcome. However, a systematic classification of these MRI changes and in particular their clinical relevance remains unclear. The aim of this project is, therefore, to systematically investigate i) the longitudinal structural brain damage using advanced quantitative MRI techniques and ii) assess its role as a possible correlate and predictor for persistent clinical and cognitive long-term deficits in NMDARE patients. The detailed MRI analyzes combined with specific assessments of neuropsychological and clinical outcome will help to better understand the disease mechanisms and long-term effects of this autoimmune brain disease. Overall, the project will thus contribute to increase diagnostic accuracy and identify more personalized therapeutic strategies in order to improve long-term outcome and help regain full cognitive performance and quality of life in these mostly young patients.

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› Tuberculosis
› Infectious Diseases
› Tropical Medicine
› Point-of-care Ultrasound

Sonographic Point-of-Care Diagnostics for Tuberculosis

Tuberculosis, declared a global public health emergency by the World Health Organization in 1993, remains a major global health concern despite worldwide efforts to increase tuberculosis control and reduce morbidity and mortality. Children are particularly vulnerable to develop tuberculosis disease and are at higher risk of severe and disseminated manifestations of tuberculosis. Tuberculosis is difficult to diagnose because clinical presentation is nonspecific, and microbiologic confirmation is only achieved in a minority of children. Imaging therefore plays an important diagnostic role. However, current imaging tools are limited by sensitivity and specificity, and in resource-constrained settings access to basic imaging is low. Pilot work from TB endemic settings showed a promising role of standardized ultrasound examinations within the diagnostic TB work-up and also for monitoring treatment response. Point-of-care ultrasound protocols focusing on the detection of pulmonary, extra-pulmonary, and mediastinal TB are particularly attractive for children in low-resource settings where other imaging is limited but can also contribute to a timely diagnosis and a better delineation of TB disease in affluent settings. The aim of this work is to better define and refine the diagnostic value of TB-focused point-of-care ultrasound protocols and develop diagnostic algorithms for integration of TB-focused point-of-care ultrasound in routine care in settings with different TB endemicity.

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Fields of Research
› Stroke
› Cerebral Small Vessel Disease
› Cerebral Imaging

Sonolysis in Prevention of Silent Brain Infarction During Transcatheter Mitral Valve Repair with The MitraClip-System

Silent cerebrovascular disease is the most commonly detected incidental finding on brain imaging. Although called silent, these brain lesions are associated with subtle deficits (e.g. cognitive and motor deficits, gait impairment, impairments in activities of living). Furthermore, risk of future overt strokes and dementia is increased in patients with silent cerebrovascular disease. (Smith et al., 2017)This project focuses on two cardinal manifestations of silent cerebrovascular disease: Covert brain infarction and cerebral microbleeds.Ischemic brain lesions without a matching clinical syndrome are described as covert brain infarction. Covert brain infarction occurs frequently after an overt stroke (Braemswig et al., 2013, 2017 & 2018) and during surgery / transcatheter cardiovascular interventions. In cooperation with the Department of Cardiology, we examine whether intraoperative sonolysis (continuous transcranial Doppler monitoring) reduces the risk of covert brain infarction during transcatheter mitral valve repair with the MitraClip-System. Cerebral microbleeds (CMB) are a common incidental finding when using blood-sensitive MRI, particularly in patients with cerebrovascular diseases. (Braemswig et al., 2019) Here, we examine the occurrence of new CMBs in specific patient cohorts and their impact on subsequent cerebrovascular events.

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Fields of Research
› Neurovascular disorders
› Diffusion-weighted imaging
› Ocular vascular occlusive disorders
› Central retinal artery occlusion

Retinal Diffusion-Weighted Imaging in Central Retinal Artery Occlusion

Central retinal artery occlusion (CRAO) constitutes a medical emergency as it leads to persistent and debilitating visual impairment of the affected eye. As the chance for visual recovery decreases with the duration of retinal ischemia, therapeutics to achieve retinal reperfusion have to be administered as early as possible. We recently identified retinal diffusion restrictions (RDR) as a frequent finding in CRAO patients on standard brain diffusion-weighted magnetic resonance imaging (DWI MRI). Our research aims to further investigate RDR and their utility for early diagnosis in CRAO with a series of retrospective and prospective clinical trials. Our main focus lies on the application of novel DWI sequence techniques, such as readout-segmented DWI and small field-of-view DWI to improve the detection of diffusion restrictions in retinal ischemia. Finally, we hope to further expand the application of retinal diffusion-weighted imaging as a diagnostic modality to other ocular vascular occlusive diseases.

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Fields of Research
› Cancer
› Senescence
› Cancer Immunotherapy

Development of Minimal Invasive Diagnostic Tools and Targeted Therapies for Tumor Cell Senescence

Despite our rapidly expanding knowledge of cancer genomes and their mutational landscapes, the functional understanding of cellular failsafe programs, which prohibit cancer development and which underly cancer treatment principles, remains incomplete. Alongside apoptosis premature senescence represents a major cellular failsafe mechanism in both mice and men, since it induces a terminal proliferation arrest of viable tumor cells. In this way senescence controls tumor growth as part of cytotoxic therapies. Although therapy-induced senescence (TIS) can prolong tumor-free survival and improve treatment outcome, senescent tumor cells also acquire harmful characteristics: They display an increased stemness potential and persistently remodel their tissue environment predominantly through their enhanced secretory activity. In this way senescence contributes to treatment resistence. However, diagnostic tools, which faithfully detect TIS in the clinic and which could subsequently guide treatment decisions, are largely missing. Moreover, the targeted elimination of senescent tumor cells presents a weakly explored therapeutic opportunity. In the Clinician Scientist Program I therefore aim to elucidate senescence-induced modifications of the tumor stroma and the immune system predominantly in mouse lymphoma as well as neuroblastoma models with the goal to develop minimal invasive senescence screens and to explore novel senescence treatment strategies.

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Fields of Research
› Obesity
› Kidney transplantation

Pathomechanisms of Obesity in the Field of Kidney Transplantation

Morbid obesity is a globally increasing disease and affects 23% of the population in Germany. It is associated with numerous co-morbidities and a high mortality. Obese kidney transplant recipients show higher rates of delayed organ function and rejections. Therefore, obese kidney transplant candidates are often denied access to organ transplantation. In Germany 50% of transplantation centers use body mass index-linked thresholds as a selection criterion to grant access to the transplant waitlist. Bariatric surgeries are discussed as a solution to this ethical dilemma. Their safety and effectiveness have been confirmed in case studies and retrospective analyses, but positive effects on organ and patient survival have not been proven prospectively. Furthermore, it has been shown that the expression of inflammatory markers, such as IL-6 and TNF-α, as well as CD4+ and CD8+ T lymphocytes can be affected by bariatric surgeries. However, it is still unclear what additional value this represents for transplant candidates. This project aims to investigate the impact of obesity and weight loss therapies for patients before and after kidney transplantation. We plan to investigate the pathomechanisms of obesity on graft function and the immunological response in a rat model with obese Zucker Diabetic Fatty rats. In addition, a clinical program for obese kidney transplant candidates will be initiated to determine the metabolic and immunological effects of conservative versus surgical weight reduction programs in these patients.

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› Acute-on-chronic liver failure
› Regeneration
› Senescence
› Cell-Cell interactions mediating organ injury

Exploring the Impact of Hepatocyte Senescence on Tissue Injury and Regeneration in Acute-on-Chronic Liver Failure

The acute-on-chronic liver failure (ACLF) is a complex disease with devastating prognosis which develops on the basis of an acute decompensated liver cirrhosis in combination with extrahepatic organ failures. Sudden disease worsening is frequently triggered by bacterial infections or other precipitating events which are known to be more harmful when liver cirrhosis is present but easy to handle in patients without liver disease. This observation suggests an organ sensitisation of the liver being the initiating mechanism for ACLF. In addition, a general lack of tissue regeneration was also linked to patients' persistent organ dysfunction and poor prognosis. Upon injury hepatocytes may develop a cell cycle arrest, so called cellular senescence, which has the potential to explain both observations. Cellular senescence alters the phenotype and receptor expression of hepatocytes and the ability to proliferate and to replace injured tissue. The main aim of that project will be to explore the mechanistic role of hepatocellular senescence in modulating the course of ACFL and severity. As a first step human liver tissue from patients with different severity grades of end-stage liver disease will be characterised for the expression and activation of regenerative and senescent pathways. Focus will be on the Mdm2-p53 pathway, which is the best-described senescence pathway. TLR4 signalling may triggers senescence and we hypothesis that this is mediated by TGF-β1 which trans-activates the p53 pathway independent of DNA damage or other forms of cellular injury. For both objectives the effect of targeted molecule silencing in vitro (e.g. siRNA) and in vivo (e.g. conditional knockout mice) allows to delineate the relevance of senescence pathways in ACLF. Furthermore we are planning to develop a liver ACLF organoid model to mimic part of the complexity of ACLF in vitro. It will allow to pre-test multiple therapeutic compounds to select those with high likelihood for in vivo efficacy. The last objective will be to test pre-selected senolytic therapies in different ACLF mouse models and to select the most effective agent for translation into humans. Therefore, this project will combine basic with translational science to understand the mechanism of regenerative response in ACLF, to develop new experimental techniques and also to pave the way for a novel treatment for a disease with still devastating prognosis.

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› Third-generation sequencing

Molecular Mechanisms of Tumor-Immune Cell Interaction in Glioblastoma

It has long been recognized that tumor-associated microglia and macrophages (TAMs) can account for 30% or more of tumor cells in glioblastoma (GBM), the most frequent primary brain tumor in adults with a dismal prognosis of about 15 months overall survival. Importantly, we have recently shown that the amount of non-tumor cells in GBM is a negative predictor of survival (Heuling et al., 2017). On the molecular level, a solid body of experimental evidence on the functional and molecular interactions between glioma and local innate immune cells convergently shows that microglia and macrophages support tumor growth in GBM. However, clinical trials of CSF1R inhibition to selectively deplete TAMs in GBM have failed. In addition, the high interindividual variability of immune infiltration across GBM remains largely unexplored. We have found strong associations between mutually exclusive key driver mutations and the amount of immune infiltration, which might explain the failure of clinical trials. The overall aim of this project is therefore to identify patients that will benefit from targeted therapy, gain mechanistic insights to establish causality and provide the diagnostic tools for patient-tailored precision oncology.

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› Cancer Immunology

Cytokine-Armed Onkolytic Vaccinia Virus for Pancreatic Cancer Therapy

Immunotherapy is rapidly evolving and fighting cancer by re-activating the patient's immune system presents a promising therapeutic strategy in addition to standard treatment options as surgery, chemotherapy, and radiotherapy. In contrast to advances in other solid malignancies, the clinical success of checkpoint inhibitors to unlock T-cell immunity has failed in patients with Ductal Pancreatic Adenocarcinoma (PDAC). PDAC is characterized by an extensive fibroinflammatory stroma interfering with an efficient anti-tumor immune response. Lacking effector T cell infiltration; CD4+ regulatory T cells, myeloid-derived suppressor cells, macrophages and mast cells present the majority of the infiltrating immune cells. Based on the results I obtained during my time as a postdoctoral fellow at Prof. David Bartlett´s laboratory, Department of Surgery, University Pittsburgh Medical Center (UPMC), we hypothesize a favorable strategy to overcome immune evasion in pancreatic cancer might be presented by oncolytic virotherapy. Our preliminary data indicate that application of oncolytic vaccinia viruses offers an effective strategy to induce an efficient anti-tumor T cell response independent of baseline T cell infiltration. Furthermore, in combination with checkpoint blockade oncolytic virotherapy elicits systemic and potent anti-tumor immunity. The project aims to explore the therapeutic potential of cytokine-armed oncolytic vaccinia virus for pancreatic cancer in a preclinical model reflecting human disease. The combination of oncolytic virotherapy with a specific stroma effect as well as checkpoint blockade to provide long-term anti-tumor memory may translate into clinical trials in human patients in the near future.

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› Protease-activated receptors
› Atherosclerosis
› Heart failure
› Atrial fibrillation

Protease-Activated Receptors in Cardiovascular Thromboinflammation

Protease-activated receptors (PARs) regulate platelet, endothelial, and immune cells as well as fibroblast and cardiomyocyte function. PARs are a family of G-protein-coupled receptors (PAR1–PAR4) with a unique activation mechanism via cleavage by the serine proteases of the coagulation cascade, like FXa and FIIa, immune cell-released proteases, and proteases from pathogens. Our group has shown that the tissue factor (TF)/FXa/thrombin/PARs pathway plays a central role for the innate immune response in the heart during myocarditis. PARs regulate immune response not only by sensing pathogens but also by direct activation of platelets and immune cells, thereby mediating proinflammatory cytokine secretion and chemokine expression. Furthermore, endothelial PARs activation, stimulates leukocyte adhesion, rolling, and migration. This cascade is initiated by TF. We have recently demonstrated that the treatment with the PAR1 antagonist, vorapaxar, reduced inflammation in a metabolic disease model. Furthermore, we have shown that PARs are important regulators of adverse extracellular matrix remodelling. Activation of PAR1 and PAR2 is associated with cardiac fibrosis. PAR1 is the most abundant G-protein–coupled receptor in cardiac fibroblasts. We have shown that PAR2 is an important regulator of profibrotic PAR1 signaling and TGF-β-receptor signaling. Targeting the pleiotropic effects of the FXa/FIIa-PAR-axis, which go beyond the anticoagulatory effects of FXa inhibitors, reduced markers of cardiac fibrosis, and diastolic dysfunction in patients with heart failure with preserved ejection fraction (HFpEF). Therefore, intervening in the FXa/FIIa-PAR1/PAR2/TGF-β-axis might be a promising synergistic approach in a selected cohort of patients with HFpEF to reduce cardiac fibrosis and inflammation. Next, we will study the role of PARs during the pathogenesis of atherosclerosis and atrial fibrillation.

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› (Epi)genetics
› Alcohol Use Disorder
› Imaging

Imaging (Epi)Genetics in Alcohol Use Disorder

Alcohol dependence and harmful use are partially heritable with an estimated contribution of genetics to phenotypic variance of between 40-60%. Recent large genome wide association studies (GWAS) have identified specific genetic variants, however such association studies require extremely large sample sizes. The combination of genetics and imaging data (referred to as imaging genetics) facilitates the identification of genetic risk variants in considerably smaller sample sizes. The first goal of this project therefore is to identify intermediate phenotypes at the brain level using imaging genetics that can, in a subsequent step, be used for classification or clinical prediction purposes allowing the consideration of genetic as well as epigenetic information. To facilitate this goal, we have collected blood and fMRI data from 150 patients with Alcohol Use Disorder and 200 Healthy Controls and will continue to collect 130 patients with Alcohol Use Disorder for replication. All patients performed basic learning paradigms during fMRI. The specific aims of the project are: To (i) perform chip-based genome wide genetic analyses of all samples and longitudinal epigenetic analyses of selected candidate genes in patient samples; (ii) to identify and replicate intermediate brain phenotypes of dysfunctional learning based on known risk variants (including polygenetic risk scores and epigenetic information as well as neuroplastic biomarkers such as BDNF) using the standard (voxel based) and a »connectomics« (network based) approach to imaging data; (iii) to use the identified intermediate brain phenotypes and epigenetic information for classification and prediction purposes.

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› Pediatric Oncology
› Gene expression regulation
› Circular RNA
› Non-coding RNA

Evaluating Circular RNAs in Neuroblastoma as Potential Therapeutic Targets

Neuroblastoma, an embryonal tumor arising from peripheral sympathetic neuron precursor cells, is the most common extracranial solid tumor of childhood. Approximately half of all children diagnosed with neuroblastoma present with high-risk disease, for which therapeutic options are aggressive and have limited cure rates of at most 40%. No curative therapeutic options currently exist for relapsed neuroblastoma, emphasizing the urgent need for the development of new strategies. Circular RNAs (circRNA) arise by a form of alternative splicing, termed backsplicing, and have recently emerged as a new class of non-coding RNAs important for regulating gene expression. They bind miRNAs or RNA binding proteins via specific sequences to inhibit their function and directly influence transcription. Circular RNAs were recently shown to be highly abundant in neural tissues, especially during development. During my Junior Clinician Scientist fellowship we could detect for the first time circRNAs in neuroblastoma by RNA sequencing. We identified a subgroup of neuroblastoma-specific circRNAs. Selected circRNAs showed oncogenic properties in neuroblastoma cells. In this subsequent Clinician Scientist project we will evaluate the therapeutic potential of circRNAs in neuroblastoma. For this purpose, we will establish a knockdown screen to identify circRNAs affecting the phenotype of the cancer cells. Moreover, we will create a pipeline by Oxford Nanopore to sequence the full-length of circRNAs. This information will help us to thoroughly characterize the mechanism of action of candidate circRNAs and finally test their therapeutic potential in cell line and xenograft models. In this way, we hope to not only add to the current understanding of neuroblastoma pathogenesis, but also define new druggable targets for high-risk disease.

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› CFTR Biomarker
› CFTR Modulators
› Airway Hydration Therapies

Functional Characterization, Pharmacological Modulation and Genotype-Phenotype Correlation of Rare CFTR Mutations in Human Airway and Intestinal Epithelia

Cystic fibrosis (CF) is the most frequent lethal hereditary disease in Caucasians and is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which results in defective ion transport in epithelial organs. Meanwhile, more than 2000 mutations have been identified in the CFTR gene. Despite the fast development of modulators for common mutations, functional consequences of many rare CF-causing mutations remain unknown. Further, large clinical trials with CFTR modulators in patients with rare CFTR mutations are often impossible. The aims of the project are therefore to first characterize the function of different classes of rare CFTR mutations in human native respiratory and intestinal epithelia, by using sweat test, intestinal current measurement (ICM) and nasal potential difference (NPD), and further correlate the genotype and CFTR function with the clinical phenotype assessed by lung function measurements, anthropometry and lung imaging with MRI. Our final goal is to perform in vitro testing of response to therapy of currently developed and already approved CFTR modulators in patient-derived nasal epithelial cells and intestinal organoids. We believe that studying these questions will provide new insights into the correlation between the CF genotype and CFTR function in the airway and intestinal epithelia and will help to establish mutation-specific therapy for patients with rare CFTR mutations.

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› Cancer Immunology
› Mucosal Immunology

Metabolic Profiling of the Monocyte-Macrophage Compartment in Crohn's Disease

Intestinal macrophages (MΦ) have pivotal roles in maintaining intestinal homeostasis, but are also implicated in chronic pathologies of the gastrointestinal tract, such as inflammatory bowel disease (IBD). These opposing properties can be attributed to the enormous plasticity of these cells, reflected by different polarization states. Large advances in our understanding of the role of MΦ in inflammatory conditions is based on murine studies. In the murine tissue, resident MΦ are constantly replenished from blood monocytes that acquire an anergic phenotype under steady state conditions. However, when recruited to inflamed tissue, they become effector monocytes that actively drive inflammation and give rise to pro-inflammatory MΦ. Data on MΦ biology and function in inflammation of the human gut is sparse. It has been suggested, that an altered monocyte to MΦ differentiation is involved in the development and perpetuation IBD. However, many aspects of human intestinal MΦ biology remain poorly understood. The high degree of plasticity with involvement of different polarization states is one of the characteristic features of MΦ. Phenotypic changes are accompanied with changes in the cells metabolism that impact the effector functions of these cells. Alterations in the metabolic signature of MΦ are present in different human diseases. For example, an atypical pro-inflammatory polarization has been discussed in metabolic diseases. The importance of MΦ metabolism is furthermore underlined by the study of tumour-associated MΦ, that impact the metabolic profile of the tumour microenvironment and have a major influence on disease progression and resistance to therapy. For inflammatory conditions, enforcing a pro-resolving MΦ phenotype could be a potential therapeutic approach. Changes in both monocyte and MΦ population have been reported in CD patients. However, it is unknown how these cells contribute to disease pathogenesis and progression. Moreover, it is not understood, if monocytes have a dual capacity to give rise to pro- or anti-inflammatory MΦ, e.g. depending on the microenvironment that they enter. Strikingly, the metabolic signature of both monocytes and MΦ in CD displays an unexplored field. The present project aims to define the role of monocyte- and MΦ-metabolism in small intestinal CD.

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› B-cell lymphoma
› Genetic screening
› Targeted therapies

Forward Genetic Screening for Analysis and Therapeutic Targeting of BCL6-Associated Lymphoma

BCL6 is a BTB/POZ zinc finger transcription factor acting as a transcriptional repressor in a sequence-specific manner. Without intact BCL6, the GC reaction cannot occur, resulting in failure to produce memory B cells and antibody-producing plasma cells. BCL6 represses various tumor suppressor genes, but also oncogenes to counterbalance the risk of transformation. BCL6 translocations and overexpression occur in up to 50% of DLBCL patients and are present in a subset of patients with adverse prognosis. The IμBCL6 mouse is a lymphoma model carrying a translocation similar to the one found in DLBCL patients, resulting in spontaneous lymphoma development. Strategies to target BCL6 are currently being tested, but drug development for targeting transcription factors and identifying patients who will profit from novel drugs is challenging, especially in high-risk or treatment-resistant patients. In DLBCL, sequencing samples from large, well-annotated patient cohorts have provided us with a plethora of evidence about genetic and non-genetic alterations in this disease. The central challenge is to identify and understand highly relevant functional alterations and distinguish them from less relevant genetic and non-genetic events. The piggyBac (PB) transposon mutagenesis system enables us to screen for functionally relevant cancer genes by activating and inactivating all genes across the whole genome. Thereby, it serves as a complementary approach to the aforementioned patient datasets to answer open questions about novel cancer genes in vivo. In this system, short DNA elements carrying promoters and gene traps called transposons (ATP2 mouse) are randomly integrated into the genome by a transposase (RosaPb mouse), allowing the identification of oncogenes and tumor suppressor genes in a single unbiased experimental approach. Transposon insertion sites can be identified with quantitative insertion site sequencing (QiSeq) with very high resolution as described. We are using PB in the DLBCL-prone IμBCL6 mouse model to find novel candidate genes relevant for lymphomagenesis. Thereby, we aim at identifying clinically relevant mechanisms of lymphoma development and progression, biomarkers for treatment response and resistance, focusing on how to overcome treatment resistance by molecularly targeted therapies.

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› Adoptive T cell therapy
› Pancreatic cancer
› Tumor stroma

Adoptive T Cell Therapy in Pancreatic Cancer: Effects of the Abundant Tumor Stroma on Tumor Rejection

Pancreatic cancer is a highly aggressive disease with limited therapeutic options in advanced stages. In recent years, adoptive T cell therapy has led to impressive responses in patients with hematopoietic malignancies and melanoma, however, its clinical efficacy for most solid tumors still needs to be tested. The complex stroma and microenvironment of solid cancers is thought to act immune suppressive, and thus could pose a challenge for T cell-based therapies. Also, the tumor stroma is an important target during T cell-mediated tumor rejection. In this context, cross-presentation of tumor antigens by stromal cells such as macrophages and potentially fibroblasts has been discussed. In addition, T cell-derived interferon-γ and tumor necrosis factor have been shown to play important roles by affecting components of the stroma including tumor vessels. Pancreatic cancer is characterized by an abundant and dense tumor stroma associated with immunosuppression and therapeutic resistance. Thus, stroma-associated aspects are of particular importance for this type of cancer. The goal of this study is to evaluate adoptive T cell therapy in pancreatic cancer using T cell receptor gene transfer. Using this approach, pancreatic cancer-specific tumor antigens can be targeted in a MHC-restricted fashion. To investigate the stroma-related role in the context of adoptive T cell therapy an orthotopic mouse model of pancreatic cancer will be used that closely mimics the complex tumor microenvironment in humans. The relevance of antigen cross-presentation by stromal cells will be determined. Furthermore, the interplay of T cell-derived effector cytokines and other components of the tumor stroma such as tumor vessels will be examined. In addition, human tumor tissue samples will be used for functional analyses. Overall, our study will test feasibility of adoptive T cell therapy in pancreatic cancer and explore possible stroma-associated mechanisms of resistance.

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› 3D printing
› Computed tomography
› Image quality
› Standardization

3D Printing of Tumor Models to Standardize Radiomics Biomarkers in Oncologic Patients

Radiomics makes quantitative information available from computed tomography (CT) images that provides new diagnostic and prognostic insights into tumor diseases. Novel radiomics biomarkers have shown high potential for better, personalized tumor therapies in numerous studies. However, as the field progresses, the quality of CT data becomes increasingly important. Radiomics features are extracted from tumor pixel information, which currently varies widely across institutions, scanners and even within the same scanner. This situation represents a major limitation for the robustness and clinical application of radiomics. Imaging phantoms are reference objects of known ground truth and represent a standard instrument in testing, controlling and comparing imaging systems. However, standard CT phantoms test and standardize technical system parameters, but do not evaluate radiomics features. Based on a new technology specifically developed for 3D printing of radiopaque objects, our aim is to develop the first reference tumor phantom for radiomics. We will use the phantom to evaluate effects of imaging technologies on the robustness of radiomics features, and we will develop methods to improve the quality of CT data, establish standardization and enable more reliable radiomics analyses.

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› Adoptive T cell therapy
› Pancreatic cancer
› Tumor stroma

Influence of Hormones on Depressive, Stress-Related, and Anxiety Disorders

Traumatic experiences and adverse life events are risk factors for numerous somatic and mental disorders. Stress- and trauma-related disorders such as depressive and posttraumatic stress disorder are associated with sex-specific differences. Following traumatic experiences, women show higher prevalence rates, as well as higher symptom severity and comorbidity rates. In our previous work we could show that both major depressive and posttraumatic stress disorder are associated with changes in cortisol and catecholamine metabolism, and that early life adversities are associated with cognitive impairments in later life. Fear conditioning is a crucial concept of learning theory, and is frequently applied to explain the development and maintenance of mental disorders. Increasing evidence suggests a pivotal role of sex hormones in fear conditioning, thus offering a possible explanation for sex-related differences. Preclinical studies, using techniques such as assessing endogenous hormone levels or by pharmacologically blocking target receptors, have shown associations between estrogen and progesterone levels and cognition. Less is known about the effects of sex hormones on cognition in humans. Therefore, we systematically investigate the effects of hormones on cognitive processes in depressive, stress-related and anxiety disorders.

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› Cognitive Neuroscience
› Clinical Psychiatry

The Neurobiology of Psychotic Disorders

My workgroup investigates underlying neurobiological mechanisms that lead to impaired learning and neurocognitive processes in neuropsychiatric diseases. We apply a broad range of techniques in order to elucidate neurobiological underpinnings of complex human traits. We investigate large cohorts and estimate differential contributions of brain structure, function as well as genetic and epigenetic contributions to cognitive capacity. We explore malleable biomarkers for interindividual differences in cognitive abilities. We apply state-of-the-art in-vivo imaging techniques using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). More precisely, I am interested in the pathophysiology of psychosis and the mesocortical dopamine system that modulates putative glutamatergic prefrontal functions like working memory. I have a particularly strong commitment to translating my increasing methodological knowledge towards clinical application. In my research, I focus on alterations in neurocognitive processes using non-invasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). Non-invasive stimulation techniques are a putative therapeutic tool for several kinds of symptoms. The understanding of the effect of non-invasive stimulation techniques will help to refine the application. I am investigating the experimental modulation of brain activation and its impact on behavioral and neurobiological outcome measures like local activity (fMRI) and effective connectivity (dynamic causal modeling, DCM). DCM is an approach that overcomes the challenge of missing mechanistic insight. DCM exploits generative models that provide parameters which explain how the measured data could have arisen from neurophysiological mechanisms like task-dependent synaptic connectivity between neuronal populations. Taken together my current work is focusing on the exploration of interindividual differences in cognitive capacity which allow possible interventions that are capable of inducing changes in network processing in the human brain.

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› Circulating tumor DNA

Evaluation of the Potential of »Liquid Biopsies« in Representing Mutational Profiles of Metastatic Tissue

In order to administer an individually tailored therapy to a cancer patient, currently, a tumor is molecularly characterized by analyzing tissue biopsies. Unfortunately, the obtainment of tissue biopsies is invasive and therefore associated with a risk of complications, and in some cases may not even be possible due to difficult accessibility. Using Liquid biopsies is a promising alternative, as it requires solely obtaining blood samples, which can be molecularly analyzed. Up to now, it is unknown, to which extent the mutational profile of metastatic tissue can be revealed by analyzing Circulating Tumor Cells (CTCs) or Circulating Tumor DNA (ctDNA), and which of these liquid biomarkers is most representative when comparing different tumor entities. To answer this question, in the current project we are analyzing blood samples from patients suffering from colorectal cancer, head and neck cancer and malignant melanoma with distant metastases. Using a panel consisting of 327 genes frequently associated with cancer, blood and tissue samples are sequenced and the mutational profiles of CTCs and ctDNA are going to be compared to the ones in metastatic tissue as well as primary tumor tissue, if applicable. We strongly believe, that liquid biopsies have the potential to expand the diagnostic repertoire in cancer patients by enabling the obtainment of molecular data non-invasively. Thus, patients may significantly benefit from our results, since the analysis of liquid biopsies will enable the administration of tailored therapy for every individual patient corresponding to the molecular characteristics of the tumor.

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› Movement Disorders
› Deep brain stimulation
› Gait assessment

Network Modulation for the Improvement of Gait Function in Parkinson's Disease

Disturbances of gait and balance and specifically freezing of gait (FoG) are clinical features of advanced stages of Parkinson's disease (PD) that are associated with an increased risk of falls, reduced mobility and impaired quality of life. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a highly efficacious treatment for motor symptoms of PD such as tremor, rigidity and bradykinesia but with limited effects on gait disability. Therapeutic effects of DBS relate to modulation of distinct brain networks connected to the stimulation area via basal-ganglia-cortical-pathways. Here, specific structural and functional connectivity patterns have been identified that are associated with and predictive of motor improvement. We will adapt this methodology to study the optimal connectivity profiles of DBS for improving gait function and particularly FoG in Parkinson's disease. To account for the diversity of gait phenomena in PD, sensor based kinematic measurements will provide high resolution, multi-parametric assessments of gait performance ON and OFF DBS. For each patient, specific profiles of network activation and connectivity will be modeled from the reconstructed DBS-electrodes based on normative structural and functional connectomes and then related to individual modulation of gait performance. This will clarify if we need to target different networks to treat gait disability in contrast to other motor symptoms of PD.This study aims to optimize DBS therapy towards a more patient- and symptom-oriented approach that may be integrated into future solutions for adaptive DBS.

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› Deep Brain Stimulation
› Neuropsychiatry and (Social) Cognition

Cognitive Effects of Dopamine and Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

Apart from motor disabilities, patients with Parkinson's disease (PD) show a variety of cognitive symptoms that are relevant in terms of prognosis and quality of life. These include increased impulsivity under dopaminergic medication and deep brain stimulation (DBS) in the subthalamic nucleus, respectively. In order to find a balance between beneficial motor effects and cognitive side effects, a better understanding of the underlying cortex-basal ganglia (BG) interactions and their modulation by our therapies is crucial. During my Junior Clinician Scientist grant period, I investigated different cognitive domains in PD patients on and off dopaminergic medication and looked at their functional basis with [123I] FP-CIT SPECT. In a first study, we were able to show that overall cognitive performance correlated with the degree of dopaminergic degeneration in the associative part of the striatum. As impulse control disorders especially affect younger patients, we looked at inhibitory control with respect to dopaminergic degeneration in a second study. With a novel Go/NoGo paradigm, we found that young onset PD patients performed worse on compared to off dopaminergic medication whereas late-onset PD patients seemed to benefit from dopamine in terms of reduced error commission rates on compared to off dopaminergic medication. By means of simulations in a neuro-computational model of the cortex – BG loops, we were able to show that these opposite effects can be explained by different patterns of striatal dopamine loss between young and late-onset PD groups: younger PD patients who dispose of a relatively intact associative striatum show impaired inhibition due to dopamine overdosing of the associative striatum. This is important when considering that younger PD patients are often candidates for DBS. The focus of my upcoming projects will be on the effects of DBS surgery on cognition and prognostic markers for cognitive outcomes in PD.

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› Pain

Study of the Pathophysiology of Pain in Dystonia by Neurophysiological and Imaging Methods

Pain is the most frequent non-motor symptom in cervical dystonia in up to 75% of patients. It might occur as the first symptom of the disease and oftentimes becomes chronic. For many patients, pain is more disabling than the sustained or intermittent muscle contractions causing abnormal movement and/ or postures which is the main motor manifestation of dystonia. Despite its severe impact on the patients' quality of life and the significant socioeconomic implications, the phenotype and the pathophysiology of pain in dystonia are mostly unknown. There is no correlation between motor symptoms and pain, and non-dystonic muscles might also be painful. Therapeutic interventions that might relief pain (e.g., injections of botulinum toxin, deep brain stimulation) do not always improve motor symptoms and vice versa. We can therefore assume, that pain in dystonia is not solely generated by dystonic muscles. Recently, it has been proposed that an insufficient descending pain inhibitory system, assessed by conditioned pain modulation, might contribute to pain in dystonic patients. With this project, we aim to phenotype the pain syndrome in large cohorts of patients with various forms of focal and generalized dystonia without and during therapy by means of questionnaires, neurophysiological markers, particularly conditioned pain modulation, and imaging methods. The results will lead to a better understanding of the pathophysiological mechanisms of pain in dystonic syndromes and create a foundation for individualized, mechanism-based therapies.

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› Osteoarthritis
› Cell-based Therapies
› Mesenchymal Stromal Cells
› Osteoimmunology

MORCA – Mechanism of Regenerative Cell Action

Osteoarthritis (OA) is the most common degenerative joint disease worldwide with a marked prevalence increase over the past decades. Primary OA is caused and characterized by a vicious cycle of micro-trauma to the cartilage and a low-grade articular inflammation, that cause chronic pain and functional disability in affected patients. Symptomatic OA treatment comprises lifestyle changes, physiotherapy and analgesia, which unfortunately cannot effectively slow down or halt disease progression. Due to the progressive nature of the disease, arthroplasty is often the only therapy that can replace, yet not restore joint integrity. Placental expanded (PLX) cells are placenta-derived mesenchymal like adherent stromal cells, that are known to exert unique immunomodulatory and regenerative properties in the treatment of muscle injury and critical limb ischemia. Administered locally, PLX cells are able to regulate the adaptive immune response and the pro-inflammatory cytokine distribution. Infiltration of the synovium and the synovial fluid with cells from the adaptive immune system and pro-inflammatory cytokines are key pathomechanisms of OA, yet PLX cells have not been exploited for intraarticular treatment of OA. With the MORCA project we strive to better understand molecular pathways by which regenerative cells including PLX cells may alter disease activity in a pre-clinical naturally occurring in vivo model of OA (Dunkin Hartley guinea pig model). Potential immunomodulatory and regenerative effects of intraarticular injections of PLX cells will be traced histologically and radiologically as well as through molecular and single cell analyses. To compare pre-clinical results with clinical reality, human OA cartilage and synovium samples will be obtained and included in the analyses. We hope to better comprehend, establish and advance novel regenerative treatment strategies for OA through the work conducted during the Clinician Scientist fellowship. A paradigm shift from a symptomatic to a disease modifying treatment approach for primary OA would have a lasting impact on affected generations to come.

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› Viral infections
› CD8 T cells
› HSV
› MRGPRX2
› Urticaria

The Role of Mast Cells in Viral Infections

Mast cells are pleotropic immune cells most abundantly found at host-environment interfaces, such as the skin, respiratory and gastrointestinal mucosa. Mast cells act as sentinel cells to sense and fight pathogens. In order to do this, they are armed with a plethora of bioactive mediators that initiate immune cell recruitment, promote the development of adaptive responses and contribute to defense mechanisms of the host against infections. Activation and subsequent mast cell degranulation are mediated through several receptors including the novel human G protein-coupled receptor (GPCR), known as Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) and the C5a receptor. Although mast cells are crucial in the defense of the host, they also play an active role in allergy, urticaria, itch and fibrosis. Herpes simplex virus type 1 (HSV-1) can cause infections in humans ranging from orolabial lesions to life threating conditions such as herpes simplex encephalitis. Using mouse and human skin mast cells as well as animal models of disease, we aim to investigate and characterize the role of mast cells in viral infections and to determine how herpes viruses modulate the phenotype and function of mast cells. In addition, we investigate the impact of MRGPRX2 and C5aR blockade in the activation of mast cells in patients with chronic spontaneous urticaria. We use a combination of cutting edge technologies, high throughput culture methods, cell cultures and mouse models viral infections. A better understanding of the mechanisms underlying mast cell activation after viral infections will allow the development of novel antiviral strategies as well as therapies to treat symptoms in mast cell associated diseases.

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› Biomarkers
› Metabolism

Homeostasis After Stroke – the Effect of Stress-Tests on Metabolic and Cerebral Biomarkers

Stroke is a major cause of death and long-term disability worldwide. Despite rehabilitation and optimal secondary prevention, many stroke survivors remain functionally dependent and at a high risk for recurrent vascular events. Impairment of lipometabolism is a risk factor for cardiovascular disease and physical fitness training is thought to promote metabolic and cerebral hemostasis. Because the etiology of stroke is heterogeneous, the use of biomarkers for individual risk prediction is promising, especially when these biomarkers can quantify the ability of the individual to maintain homeostasis. We have initiated the prospective observational Berlin Cream and Sugar study (NCT01378468) to evaluate the metabolic changes after stroke and assess the effect of an oral glucose and triglyceride tolerance test on metabolic homeostasis for individual vascular risk prediction. A second study is the randomized-controlled PHYS-STROKE trial (NCT01953549), where subacute stroke patients receive physical fitness training or relaxation sessions for 4 weeks in addition to usual care. Blood and imaging analyses are performed before and after the intervention to establish new biomarkers for vascular risk prediction and assess potential protective effects of fitness training early after stroke (Nave et al. 2013). In this research project, we hypothesize that A) investigation of hemostatic control of lipometabolism in the acute phase of stroke following a stress test, i.e. oral triglyceride tolerance test (OTTT), will improve the individual risk prediction after stroke. B) Application of anaerobic fitness training after stroke in addition to usual care will lead to a better functional outcome and will improve markers of metabolic homeostasis compared to relaxation sessions. These new markers will include conventional markers of metabolism as well as novel markers, such as different types of microvesicles and expression levels of isolated exosomes. The work will lead to more insight into the role of homeostasis as a key concept in understanding the role of biomarker research.

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› Cardioprotection
› Extracellular Vesicles

Targeting Inflamed Endothelium with Smart Exosomes for Cardioprotection

With the incident of cardiovascular disease on the rise, the natural clinical course in patients after cardiovascular events has become a significant economic burden on our society. In the heart, acute ischemia and reperfusion injury leads to remodeling, and ultimately, to impairment of functionality in affected myocardium. Remodeling is preceded by tissue inflammation, followed by fibroblast migration and proliferation in the damaged myocardium. Cell based therapies, including neonatal and adult mesenchymal stem cells (MSC), have aimed to prevent myocardial remodeling. In this setting, the cardioprotective effect is in part mediated by extracellular vesicles, particularly exosomes. Exosomes contain miRNAs and proteins that can facilitate an anti-fibrotic, angiogenic and immune-modulatory effect after ischemia reperfusion injury. Despite promising pre-clinical trials, clinical studies utilizing MSCs in the acute setting of myocardial ischemia failed to demonstrate the reduction of remodeling . It is hypothesized that the positive impact of cell-based therapies on remodeling is inhibited by the low retention rate and survival of MSCs after transplantation. Significant titers of paracrine factors including exosomes are only achieved during the first 24-48 hours after allocation of MSCs (»hit-and-run« mechanism) due to limited retention and engraftment of cells. While application of MSCs is usually limited to a one-time injection during cardiac surgery or percutaneous intervention the application of exosomes may allow for repetitive treatments via intravenous applications. The overall objective of this project is to develop a therapeutic exosome product that targets inflamed endothelium in the infarcted myocardium. These smart exosomes (SExs) should exhibit thecapacity to accumulate in the myocardium after ischemia and revascularization upon systemic delivery. Furthermore, they should allow for repetitive application via minimally invasive /percutaneous routes. Finally they should act cardioprotective in situations of myocardial ischemia such as acute infarction.

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Mechanisms of Antibody-Mediated Encephalitis in Tumor Disease

Encephalitis associated with antibodies against the metabotropic glutamate receptor 5 (mGluR5) is an autoimmune disease characterized by a complex neuropsychiatric syndrome (Ophelia syndrome). It often affects young adults and is associated with Hodgkin lymphoma. mGluR5 belongs to the family of G protein-coupled receptors and activates an intracellular signal cascade. In the past, receptor dysfunction has been associated with schizophrenia, autism, fragile-X syndrome, and Parkinson's disease. The role of anti-mGluR5 in autoimmune encephalitis though, the underlying pathomechanisms of antibody binding and the link between tumor and autoimmunity remain unclear. Recently, we treated a young patient with Ophelia syndrome and anti-mGluR5 antibodies. We generated monoclonal antibodies of this and other patients' CSF by using single cell cloning. With tissue- and cell-based assays we characterize the binding patterns and affinities of these anti-mGluR5 antibodies. To address functional effects of the antibody binding we now look for receptor internalization, shifts in cluster localization and impact on cell viability after antibody incubation with neuronal cell cultures. After the encephalitis, the very same patient developed a Hodgkin lymphoma. Immunohistochemistry on biopsy material might now reveal anti-mGluR5 antibody binding. We will compare the results to anti-mGluR5 binding on tumors from non-encephalitic Hodgkin patients as controls With this project we want to provide new insight into autoimmunological pathomechanisms on the metabotropic receptor mGluR5 as well as on the link between tumor and autoimmunity. A better understanding of the pathophysiology may modify treatment strategies and serve patients with autoimmune encephalitis in general.

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› Autophagy
› Metabolism

Fine-Tuning the TSC2-MTOR Axis in Diabetic Cardiomyopathy

Diabetes mellitus (DM) is linked with heart failure even after controlling for coronary artery disease and hypertension. This type of heart failure is called diabetic cardiomyopathy (DM-CMP). DM-CMP has become an increasingly recognized entity among clinicians, hence a better understanding of its pathophysiology is necessary for diagnosis and treatment strategies. In this project we address the relevance of a novel phospho-site S1365 on TSC2 in DM. In several murine DM models mTOR is known to be hyperactivated. Our mouse model (S1365A and S1365E knock-in) can potentially alter mTOR signalling in the diabetic heart and change disease course via several mechanisms including metabolic substrate shift and altered autophagic flux. This discovery has not only implications beyond the cardiomyocyte and the heart but it also reveals a novel mechanism by which PKG works as a strong and drugable command point.

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› Neuroimmunology

Comprehensive Analysis of the Relation Between EBV-Infection and Intrathecal Ig Production in Multiple Sclerosis

Multiple sclerosis (MS) is the most frequent chronic inflammatory demyelinating disease of the central nervous system (CNS). Time of onset typically is in young adulthood, neurological deficits tend to be irreversible with a rapid decline in autonomic living. Early detection and anti-inflammatory treatment is the key for preserving quality of life. Unfortunate for patients and clinical physicians, there is no biomarker for MS. The most characteristic laboratory finding comprises an intrathecal production of immunoglobulins (Ig) which is not found in healthy individuals. While intrathecal production of IgG is detectable in >90% of MS patients, intrathecal production of IgA and IgM occurs in 10% and 20% respectively. They all result from the invasion of the CNS by antibody producing B lineage cells, but the trigger for and the time of CNS invasion are elusive. Importantly, it is well-established that the intrathecal immune response in MS is polyspecific (i.e., directed against a variety of different target antigens) and frequently comprises antibodies to common viruses such as measles virus, rubella virus, and varicella zoster virus. Compelling evidence for an association of infection with the Epstein-Barr virus (EBV) and MS can be found, to the point that from an epidemiological perspective, MS can be regarded as a late complication of EBV infection, a herpesvirus causing strong activation of B lineage cells during primary infection. Nevertheless, the underlying mechanisms remain unknown. In this translational-mechanistic experimental research project we want to investigate the relation between EBV infection (the most important environmental risk factor for MS) and intrathecal Ig production (the most important laboratory feature of MS) by addressing 2 research questions: 1. How strong is the correlation of infection with EBV, as measured by levels of antibodies to Epstein-Barr nuclear antigen-1 (EBNA-1) in serum, with the extent of a quantitative intrathecal IgG, IgA and IgM production in patients with MS? 2. Is there a difference in the frequency distribution of intrathecal antibody production to EBV and to other common viruses in patients with MS? The ultimate aim of this project is thus to improve treatment of patients with MS through a better understanding of pathogenic mechanisms operating in MS.«

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› Innate Immunity
› Hepatology
› Intravital microscopy

In Depth Phenotyping and Functional Profiling of Macrophage Subsets in Chronic Liver Injury and Regression

The liver is an important immune organ and provides the critical filter to prevent dissemination of blood-borne pathogens. The filter function is mediated by specialized liver macrophages, Kupffer cells, that are embryonically derived tissue resident macrophages. Kupffer cells have a unique intravascular location and an arsenal of specialized receptors to capture pathogens under flow conditions. Furthermore, as intrahepatic sentinels, Kupffer cells initiate or suppress immunity in the liver via crosstalk with many other resident and infiltrating immune cells. Liver inflammation leads to a sustained influx of monocyte-derived macrophages that augment the pool of liver macrophages. These bone marrow-derived cells infiltrate as pro-inflammatory cells fueling liver inflammation or as cells with a repair phenotype. To date, the functional consequence of this macrophage heterogeneity and the fate of different macrophage subsets in chronic liver disease is enigmatic. Since patients with chronic liver diseases are hallmarked with immune dysregulation, inefficient pathogen clearance on the one hand and exaggerated immune responses on the other hand, understanding the contribution of different macrophage subsets in the liver is of critical importance. Using a combination of novel linage-tracing tools with state-of-the-art intravital microscopy, we plan to investigate the fate and function of different macrophage subsets in liver disease models. Genetic fate mapping will allow us to differentiate bona fide Kupffer cells from monocyte-derived macrophages. By using multicolor intravital microscopy, we can investigate the function of these subsets with regards to their critical function: capturing of blood-borne pathogens and initiating / suppressing immune responses in the liver via crosstalk with other cells. These investigations will be complemented by using 25-color spectral flow cytometry to further phenotype the different macrophage populations identified. In addition, as a translational approach, we will investigate liver biopsies of patients with various chronic liver diseases. We will isolate and phenotype liver macrophages with multicolor flow cytometry and correlate the findings with clinical characteristics to better understand macrophage biology in humans. Ultimately, by gaining a better understanding of the functional consequences of liver macrophage heterogeneity, we hope to identify novel pathways that can the targeted therapeutically in patients.

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› Hypothermia

»Of Heart and Mind«: A Longitudinal Neuropsychological Evaluation of Children with Congenital Heart Disease

Neurodevelopmental deficits are the most common, and potentially most disabling long-term complications for patients with congenital heart disease (CHD) and their treatment. However, only a few studies have investigated the development of the child longitudinally. That is why we would like to test these patients using different neurological and developmental tests. This prospective longitudinal study evaluates the neuropsychological outcome of children who had a heart operation in the newborn or infant age. Project 1: Common CHD: This patient group includes children with common CHD who required an operation in the new-born and infant period, i.e.: patients who had an arterial switch operation with transposition of the great arteries (TGA), as a common operation in the new-born period; children who had an operation of a ventricular septal defect (VSD) as the most common CHD; and children with surgical repair of a tetralogy of Fallot (TOF) as a cyanotic CHD. Project 2: Resuscitation and mechanical circulation support: Included is patients who had a resuscitation (longer >five minutes) and an implantation of an extracorporeal membrane oxygenation and ventricular assist device. The central measurement instrument is the Bayley Scales of Infant Development, which is a pediatric development test and consists of a series of developmental play tasks used to derive a developmental quotient. The patients will be tested at the age of one, two and three years. In summary, we would like to evaluate the neuropsychological development of children after surgical repair of a TOF, VSD or TGA, compare it to the normal development of children, and determine if there are differences between these patient groups. Finally, we will study the neuropsychological development of children after resuscitation and mechanical circulation support.

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› Depression
› Metabolic disorders

Exploring Inflammatory Pathways Linking Depression and Comorbid Obesity

Major depressive disorder (MDD) is associated with alterations in numerous biological systems, including a dysfunction of the immune system. While the cellular source of inflammation in MDD is still poorly understood, accumulating data point towards an increased activation of monocyte cell populations in depressed patients. Indeed, several studies, including prior work of our group, demonstrated that patients with MDD show an expansion of non-classical monocytes (also commonly referred to as »proinflammatory monocyte phenotype«). In addition, MDD frequently co-occurs with other inflammation-related conditions, such as metabolic syndrome and obesity. Interestingly, obese patients are reported to show a proinflammatory monocyte phenotype, which parallels previous findings in MDD. However, prior research has evaluated the proinflammatory monocyte phenotype in MDD and obesity only in separate studies. Furthermore, given that MDD and obesity have both been linked to inflammation, patients with comorbid MDD and obesity might be especially suitable candidates for clinical trials of anti-inflammatory agents. Thus, the present BIH-project comprises two studies: a cross-sectional and a longitudinal study. The cross-sectional study examines putative differences in the proinflammatory monocyte phenotype and molecular signature across patients with MDD, obesity, comorbid MDD and obesity, and healthy controls. The longitudinal study, embedded in an ongoing RCT, examines whether add-on simvastatin (a lipid-lowering agent with pleiotropic effects including anti-inflammatory properties) to standard antidepressant treatment alters the proinflammatory monocyte phenotype and molecular signature in patients with MDD and comorbid obesity. The present BIH-project aims to provide new insights in the shared cellular and molecular inflammatory pathways of MDD and comorbid obesity, which could translate to new antidepressant therapies for comorbid patients.

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› Imaging

Immunological and Morphological Signatures in Non-Infectious Chorioretinitis to Improve Therapy

Non-infectious chorioretinitis, a form of posterior uveitis encompasses a group of potentially blinding disorders, predominantly occurring in the working age group. Birdshot-Retinochoroiditis (BSRC) and Punctate Inner Choroidopathy (PIC) are an organ-specific inflammation with distinct morphological and genetic characteristics. Disease hallmarks manifest as distinct multiple hypopigmented chorioretinal lesions in BSCR, small punctate lesions and choroidal neovascularization in PIC patients. Both diseases show a clinically progressive course with atrophy of the outer neurosensory retina and formation of fibrotic scars in the final stage. The etiology and pathogenesis are largely unknown but considered as driven by an autoimmune response. It is assumed that BSRC is a chronic T-helper 17-cell mediated inflammation, but only few studies with single parameters and a small number of patients were reported. Therefore, the aim of my research project is to identify immunological and morphological biomarkers in BSCR and PIC patients for better monitoring of inflammatory activity and prediction of disease progression. The T-cell subpopulation will be characterized and phenotyped by mass cytometry. The assessment of morphological signatures will be detected by using multimodal imaging techniques, such as optical coherence tomography, fluorescence- and indocyanine-green angiography, fundusautofluorescence, and a new non-invasive modality the optical coherence tomography angiography (Pohlmann D et al., Ocul Immunol Inflamm. 2017; Pohlmann D et al. Br J Ophthalmology. 2019, Pohlmann D et al. Br J Ophthalmology. 2019). All collected data will be brought into an overall context, in order to get a better understanding of these two diseases and potentially translate to more targeted therapy.

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› Cellular mechanisms of contractile dysfunction and arrhythmias

Sudden Cardiac Death, Arrhythmias and Cardiac Contractile Dysfunction in HFpEF

Heart failure with preserved ejection fraction (HFpEF) is an increasingly common syndrome with poor prognosis, high mortality and morbidity. Sudden cardiac death (SCD) is the most common mode of death in HFpEF (26% SCD in I-Preserve and 24.3% in TOPCAT. However, the pathogenesis of sudden cardiac death in this patient population is not well-understood. The major aims of the project are to investigate underlying cellular causes of contractile dysfunction and calcium mediated arrhythmias in cardiorenal and metabolic HFpEF.

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› Imaging

Functional Brain Changes and Pain Reduction in Patients with Inflammatory Bowel Disease

Brain Changes and Pain Reduction in Patients with Inflammatory Bowel Disease Inflammatory bowel diseases (IBD) are associated with chronic pain in up to 38% of patients. Several chronic pain conditions have previously been shown to result in functional and structural changes in both the peripheral and the central nervous system (CNS). Those so-called maladaptive changes are described as the phenomena of hyperexcitability and hypersensitivity. Recently published work suggests a bidirectional interaction between the central and the enteric nervous system (ENS). Visceral pain in chronic pancreatitis has been associated with an inflammatory infiltration of pancreatic perineuria that includes macrophages, T-cells, and mast cells. We have previously shown that transcranial direct current stimulation (tDCS), a non-invasive method to transcranial modulate neuronal plasticity, is efficient to treat pain in IBD patients (Prüß/Volz et al., Pain 2016). Since the impact of tDCS on the CNS of IBD patients as well as putative effects on the mucosal immune system via activation of the ENS have not been studied yet, we aim to analyze the brain-gut axis by performing a prospective clinical phase-III-trial: tDCS will be applied to IBD patients to ameliorate IBD-associated pain. In parallel, the impact of tDCS on CNS structure and function (fMRI) as well as IBD disease activity and the dynamics of immune cell activity (mucosal and in peripheral blood samples) will be studied in patients before and after tDCS treatment. Finally, in search of the mechanistic link between stimulation of the CNS and mucosal inflammation, we will switch to a mouse model of colitis-associated chronic visceral pain. This will allow to address the interrelation of CNS, ENS, neurotransmitters production and mucosal inflammation and to study underlying mechanisms by assessing the role of a distinct set of neurotransmitters as well as the contribution of inflammatory cellular infiltrates. With this approach, we aim to decipher mechanistic insights of the gut-brain-axis and hence identify novel therapeutic targets.

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› Immunology
› Metabolism
› Treatment strategies

In Depth Phenotyping and Functional Profiling of Macrophage Subsets in Chronic Liver Injury and Regression

Non-alcoholic fatty liver disease (NAFLD) became the most common chronic liver disease worldwide and its prevalence is still increasing. NAFLD is closely associated with the metabolic syndrome and can progress to non-alcoholic steatohepatitis (NASH), which can further advance to fibrosis and ultimately liver cirrhosis. Strikingly, liver fibrosis is the main determinant of liver-related and overall mortality and in contrast to cirrhotic stages, liver fibrosis and NASH are considered as reversible. At present, therapeutic options beyond lifestyle modifications are limited and difficult to sustain – approved pharmacological therapies are still lacking. During disease progression of NASH and hepatic fibrosis multiple signalling pathways (e.g., disrupted metabolic and inflammatory responses) are dysregulated. Latest pathomechanistic insights prompted the experimental and clinical exploration of many new potential drug targets. In the current project we will further elucidate mechanistic insights of the cross-links between metabolism and inflammation in NASH and fibrosis progression. Going into detail, we will investigate effects of metabolism modifying interventions on macrophage functionality in experimental and human NASH employing up-to-date techniques (e.g., Single-cell RNA sequencing, 3D liver biochip system). Among potential inflammatory targets myeloid liver cells (Monocytes and Monocyte-derived Macrophages) emerged as key players orchestrating disease progression. Therefore, we will further elucidate effects of pharmacologically targeting macrophage recruitment on dysmetabolism in NASH and fibrosis. In a recent study we could demonstrate that targeting several PPAR isoforms in different cellular components of the liver (e.g. hepatocytes – PPARα, macrophages – PPARδ, stellate cells – PPARγ) dramatically improved the NASH phenotype over single PPAR isoform targeting in experimental mouse models (Lefere S*, Puengel T* et al, JHEP 2020). Based on these findings and as currently still ongoing clinical trials indicate that single drug treatments demonstrate lacking efficacy in reaching relevant endpoints such as fibrosis regression, we will additionally explore the prospects of rationally designed combination therapies in NASH and fibrosis.

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› Acute Anterior Uveitis
› Arthritogenic Antigens

Gut-Joint-Eye Axis – Arthritogenic Antigens and Their Relevance in Acute Anterior Uveitis and Spondyloarthritis

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease which primarily affects the sacroiliac joints and axial skeleton, though also extra-spinal and extra-articular manifestations occur. Acute anterior uveitis (AAU) is the most frequent extra-articular manifestation, present in a third of axSpA patients. We initiated a prospective cohort of 200 patients with non-infectious AAU (GESPIC-Uveitis), who underwent a standardized rheumatological assessment at inclusion as well as an MRI of the sacroiliac joints. In a preliminary analysis, 60% of the AAU patients had concomitant axSpA (Rademacher et al, EULAR 2019). Though the exact pathogenesis remains unknown up to date, both, axSpA and AAU seem to result from a complex interplay between a genetic background (mainly HLA-B27 positivity), external influences such as mechanic stress, (bacterial) infection and microbiota. According to the »arthritogenic antigen hypothesis« of pathogenesis, peptide antigens presented by HLA-B27 to CD8+ T cells might initiate autoimmunity in SpA. Our hypothesis is, that arthritogenic antigens might be part of the microbiome and lead to an activation of antigen-specific T cells in genetically predisposed individuums via disturbed gut and or skin barrier, thus triggering inflammation as autoimmune reaction in specific tissues (eye, gut, joint). The objective of this project is to identify disease-specific clonal expanded T cell receptors and possible shared and distinct arthritogenic antigens in axSpA and AAU. The analysis of T cells from different tissues (peripheral blood, inflamed joint, anterior chamber of the eye) will enable us to compare their T cell receptor repertoire and challenge the arthritogenic antigene hypothesis. Furthermore, we will analyze whether those antigens are part of the gut microbiota. In a confirmatory analysis, we will verify our findings in the patients of the GESPIC-Uveitis cohort. We thereby aim to get a deeper understanding of the pathogenesis of axSpA and the gut-joint-eye axis.

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› Immune Therapy
› Head and Neck Cancer
› Tumor Biology

Development of a Translational Precision Oncology Program for Head and Neck Cancers

Outcome is dismal for patients with advanced cancers, including patients with tumors of the head and neck. Tumors are characterized by genomic alterations. Novel sequencing techniques allow for a rapid and comprehensive identification of these alterations. The integration of molecular tumor analyses into an individualized treatment plan promises an improved outcome with limited toxicity. However, the complexity of genomic alterations, difficulties in clinical trial design, availability of drugs and many more challenges still limit the application of precision oncology in the clinic. In my clinician scientist project, I am working on the integration of molecular data into the clinical management of patients with advanced cancers with a focus on head and neck neoplasms. My research focuses on the reproducible interpretation of genomic data to identify therapeutic targets, as well as an improved understanding of tumor biology in immune escape and complex cancer genomes.

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› Organ Allocation
› Allorecognition
› Colonic Diverticulitis

The Impact of Donor Derived Microparticles Following Solid Organ Transplantation

Following solid organ transplantation, leukocyte migration and trafficking through the recipient´s body and subsequent allorecognition are the prerequisites for the development of an alloimmune response. Trafficking of leukocytes through blood or lymphatic vessels, as well as their migration in lymphoid or solid organs, is critical for antigen presentation initiating either allograft rejection or mediating allograft acceptance (tolerance). In general, the current understanding of alloantigen recognition by the recipient's immune system ultimately shaping the specific graft rejection mechanism implies two forms of donor antigen recognition that are defined by the source of APC: during »direct« presentation donor-derived cells display donor major histocompatibility complex (MHC) molecules to the recipient, whereas during »indirect« presentation donor-derived antigens are acquired by recipient APCs that process and present these peptides to the host. Although the direct pathway of allorecognition has been described as playing a tremendous role in initiating the adaptive immune response, antigen recognition in the long-term is attributed to the indirect pathway. During the past decades, the idea that secondary lymphoid organs are supposed to be the major sites of antigen presentation is a widely accepted concept. Key to the following project is the comprehensive analysis of passenger leukocytes, their pathway through the body and the sites of alloantigen recognition by the recipient. Especially lymphatic vessels and their function as »leukocyte highway« will be brought into focus. The fact that surgeons do not reconnect lymphatic drainage of solid organs during transplantation questions traditional textbook knowledge but simultaneously offers new scientific possibilities to study passenger leukocytes and other donor derived antigen carriers like micro particles. What is the fate of passenger leukocytes after transplantation? How long do they survive in the recipient? Is there a formation of donor derived micro particles? What is the role of these micro particles?

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› Multiple Myeloma
› Dendritic Cell
› Cancer Vaccine

Augmenting Dendritic Cell Function for Rational Immunotherapies in Multiple Myeloma

Multiple Myeloma (MM) is a heterogeneous hematologic malignancy with courses varying from asymptomatic stages to aggressive disease. Despite a plethora of approved therapies the disease largely remains incurable. Hence, novel anti-cancer therapeutic approaches combining efficacy, tolerability and minimal treatment burden are much-needed. Cancer vaccines have shown to be mainly well-tolerated and can promote long-term specific anti-tumor immune responses. Dendritic cells (DCs) as the most potent antigen-presenting cells are vital players in inducing, maintaining and regulating these immune responses and therefore represent a crucial component of vaccination. Considerable objective responses have been achieved with DC-based vaccines. However, this approach alone has not yet met expectations concerning the clinical outcome. Considering this low clinical efficacy, approaches combining therapeutic cancer vaccine strategies with approved agents are being designed. This provides the opportunity to introduce cancer vaccines into treatment at an early point of disease before onset of severe immune exhaustion. However, a critical challenge in using therapeutic agents to promote cancer immunotherapy is that they potentially also influence immune cells in the tumor microenvironment, possibly further impairing their ability to mount immune responses to dying tumor cells. Our group and others have previously demonstrated altered DC phenotype and impaired function by exposure to various therapeutic agents and we focus on elucidating the influence of further therapeutic drugs in order to identify optimal partners for DC-based immunotherapies. Another scientific interest is the role of checkpoint molecules in MM. In contrast to a variety of other cancers, immune checkpoint blockade, e. g. using blocking antibodies to the Programmed cell death protein 1 or its ligand to date has failed to achieve clinical efficacy in MM. Here too, an exhausted immune system may be the reason for missing response. Even though DCs are dominant partners of T cells, the role of DCs in this setting is not well-characterized. Furthermore, other immune checkpoints may be of relevance. One molecule we seek to further analyse in DCs is Osteoactivin, which was recently shown to be an immune checkpoint that impairs T-cell activation. We plan to further elucidate the role of checkpoint molecules in DCs for a possible targeted manipulation of T cell responses in the context of DC-based immunotherapies.

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› Oxidative Stress

Role and Regulation of Nox4 in Retinal Cells During Diabetes

Anti-VEGF therapies have tremendously improved the treatment of proliferative diabetic retinopathy (DR) and macular edema, the two ocular late manifestations of diabetes, but there are still no therapies targeting early stages of the disease to prevent alterations of the neuroretina and thereby preserve visual function. We and others reported on the early neurodegeneration in DR, triggered by pathomechanisms such as inflammation and the ER stress response in retinal neurons and Müller glial cells (MGCs) subjected to diabetes-related metabolic stress conditions and in streptozotocin (STZ) – induced diabetic mice. Numerous reports indicate the importance of oxidative stress in the development of the early neurodegenerative changes in DR. Hyperglycemia-dependent generation of reactive metabolites lead to excessive reactive oxygen species production (ROS), which are likely to be a key contributor to the development of DR. NADPH (Nox) enzymes generate reactive oxygen species (ROS) and they are widely distributed throughout the retina. Compelling evidence suggests, that in particular Nox4 is an important source of ROS in the retina during DR and thus contributes to the vascular pathology in DR. Still today, there is a gap of knowledge regarding the role and regulation of Nox4 in cell types other than vascular cells, namely retinal neurons, MGCs, and pericytes. Thus with this proposed research project, I aim to develop a complete picture of Nox4 activity in the retina during diabetes by evaluating the role and regulation of Nox4 as a major source of ROS in the aforementioned cells under diabetic conditions in vitro and in two models of diabetes (type 1 & 2) in vivo. We further want to evaluate the rationale of Nox4 inhibition in preventing oxidative stress-induced early neurodegenerative changes in DR. If such a treatment could be realized, it may be possible to arrest DR at the earliest stages of its development.

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› Multiple Myeloma
› Drug resistance
› CRISPR screenings

Functional Characterization of Genomic Networks in Acute Myeloid Leukemia Using CRISPRi/a Screenings

While large sequencing studies have comprehensively characterized recurrent gene mutations in acute myeloid leukemia (AML), the functional consequences of these mutations and the impact of genetic interactions that drive leukemogenesis are less well understood. Mutations in epigenetic modifying genes, such as Isocitrate dehydrogenase 1 and 2 (IDH1/2) and Additional sex combs like 1 (ASXL1), occur frequently in AML patients. It is known that these mutations alter methylation status, which affects cell differentiation and gene expression. In mouse models however, these mutations alone did not induce leukemia, pointing to additional genetic alterations that play a role in leukemogenesis. Genome wide CRISPR screens are powerful tools to identify and functionally characterize genes and vulnerabilities in cancer. In addition to CRISPR-Cas9 knock-out screenings, which are commonly used in most studies, more recently gain- and loss-of-function CRISPRa/CRISPRi screenings have been developed, which enable to comprehensively study activation and inhibition of gene expression. Within my project, we plan to perform genome wide CRISPR activation (CRISPRa) and CRISPR interference (CRISPRi) screenings to identify novel genes and pathways that promote leukemogenesis with focus on mutations in epigenetic regulating genes (IDH1, ASXL1). Besides a deeper understanding of the genomic network that promotes leukemogenesis in the context of these specific mutations, we eventually aim at finding new vulnerabilities that can be used for pharmacological targeting, thus translating our findings into the clinic.

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› Immunology
› B cells
› SLE
› COVID
› Vaccination

Epigenetic Regulation of Plasma Cell Differentiation in Systemic Lupus Erythematosu

Patients with Systemic Lupus Erythematosus (SLE) show epigenetically mediated altered differentiation of plasma cells (PC). PC represent ultimately differentiated B cells producing protective antibodies in the bone marrow, but in case of autoimmune conditions such as SLE, also pathogenic autoantibodies. Plasmablasts (PB) are immature PC that circulate in the peripheral blood. In patients with lupus flares an expansion of the PB population is detectable which contains autoreactive PB and correlates with SLE activity. Very recently, increasing interest focusses on epigenetic regulation of PC differentiation via histone methylation. It has been shown in mice as well as in a human in vitro model that enhancer of zeste homolog 2 (EZH2) catalyzing the histone methylation of H3K27me3 is one of the key mechanisms of PC development. We hypothesize that patients with SLE differ from healthy controls in PC differentiation and that this is in part epigenetically mediated through H3K27me3. Further, we propose that a modification of H3K27me3 during PC differentiation via inhibition of EZH2 or the demethylating opponent of EZH2, jumonji domain containing-3 (JMJD3), can revert aberrant PC differentiation and function in SLE and holds promise for therapy.

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› Macrophage Migration Inhibitory Factor
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› Emergency General Surgery

Role of MIF in Human Acute Peritonitis

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, is a leading cause of death in intensive care units worldwide. Management of sepsis includes timely control of the infection source, which in sepsis resulting from intraabdominal infection often requires emergent surgery. Delay of surgical intervention and inability to obtain source control dramatically increase mortality. However, it remains controversial whether source control should be followed by complete reconstruction of the gastrointestinal tract during emergent surgery or whether limited and repeated surgical interventions according to a damage control strategy pose additional benefit. Macrophage migration inhibitory factor (MIF) is an immunoregulatory cytokine that is of special interest in sepsis pathophysiology because functional MIF polymorphisms predict mortality in different infections, and experimental studies indicate that anti-MIF improves survival even when administered eight hours after infectious insult. Our preclinical data indicate that MIF levels are elevated in septic shock, that MIF recruits highly proinflammatory macrophage subsets to the site of peritoneal infection and that MIF regulates macrophage activation responses that mediate lethal septic shock, thus suggesting avenues for new therapeutic approaches to sepsis. We hypothesize that the severity of peritoneal infection and the precise nature of intraabdominal inflammation with respect to macrophage activation determine the success of surgical reconstruction in the acute setting. Our preclinical data indicate that MIF substantially aggravates sepsis disease progression and suggest that pharmacologic inhibition of MIF may be of therapeutic value. To further define mechanisms that control favorable surgical results and, thus, sepsis outcome we propose two specific aims: 1. To precisely characterize macrophage responses in human acute peritoneal infection/inflammation, and 2. To establish mechanisms by which MIF aggravates human disease progression, and to test the value of pharmacological MIF inhibition as a potential therapeutic target to diminish sepsis-related mortality.

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Molecular Characterization of Spinal Paragangliomas

Paragangliomas are rare neuroendocrine neoplasms that can develop at various body sites including the head, neck, thorax, and abdomen. Approximately 25% have an unfavorable course and patients with metastatic paragangliomas have limited treatment options and poor prognosis. Unlike other types of cancer, there is no established grading system and no reliable predictive and prognostic markers based on morphology and immunohistochemistry. Comprehensive epigenetic and genetic characterization of non-spinal paragangliomas revealed a diversity of driver alterations affecting multiple genes and pathways and resulted in the establishment of molecularly defined subtypes correlating with clinical outcome. Moreover, at least one-third of non-spinal paragangliomas are associated with inherited cancer susceptibility syndromes, which is the highest rate among all tumor types. Paragangliomas of the central nervous system instead occur almost exclusively in the cauda equina and are considered non-familial. However, genetic and epigenetic alterations in spinal paragangliomas have not been investigated so far. In order to gain further insights into the molecular background of cauda equina paragangliomas and their ontogenetic relationship to non-spinal paragangliomas and other neuroendocrine tumors, we investigate a comprehensive series of cauda equina paragangliomas using a combination of whole exome sequencing and genome-wide DNA methylation profiles. We further aim to identify molecular risk factors for better predicting clinical outcomes and druggable targets for future personalized therapy strategies in patients with malignant tumors.

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Neuromuscular Involvement in Systemic Sclerosis

The aim of my project is to assess the prevalence and nature of neuromuscular involvement in Systemic Sclerosis (SSc). SSc is a rare connective tissue disease characterized by the pathophysiological triad of microvascular dysfunction, tissue fibrosis and autoimmune inflammation. Specifically, we will screen patients for symptoms of small fiber neuropathy (SFN) and confirm the diagnosis by skin biopsy. Recent studies show that approximately 45% of all patients suffer from neuropathic pain. However, there is no study systematically evaluating potential causes of neuropathic pain in SSc. Even though SFN is a well-recognized complication of other connective tissue diseases such as Systemic Lupus Erythematosus, it has not been assessed as a cause for neuropathic pain in SSc, yet. Our hypothesis is that SFN is a common complication of SSc. In a second project we will perform a retrospective analysis of SSc muscle biopsies according to current neuropathological standards. We will try to identify a morphological pattern that is specific to SSc. We reckon that the origin of neuromuscular involvement in SSc is not only destructive fibrosis and obliterative vasculopathy, but that the interplay between immune cells and nerve cells is responsible for peripheral tissue damage.

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› Asthma
› Pulmonary th2 inflammation

Role of Spleen Tyrosine Kinase (Syk) in Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension (PAH) is a fatal condition characterized by pulmonary vasoconstriction and pulmonary arterial remodeling leading to increased pulmonary vascular resistance and ultimately right heart failure. Intense research within the past three decades led to successful translation of pharmacological compounds, which are able to improve both quality of life and survival of PAH patients. However, despite modern PAH-specific therapy, PAH remains to be a lethal disease and further research is required. From previous studies we learned that in the airways the non-receptor tyrosine kinase spleen tyrosine kinase (Syk) promotes inflammation, smooth muscle cell proliferation and contraction (Tabeling, C. et al. Allergy 2017 Jul;72(7):1061-1072). However, little is known about the expression and role of Syk in the vascular compartment of the lung. Therefore, in this ongoing project, we analyze Syk expression and function in the pulmonary vasculature and its possible involvement in the pathogenesis of PAH. To date, Syk expression was assessed in human (PAH vs. donor) and murine lungs by immunofluorescence and spectral confocal microscopy. Syk function was analyzed in human precision-cut lung slices (PCLS) and in isolated perfused lungs of wild-type mice or mice deficient in eNOS, PKCα or mast cells with or without inhibition of Syk, protein kinase C (PKC), rho kinase and/or nitric oxide (NO) synthase. Pulmonary vascular hyperresponsiveness was investigated following induction of pulmonary Th2 inflammation. Our data identify Syk as a central regulator of pulmonary vasoconstriction. Syk was expressed in pulmonary arterial smooth muscle cells of both control and PAH lungs. Syk inhibition diminished pulmonary vasoconstriction in human PCLS and in isolated mouse lungs independent of eNOS, PKCα or mast cells. In preconstricted lung vasculature, Syk inhibition rapidly reversed vasoconstriction in a NO-independent manner. Pulmonary vascular hyperresponsiveness was markedly reduced following Syk inhibition. Thus, Syk may be a promising target in PAH therapy and the effects of Syk inhibition on pulmonary arterial remodeling and pulmonary hypertension will be further analyzed in this project. Moreover, we attempt to further characterize the intracellular Syk-mediated signaling cascade leading to pulmonary arterial smooth muscle cell contraction.

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› Identification of new
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› Dissecting the biology of CRC

Studying the Concordance of Molecular Subtypes of Primary and Metastatic CRC in Patient Samples and Organoids

Focus on my research is the better understanding of the CRC biology in order to identify new therapeutical options for the treatment of CRC. To this end, we use CRC organoid models and we compare in vitro data with in vivo data. We furthermore stratify our models, as well as patients samples in different molecular subtypes in order to define subgroups who may benefit from exsisting and new emerging treatments.

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Fields of Research
› bone healing
› immune system

Biomarker for Impaired Bone Healing of the Mandible

This prospective research project is a hypothesis-testing blinded study design. The project objective is to prospectively validate CD8+ TEMRA cells as a biomarker for impaired fracture healing in (A) mandibular corpus fractures and (B) mandibular osteotomies in the setting of mandibular displacement surgery. The project hypothesis here is that CD8+TEMRA cell expression acts as a potential prognostic biomarker with high diagnostic precision in terms of differentiating between normal and impaired fracture healing.

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Fields of Research
› Neural Correlates of Consciousness

The Role of Prefrontal Cortex in Conscious Experience

Despite considerable progress, it is still unclear how conscious experience emerges from brain activity. In the search for the neuro-computational underpinnings of consciousness, the role of prefrontal cortex is particularly controversial: Its activity may shape conscious experience by modulating perceptual processes in sensory brain regions. Alternatively, prefrontal cortex may become active merely as a consequence of conscious experience, serving subsequent cognitive functions such as introspection or response preparation. In this project, we investigated role of prefrontal cortex in consciousness using both virtual and structural lesions. In a series of three experiments, we studied the effects of perceptual conflict on conscious experience, combining computational modeling, functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). Human participants reported periodic changes in conscious experience that were induced by perceptual conflict during bistable perception. Two model-based fMRI experiments showed that prefrontal brain activity in the inferior frontal cortex (IFC) signals the accumulating conflict between conscious experience and ambiguous visual inputs. In a third experiment, inhibitory TMS revealed that a disruption of neural activity in IFC leads to a decrease of conflict-driven changes in perception, indicating a causal influence of IFC on conscious experience. A forth experiments will test whether this effect is also presents in patients who suffered a structural lesions in IFC.

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Fields of Research
› Subarachnoid hemorrhage (SAH)
› extracellular RNA
› brain-heart axis

Microglia-Associated Inflammation after Subarachnoid Hemorrhage (SAH)

Subarachnoid hemorrhage (SAH), caused by the rupture of an intracranial aneurysm contributes for a third of all hemorrhagic strokes and is a devastating disease with a mortality of approx.. 25% and 40%. This pathology poses a unique role in hemorrhagic stroke, since it occurs outside the brain parenchyma at the base of the brain within the basal cisterns that then leads to intraparenchymal damage in an outside-in fashion. Previous studies from our laboratory have shown that microglia accumulation and activation within the brain induces neuronal cell death after experimental subarachnoid hemorrhage, which in turn may contribute to secondary brain injury. This project aims at further characterizing the functional phenotype of resident CNS-macrophages/microglia, and studying their association with the pathological hallmarks of secondary cellular brain injury following SAH in an animal model (filament perforation model). MRI in vivo and ex vivo studies are undertaken to confirm the bleeding and study imaging patterns of SAH. Microglia cells are isolated for RNASeq studies, and further immunofluorescence studies and behavior studies are performed to dissect the dynamics within the course of SAH. In parallel, blood and CSF samples from SAH patients are collected in a prospective study which will be analyzed for potential targets of the immune system.

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Fields of Research
› Calcium Signaling in Heart Failure
› Excitation-Secretion Coupling in Cardiomyocytes

The Heart as an Endocrine Organ: Chromogranin B and the Inositol-1,4,5-Trisphosphate Receptor in Excitation-Secretion Couplingin Cardiomyocytes

In endocrine cells, a crucial role of chromoganin B (CGB) and the inositol-1,4,5-trisphosphate receptor (IP3R) in exocytosis of vesicles and hormone secretion is known. The heart owns characteristics of an endocrine organ as well. We could show that CGB as a marker of secretory granules is also expressed in cardiomyocytes and demonstrated a pathophysiological pathway of the CGB and IP3R interaction in cardiac hypertrophy and heart failure. While excitation-secretion coupling is well described in other excitable cells such as neurons, this concept is novel and not yet studied in cardiomyocytes. Aim of this project is to examine the functional role of CGB and the IP3R in excitation-secretion coupling in cardiomyocytes and in murine models of heart failure with preserved ejection fraction (HFpEF). Final goal will be to establish a pathway that can serve as a new target in heart failure treatment.

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Fields of Research
› Glioblastoma Multiforme
› Vascular Targeting
› Radiosurgery
› Virtual Reality
› Moyamoya Disease

Inhibition of the CXCL2/CXCR2 Signaling Pathway in Glioblastoma Multiforme as a Therapeutic Option

Glioblastoma multiforme (GBM) is the most common and most malignant astroglial brain tumor with an overall median survival of around 15 months. Despite intensive research in recent decades on new therapeutic strategies no considerable advance in glioma treatment was achieved. Thus, novel and innovative therapeutic approaches are required to prolong survival and improve the quality of life for patients with malignant astroglial tumors. High angiogenesis of GBM is one of the causes of high malignancy, thus angiogenesis represents one of the promising therapeutic targets. However, the therapeutic effect of antiangiogenic treatments has been so far limited by diverse resistance mechanisms. Beside the strong vascularization of gliomas, a high accumulation of microglia/macrophages was shown. In addition, Roggendorf et al. proposed a direct correlation between the grade of gliomas and the number of tumor-associated microglia and macrophages. Therefore, these immune cells could represent an effective therapeutic target. We have already published that resident microglia are the main source of brain tumor mononuclear cells, thus these cells represent a promising novel therapeutic target for patients suffering from this tumor. We observed in our glioma mouse model that depletion of microglia/ macrophages resulted in diminished angiogenesis and reduced tumor volumes. We have also discovered a potential new feature of microglia/macrophages in a glioblastoma mouse model by secreting different chemokines. Due to high overexpression as well as indications in the literature the potential contribution of CXCL2 to glioma angiogenesis awakened our interest at most. Thus, the aim of our study it to establish a new therapy with blocking CXCL2 signal way induced angiogenesis in gliomas and to analyze the role of this pathway in recurrent GBM.

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Fields of Research
› Cardiac Electrophysiology
› GPCR/G-protein signaling
› Cardiovascular mechanotransduction and metabolism

Metabolic Plasticity of Smooth Muscle Cells in Human Vascular Disease

Unlike cardiac or skeletal myocytes, vascular smooth muscle cells (VSMCs) are highly plastic and able to switch from a contractile, quiescent state, towards phenotypes of increased proliferation, migration and secretory capacity (Althoff et al. J Mol Med. 2015). This ability to dedifferentiate and redifferentiate is a prerequisite for vascular remodeling processes, which in turn are centrally involved in virtually all vascular diseases. The differentiation state of VSMCs is influenced by a myriad of extracellular cues and tightly regulated by two distinct G-protein mediated signaling pathways, as we have recently demonstrated (Althoff et al. J Exp Med. 2012). Using mass spectrometry, we have now discovered that dedifferentiation of VSMCs is accompanied by a highly dynamic regulation of key metabolic enzymes, indicating a fundamental alteration of VSMC metabolic state. Such metabolic switch has been confirmed by us in metabolic studies on primary VSMCs using an extracellular flux analyzer (Seahorse Bioscience) and in in vivo models for vascular remodeling. Currently we are studying the pathophysiological relevance of this VSMC metabolic plasticity using different murine vascular disease models. Moreover, to determine whether our findings from cultured cells and mice can be analogously applied to human vascular disease, we are performing a patient study in collaboration with the German Heart Center Berlin. In this study we are acquiring vascular samples from patients undergoing surgery in terms of ascending aneurysm repair, coronary artery bypass graft or heart transplantation for ischemic and dilated cardiomyopathy, respectively. Ultimately, we aim to identify strategies that target cellular metabolism for the treatment of cardiovascular disease.

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› Hepato-Biliary Tumors
› Monocytes/Macrophages
› Immunomodulation
› Biomarkers

The Importance of Immune System and Purinergic Pathways in Hepatocarcinogenesis

Hepatocarcinogenesis is associated with chronic inflammation, which is linked to immune dysregulation. The role of purinergic signaling in hepatocarcinogenesis is poorly understood. Disordered purinergic signaling via receptors for danger-associated molecular patterns (DAMPs), i.e. adenosine triphosphate (ATP) and adenosine diphosphate (ADP), is associated with carcinogenesis. Nucleoside triphosphate diphosphohydrolase-1 (CD39/ENTPD1) is an ectonucleotidase that regulates these extracellular nucleotide/nucleoside concentrations by scavenging nucleotides to ultimately generate adenosine. CD39/ENTPD1 is the dominant ectonucleotidase expressed by regulatory T-cells (Tregs). CD39 drives the sequential hydrolysis of both ATP and ADP to AMP. Adenosine promotes immune suppression and tumor progression by stimulating vascular endothelial cell proliferation, and inhibiting immune cell cytokine synthesis, transendothelial migration, and anti-tumor effector responses. Taken together, these properties inhibit anti-tumor immune responses and promote angiogenesis. Based on our previous findings implicating the key role of monocytes/macrophages in hepatobiliary tumors, we hypothesize their function to be mechanistically modulated in a CD39-dependent manner and linked to Tregs activities. With this in mind, we established a tumor model in mice emulating human hepatocarcinogenesis, and were able to demonstrate presence of functionally active purinergic receptors on human monocytes/macrophages. We previously reported angiogenic monocytes/macrophages to associate with tumor growth, metastasis, recurrence and clinical prognosis in primary liver malignancies. Consequently, we focused especially on cytokine levels, apoptosis rate and purinergic receptor profiles, as well as immune cell responses and infiltrates. By performing pharmacologic blockade with selective inhibitors of CD39 activity, and consecutively reducing extracellular adenosine concentrations, we demonstrated therapeutic effects in wild type tumor mice. The survival rates of treated animals were significantly improved compared to control groups. In addition, tumor volumes and numbers were markedly reduced after treatment. A successful chemotherapy implies that an immunologic checkpoint inhibition of CD39 enzymatic activity may find utility as an adjunct therapy for hepatic malignancies.

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Fields of Research
› Acute Lymphoblastic Leukemia
› Molecular Leukemogenesis
› Genotype Informed Treatments

Oncogenic Drivers in the Molecular Pathogenesis of Acute Lymphoblastic Leukemia

The prognosis of adult patients suffering from B cell precursor acute lymphoblastic leukemia (BCP-ALL) is still poor, especially in case of relapsed disease. Detailed knowledge of leukemogenic drivers is required for targeted therapeutic interventions. We integrate high resolution profiling of gene fusions, sequence mutations, copy number alterations as well as gene expression- and DNA methylation profiles together with clinical phenotypes to characterize novel drivers and resistance factors in BCP-ALL. With-in a cohort of 250 BCP-ALL patients we have established a novel molecular subgroup by a distinct gene expression and DNA methylation profile. We identified a combination of sequence mutations in the hematopoietic transcription factor PAX5, copy number loss in the cell cycle regulator CDKN2A and activating RAS/MAPK- or JAK/STAT-pathway mutations as bona-fide drivers of the disease these patients, thus representing an interesting disease model where hallmark signaling pathways each are affected by a single defined alteration. Analyzing a cohort of 90 matched diagnosis – relapse sample pairs, we observed the frequent acquisition of mutations in histone methylation regulators during BCP-ALL relapse. We perform ChIP-Seq analysis of mutated primary patient samples and cell line models to delineate the impact of these alterations on gene regulation. Using CRISPR genome editing, we create functional models of the identified mutations to dissect the signaling mechanisms involved and to validate potential therapeutic targets. Further oncogenic signaling dependencies are explored in a drug sensitivity profiling of primary BCP-ALL samples and cell lines with defined genomic background. Together, these analyses provide the framework for a molecular tumor board to guide individual treatment decisions in relapsed/refractory BCP-ALL. Together with our cooperation partners, we are currently developing this tumor board within the German Acute Lymphoblastic Leukemia Study group.

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Fields of Research
› Adipocytokines
› Cardiomyopathy

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The Role of Adipocytokines on the Coagulation System in Patients with Cardiomyopathy

Patients with cardiomyopathy show multiple risk factors for the development of thromboembolic events. These include hemodynamically relevant parameters such as impaired contractile force and the resulting pathological wall movements of the myocardium, as well as differentially exposed cytokines that may influence blood hemostasis parameters. Adipocytokines such as adiponectin, leptin, resistin, and visfatin are largely released from adipose tissue into the systemic circulation. They exert a central role in the regulation of energy balance in humans. In addition, they also possess modulatory properties in the field of hemostasis. For example, adiponectin, classically considered to be anti-inflammatory, shows inhibitory influences on procoagulant parameters such as tissue factor (TF). These effects are differentiated depending on the molecular structure of adiponectin. In contrast, the adipocytokines leptin and resistin, which are described as inflammatory, have procoagulant properties due to the increased expression of parameters such as TF, coagulation factor VIII, fibrinogen and Von Willebrand factor. Patients with clinical cardiomyopathy show different expression patterns for adipocytokines. In this context, it seems necessary to consider not only systemic serum levels but also local cardiac expression processes of adipocytokines in order to describe their effects on hemostasis in the circulation. In this project, the first step is to describe a complete picture of the expression of adipocytokines such as adiponectin, leptin, resistin, and visfatin in patients with nonischemic cardiomyopathy. By obtaining endomyocardial biopsies, cardiomyopathy is defined particularly by the possibility of describing cardiac inflammatory processes. The expression level of adipocytokines is determined on a cardiac local as well as on a systemic level. Based on this, the second step focuses on describing the effects of the adipocytokines on the regulation of parameters of coagulation and fibrinolysis.

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› Experimental Neurology
› Neurotoxicity
› Chemotherapy Induced Neuropathy

Pathophysiology and Prevention of Chemotherapy-Induced Neuropathy

Neurotoxic phenomena are among the most common side effects of cytostatic chemotherapy and affect a large number of patients. They further increase the burden of disease for patients and directly affect prognosis by necessitating treatment changes. Despite the high relevance for patients, comparatively little research efforts are allocated to neurological side effects of chemotherapy. In the past, neuroprotective interventions for neurological diseases such as stroke have failed in clinical trials due to the unpredictable onset of damage. In contrast, chemotherapy-induced neurotoxicity is ideally suited for a preventive therapy, as the time point of damage is well defined and evidence suggests that the molecular mechanisms of neurotoxicity differ from the cytostatic mode of action in many chemotherapeutic agents. We hypothesize that an impaired intracellular calcium (Ca^{2+}) homeostasis is an important aspect of chemotherapy-induced peripheral neuropathy (CIPN) and a potential therapeutic target. In an initial step, we thus established cell- and animal models of chemotherapy-induced neuropathy for a number of clinically relevant cytostatic drugs. These models are then used to further elucidate the role of a deranged intracellular Ca^{2+} homeostasis in CIPN. In addition to this line of experiments, we use a screen of differentially regulated miRNAs to identify novel disease mechanisms. Understanding the molecular mechanisms underlying CIPN development will not only improve our understanding for the (patho-)physiological states of sensory neurons, but also enable us to develop new strategies for the prevention and treatment of CIPN.

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Fields of Research
› Ovarian cancer
› Ultrasound imaging

BERLINER Study – The Role of Circulatory Biomarkers Alone and in Combination with Systematic Ultrasound to Identify the Risk of Ovarian Cancer in Pelvic Mass Patients

Ovarian cancer is the main cause of death due to gynecological malignancies. Ovarian cancer is called the »silent killer« due to lack of specific symptoms. This fact leads to most of ovarian cancer patients being diagnosed in advanced stages, with only 25% of the cases diagnosed in stage I and II, when the disease is limited to the pelvis. Early stages patients have a significant improved overall survival, compared with patients in advanced stages. Therefore finding new effective methods for the early diagnosis of ovarian cancer is mandatory in order to significant improve survival rates. The most used biomarker for assesing the risk in pelvic mass patients, is the cancer antigen 125, CA125. CA125 is increased in 80% of advanced stages, but only 50% of the early stages, furthermore is increased in benign diseases leading to false positive results. Therefore there is an urgent need to identify new serologic biomarkers, and to analyse their diagnostic role alone and in combination with clinical parameters such as transvaginal ultrasound. Aim of this study was to develop a new algorithm for the early diagnosis of ovarian cancer that will combine CA125, HE4 and other serological and genomic biomarkers with systematic transvaginal ultrasound.

As secondary aims we would like to

- Identify new predictive biomarkers in Serum and Urine, as also genetic changes that could predict the response to the platinum-based chemotherapy and to bevacizumab.
- Identifycirculatorybiomarkerasalsogenetic-changestopredictsurgicaloutcome.

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Fields of Research
› Psychopharmacology
› Pharmacogenetics
› Transcultural psychiatry

Psychosocial and Genetic Factors Influencing Antidepressant Response in Patients of Turkish Origin

Genetic factors are known to influence the risk for psychiatric disorders as well response to psychopharmacological treatment (e.g., Brandl et al., 2014, Lett et al., 2016). However, only few findings have yielded independent replication, and pharmacogenetic testing has not yet been successfully established in clinical practice (Müller/Brandl et al., 2018). Further research is required to achieve a more detailed understanding of genetic underpinnings of treatment response. In particular, the interaction between genetic and psychosocial factors influencing treatment response is poorly understood. Moreover, there are a number of ethnic groups where pharmacogenetic factors have not been studied sufficiently in psychiatric research. Therefore, this research project investigates psychosocial as well as pharmacogenetic influences on antidepressant response in patients of Turkish origin. Migrants with Turkish background have a high risk for development of depression and other psychiatric disorders. They show a high symptom load and more often receive polypharmacy (Brandl et al., 2018), reflecting poorer treatment response compared to patients without migration background. However, there is only sparse literature on psychosocial factors influencing antidepressant treatment response in migrants in general as well as on pharmacogenetics of antidepressant response in patients of Turkish origin. The project investigates antidepressant response in patients of Turkish origin with major depression over the first eight weeks of treatment and aims to identify psychosocial as well as genetic factors associated with treatment response. The results of the project will not only contribute to pharmacogenetic research but may also help to improve psychiatric treatment for this underserved population in the future.

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› Retinal vascular diseases
› Neurodegeneration
› Angiogenesis
› Choroidal pathologies

Interaction Between Pathological Angiogenesis and Retinal Neurodegeneration

In recent years, treatment and prevention of vascular retinal diseases has decisively improved, in particular with regard to age-related macular degeneration, diabetic and veno-occlusive retinopathy. Nevertheless, current first-line therapy with inhibition of the vascular endothelial growth factor (VEGF) is limited. Pathological vessel growth can be inhibited as long as continuous intravitreal anti VEGF injections are given, however, in long-term use it causes irreversible retinal ischemia and atrophy. Based on this background, detailed interaction between inhibition of pathological angiogenesis and retinal neurodegeneration is poorly understood. The aim of my research project is to analyze the interaction between pathological angiogenesis and retinal neurodegeneration. Using animal experimental approaches molecular mechanisms of mutual influences will be investigated. Furthermore, pathological processes of vascular and primary neurodegenerative retinal diseases will be compared. Thereby fundamental pathomechanisms of degenerative retinal diseases should be better understood to develop novel treatment strategies. Finally, results obtained should be compared with outcome of clinical studies.

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Influence of the Complement System on the Myofibroblast Activation During Corneal Wound Healing

Degenerative eye disorders, which are associated to a severe loss of visual acuity very often are the result of misguided angiogenesis or wound healing/fibrogenesis; and thereby are the response to ischemic of inflammatory processes. Today, there are no causal therapeutic approaches for the treatment of fibrotic eye disorders. Hence, the aim of my BIH Charité Clinician Scientist project is to investigate the Influence of the complement system on the myofibroblast activation during corneal wound healing. Therefore, we will analyze molecular mechanisms of human specimens and perform animal experiments to identify involved key processes. Thereby we will contribute to a better understanding of fundamental pathomechanisms of corneal wound healing. Finally, current treatment regimes shall be optimized and new therapeutic approaches may be derived.

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Fields of Research
› Image-Guided Ablative Tumor Therapy

Beyond the Margin of Local Ablation: Perifocal Immune Responseand Tumor Progression After Image-Guided Ablative Tumor Therapies in a VX2 Liver Tumor Model

While surgery remains the favored treatment option for resectable liver malignancies, only a minority of patients is amenable to surgery at presentation. This situation has led to the development of various minimally invasive tumor ablation techniques for patients with unresectable liver tumors. The most commonly used and best-understood ablative technique is radiofrequency ablation (RFA), which has now been officially included into international treatment guidelines and, since 2012, has been the therapy of choice in patients with very early hepatocellular carcinoma not amenable to liver transplantation. The underlying tumoricidal effect of RFA relies on the generation of frictional heat, which results in thermal coagulation necrosis of the tumor and the surrounding peritumoral tissue. However, only limited knowledge is available on the perifocal ablation zone beyond the ablation margin and immune response observed after image-guided tumor therapy. Initial evidence suggests that perifocally expressed immunomodulators have a role in tumor progression following local ablation. Hence, the overall goal of our project is to characterize the tissue rim surrounding the ablation zone following use of different ablative modalities and to elucidate the effects of local ablation on residual tumor deposits and systemic spread in a VX2 liver tumor model.

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Fields of Research
› Glioma angiogenesis
› Molecular mechanism of spinal metastasis
› Moyamoya disease

The Role of EphrinB2-EphB4 Signalling for Vascular Resistance Development in Malignant Glioma

Targeting glioma vasculature with antiangiogenic agents has become a clinically established medical therapy in order to control glioblastoma multiorme growth and tumor associated edema. Despite increasing clinical use, antiangiogenic agents have not been approved as first line treatment for malignant glioma due to the lack of superiority proof in diverse randomized controlled trials. Despite the initial assumption that antiangiogenic therapy may be resistant against resistance mechanisms, glioma studies have shown that malignant glioma develop several mechanisms to induce resistance against antiangiogenic therapy. A major player for developing vascular resistance against antiangiogenic therapy are pericyte-endothelial cell interactions. The EphrinB2-EphB4 signalling cascade is the major regulator of pericyte-endothelial cell interactions in malignant glioma. In our clinical scientist project we investigated the influence of the EphrinB2-EphB4 system on vascular resistance mechanisms against antiangiogenic therapy in experimental glioma focusing on pericyte-endothelial cell interactions. Using different in vivo glioma models, small animal MR imaging and intravital microscopic techniques the results of our project showed that endothelial EphB4 overexpression led to stabilization of pericyte-endothelial cell interactions and consequently to vascular resistance against anti-VEGF therapy i.e. glioma vacsularization was not reduced in response to VEGF inhibition. In turn, endothelial EphrinB2 knock out induced increased sensitivity for antiangiogenic treatment. Correspondingly, EphB4 overexpressiong glioma did not show reduced tumor growth in response to antiangiogenic treatment. The results consequently identify EphrinB2- EphB4 mediated modulation of pericyte-endothelial cell interactions as an important factor in the development of vascular resistance in malignant glioma.

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› Clonal Hematopoiesis and Preleukemia
› Lymphomagenesis

Molecular Characterization of Hematopoietic Stem and Progenitor Cell Involvement During Leukemo- and Lymphomagenesis

The hematopoietic system is organized as cell hierarchy having at its top, a hematopoietic stem cell (HSC) and organized in three cell compartments, the hematopoietic stem cells compartment, the progenitor compartment and the mature cells compartment. The hematopoietic stem cell functions are tightly regulated by a specific microenvironment mainly located in the bone marrow for the HSC, but other microenvironments are involved in the differentiation of lymphoid progenitors such as the thymus for early T cell differentiation. Leukemia (or lymphoma) development results from the accumulation of mutations, generally somatic. We and others have reported that acquired mutations affecting early progenitors occur in various myeloid malignancies such as acute myeloid leukemia, or myelodysplastic syndromes. However, the contribution of progenitors to lymphomagenesis is less understood. We investigated the repartition of acquired mutations in the hematopoietic differentiation tree of chronic lymphocytic leukemia (CLL) patients. Our findings establish the presence of acquired mutations in multipotent hematopoietic progenitors and show that CLL develop from a pre-leukemic phase and propose abnormality in hematopoietic and early B-cell differentiation through deregulation of the MAP kinase pathway as a paradigm for the initial steps of CLL development (Damm et al., Cancer Discovery 2014). In order to gain further insights into the role of progenitor involvement of different lymphoid malignancies, we investigate patients suffering from various types of lymphomas, using a combination of whole-exome and targeted deep resequencing. We study the ontogeny, clonal hierarchy, their dynamics and evolution during the clinical course. To this aim, flow-sorted cell fractions, single cells, and different compartments are analyzed.

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› Bone Development
› Inborn Errors of Metablism

Functional Characterization of the Protein TGDS and the Pathophysiology of Catel-Manzke Syndrome

Rare monogenetic skeletal malformations and connective tissue diseases are models for the development and metabolism of the skeleton and connective tissue. The underlying genetic alteration of a large number of such diseases is unknown at the present time, although knowledge of the genetic cause is of great importance to affected families. Catel-Manzke syndrome is an autosomal recessive skeletal disorder, characterized by retrognathia and cleft palate (Pierre-Robin sequence), heart defect, short stature and a unique hand malformation with a bilateral deviation of the index fingers. Recently we identified mutations in the gene TGDS as the cause of Catel-Manzke syndrome. We assume a role of the protein TGDS in proteoglycan synthesis or turnover since overlapping skeletal disorders are due to alterations in these processes and TGDS shows similarities to an enzyme involved in proteoglycan synthesis. This project aims to characterize the molecular function of TGDS and the pathomechanism of the disease. Using CRISPR/Cas, a mouse model will be generated and analyzed with cell and molecular biology as well as histological methods. In addition, we intend to use genome sequencing to identify the so far unknown molecular basis of skeletal disorders similar to Catel-Manzke syndrome (»Catel-Manzke-like syndrome«). We expect our results to reveal new aspects of limb, heart and craniofacial bone development and expand the understanding of proteoglycan metabolism, which is involved in a large number of development and aging processes by modulation of various pathways. In addition, we aim to improve the genetic counseling and clinical care of the affected patients and their families.

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› Immunology
› T cells

Cellular Urinomics – Flow Cytometric Detection of Urinary Cell Signatures as Noninvasive Approach to Diagnose and Investigate Renal Diseases

Simplified, the pillars of the classic laboratory workup of renal diseases consist of an evaluation of the renal glomerular filtration rate (creatinine, cystatin C), assessment of the function of the filtration barrier (proteinuria) and a microscopic analysis of the urine sediment. Analysis of the sediment in particular holds clues to whether an inflammatory kidney disease is present. However, it mainly relies on a semi-quantitative evaluation of unstained cells, is observer-dependent and does not have a high sensitivity or specificity. Normally the urine is almost devoid of immune cells and contains only small numbers of epithelial cells. This changes dramatically in different renal diseases. In previous studies we were able to demonstrate high numbers of urinary CD4+ T cells in patients with active lupus nephritis (LN) using flow cytometry. Applying the amount of urinary T cells as a biomarker in a systemic lupus eythematosus cohort (n=147) we were able to detect patients with acute LN with a very high sensitivity and specificity. Interestingly, monitoring the amount of urinary T cells in the follow up was able to identify patients with remission and those with refractory disease. Aim of our present work is to establish different cellular signatures in the urine applying flow cytometry. Besides different immune cell subsets we will also detect and quantify renal cells like tubular epithelial cells and podocytes. We predict that the analysis of urinary immune cells, tubular epithelial cells and podocytes will enable us to identify different renal diseases and separate the elements of renal inflammation, acute tubular necrosis and glomerular damage.

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› Liver Fibrosis
› Purinergic Signaling
› Macrophage Physiology

Purinergic Immune Regulation in Acute and Chronic Liver Injury

Liver fibrosis is caused by various chronic liver diseases, including inflammatory, toxic and metabolic diseases, and can result in liver cirrhosis and organ failure. Liver cirrhosis is among the ten most frequent causes of death in Germany. Liver transplantation remains the only therapeutic option of end-stage liver cirrhosis. Further research is needed to better understand the underlying pathophysiology, to refine non-invasive diagnostic tools and develop effective antifibrotic therapies. Liver fibrosis is characterized by excessive formation of scar tissue that replaces healthy liver cells, mainly produced by activated hepatic stellate cells that transdifferentiate into myofibroblasts. Different subsets of macrophages modulate the activation of stellate cells and thereby regulate development and resolution of fibrosis. The functions of both macrophages and stellate cells are controlled by their microenvironment that is altered by inflammatory and metabolic changes in surrounding cells, including the secretion of cytokines and metabolites into the surrounding extracellular space. Purinergic signaling by extracellular purines such as ATP and adenosine is one of the pathways that effect both macrophage phenotype and stellate cell differentiation. ATP is secreted in situations of cell stress, cell death and inflammation. The CD39 family of ectonucleotidases controls the concentrations of extracellular ATP and adenosine by hydrolyzing ATP and ADP to AMP which is further degraded to adenosine. Members of this family are expressed on macrophages and have also been observed on circulating cellular microparticles. The project aims to further define the underlying cellular and molecular mechanisms of purinergic regulation of macrophage function in liver fibrosis.

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Studies on the Functional Role of the Protein Kinase PKN1 in the Regulation of the Intestinal Barrier Function

The intestinal barrier represents an essential interface within the human body, separating the intestinal lumen from the finely regulated interior milieu. Numerous in vivo and in vitro observations demonstrate that disruptions of this barrier play a significant role in the pathogenesis of chronic inflammatory bowel diseases by leading to an uncontrolled transfer of antigens into the interstitium, which may subsequently lead to the initiation of an inflammatory response. Changes in the structure and function of the tight junctions between neighboring epithelial cells are of particular importance; however, the responsible molecular mechanisms have only been incompletely characterized so far. In particular, the signal transduction pathways that mediate barrier disruption induced by proinflammatory cytokines such as TNFα are not fully known, and thus a therapeutic approach aimed at improving intestinal barrier function for the treatment of inflammatory bowel disease has not yet been successfully developed. This project focuses on the investigation of whether PKN1 is involved in barrier regulation in intestinal cells. A particular focus here will be to characterize the role that PKN1 plays in mediating TNFα induced barrier dysfunction. Specifically, the following goals are pursued: (1) To investigate the effects of PKN1 activation and inactivation on basic Parameters of the epithelial barrier in vitro. (2) To investigate the role of PKN1 in steroid-induced tight junction sealing in the intestinal epithelium. (3) To investigate the role of PKN1 in TNFα-induced barrier disruption.

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› Clonal Hematopoiesis and Preleukemia
› Myeloproliferative Syndromes

Investigation of Functional Consequences of Clonal Hematopoiesis

Clonal hematopoiesis – defined by the presence of a somatic hematologic-cancer-associated gene mutation – occurs in the peripheral blood of at least 10% of persons older than 60 years of age without any history of hematologic disorders and defines a premalignant state. The presence of this common phenomenon is associated with an increased risk of hematologic cancers and overall mortality, which cannot be explained by hematologic cancers alone. Clonal hematopoiesis is believed to originate in the stem cell compartment, as mutations occur in the hematopoietic stem cells or in progenitor cells. The most frequent mutations of clonal hematopoiesis belong to four functional groups: (1) epigenetic regulators of transcription (e.g. DNMT3A, ASXL1, and TET2), (2) RNA-processing (e.g. SF3B1, SRSF2, U2AF1), (3) signal transduction (e.g. JAK2, K-/N-RAS, STAT3), and (4) tumor suppressors and oncogenes (e.g. TP53, BRCC3). Functional relevance of these mutations has been demonstrated in mouse models. If the mutation occurs at a variant allele frequency of at least 2%, the phenomenon is called clonal hemaptopoiesis of indeterminate potential (CHIP). At present, caution is needed when predicting clinical consequences from a cancer-associated gene mutation, especially with regard to the stem cell compartment. In the first part of the project, I investigate the effect of CHIP on the differentiation process of hematopoietic stem cells in elderly individuals without cancer using targeted deep sequencing in flow-sorted cell fractions. A second part of my project aims at describing the clinical effects of CHIP in elderly patients with solid cancer receiving myelotoxic (radio-)chemotherapy, looking at outcome parameters such as frequency of neutopenic fever, transfusion necessity, chemotherapy dose reductions, etc. Clonal dynamics under the evolutionary pressure of chemotherapy are also investigated.

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› Fetal Programing After Diabetic Pregnancy
› Uterine Natural Killer Cells in Preeclamptic Pregnancy

Epigenetic Modification in Fetuses of Diabetic Pregnancy

Intrauterine environment during pregnancy influences offspring later life health, a phenomenon known as fetal programming that has enormous impact on global public health. Maternal physical and mental state, as well as nutrition and life style determine intrauterine environment during pregnancy. Maternal diabetes during pregnancy has an increasing prevalence in western countries of up to 10% of pregnancies. It leads to a pathological intrauterine environment by inducing fetal hyperglycemia and increases risk for diabetes and obesity in offspring later life. The molecular mechanisms for this phenomenon are not well understood, but epigenetic mechanisms influencing gene expression are suspected. We focus on deciphering epigenetic changes and its pathophysiological role in diabetic rat pregnancy. We have shown that rat fetuses of diabetic pregnancy display relevant hypermethylation in the promoter region of Srebf2, a transcription factor and master regulator of cholesterol metabolism, which is paralleled by downregulation of Srebf2 gene expression in liver and brain (Golic et al., Hypertension 2018). We are currently phenotyping adult offspring of diabetic rat pregnancy with regard to glucose and fat metabolism and cardiovascular system to address the pathophysiological relevance of our finding and to elucidate whether the epigenetic changes are persistent. We are also interested in characterizing reversible epigenetic changes and to analyze the environmental factors that induce removal of epigenetic modifications. Knowledge about pathophysiological consequences of epigenetic modifications and its removal could enable development of new therapeutic strategies. In addition, it offers insight into development of diabetes and understanding how environment influences health on a molecular level.

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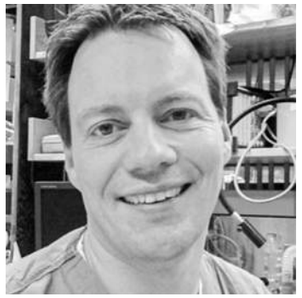

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› Acute Respiratory Distress Syndrome
› Hemolysis
› Blood Transfusion

Transfusion-Associated Effects of Extra-Cellular Hemoglobin on the Development and Severity of Ventilator-Induced Lung Injury

Mechanical ventilation is used to support millions of critically ill patients each year. However, despite its life-saving potential mechanical ventilation can cause injury and complications. The most important adverse effect of mechanical ventilation is the ventilator-induced lung injury (VILI). Among others, patients on the Intensive Care Unit are challenged with increased levels of circulating intravascular cell-free hemoglobin which causes vasoconstriction by depletion of endothelial nitric oxide, oxidative stress, and inflammation. Furthermore, cell-free hemoglobin contributes to tissue injuries such as renal failure and intestinal mucosa damage after cardiac surgery and is associated with an increased mortality in patients with sepsis. Recently, we demonstrated that increased plasma concentrations of cell-free hemoglobin and heme after transfusion of stored packed red blood cells potentiate a primary injury induced by prolonged hypotension. With this project, we would like to extend our knowledge and explore in more detail the mechanisms by which cell-free hemoglobin and heme might aggravate VILI. We study whether increased plasma concentrations of cell-free hemoglobin accelerate the development and increase the severity of VILI. Both, VILI and extracellular hemoglobin independently induce systemic pro-oxidant and pro-inflammatory effects. Therefore, we explore pulmonary and additional extra-pulmonary foci of inflammation and apoptosis in VILI with and without exposure to cell-free hemoglobin. Furthermore, we study whether the adverse effects caused by cell-free hemoglobin might be attenuated by therapy with the hemoglobin scavenger haptoglobin.

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› T cell immunology
› Tumor immunology
› Single cell technologies

Phenotypes, Clonal Relatedness and Functions of Multiple Myeloma-Infiltrating T-Cells

Multiple myeloma is characterized by the accumulation of neoplastic plasma cells in the bone marrow and develops from a non-malignant pre-cancer, called monoclonal gammopathy of undetermined significance (MGUS). T-cells influence disease development, therapeutic responses, and survival, yet, little is known about their clonal restriction, differentiation states, and functions at the single cell level. Technologies such as cytometry by time-of-flight (CyTOF) and next generation sequencing allow the high-dimensional detection of even rare immune phenotypes on the single cell and molecular level. We hypothesize bone marrow-infiltrating multiple myeloma-reactive T-cells to show unique immune phenotypes, clonal expansion, and functional aberrations that successively render them incapable of eliminating the malignant T-cells during disease progression. 40-dimensional CyTOF phenotyping and functional analyses of multiple myeloma, MGUS, and healthy bone marrow will detect unique disease-associated T-cell phenotypes and patterns of disease progression. Parallel single cell sequencing of paired α and β T-cell receptor, cytokine, and transcription factor genes from bone marrow-infiltrating T-cells will identify expanded and most likely multiple myeloma-reactive T-cell clones. The T-cell receptors of predominant clones will be reconstructed, recombinantly expressed, and screened against peptide-MHC libraries to identify their possible ligands. Finally, we will use phosphorylation-specific flow cytometry to determine whether bone marrow lymphocyte signaling alterations are cytokine milieu-driven or T-cell intrinsic. Determining detailed bone marrow lymphocyte phenotypes, clonal relatedness, specificities, and functions, our study will add substantially to the field of multiple myeloma biology and possibly lead to new therapeutic strategies in cancer immunology.

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Retinoic Acid Homeostasis in Major Depression

The central research question of this project is to elucidate a putative link between an altered retinoic acid (RA) signaling in the pathogenesis of major depression. RA, the most active metabolite of Vitamin A, plays a key role as a morphogen during embryonic development and represents an endogenous neuroprotectant and anti-inflammatory agent in the adult CNS. Several lines of evidence suggest altered cerebral RA signaling in affective disorders. Preliminary own work has demonstrated strong effects on local RA-homeostasis for select antidepressants and also for the pleiotropic anti-inflammatory antibiotic minocycline, for which antidepressant effects have recently been discussed on the basis of its potent actions on microglial cells, inhibiting microglial activation. Therefore, we will further investigate putative RA-modulating effects of minocycline and of several antidepressants in a preclinical subproject. In parallel, we will assess altered parameters of RA-homeostasis in drug-free depressed patients and matched controls. Furthermore, we will conduct a randomized, placebo-controlled clinical trial to assess putative anti-depressant effects of minocycline in so far treatment-refractory depressed patients. In the same study, we will systematically assess an impact of minocycline on RA-homeostasis-related parameters over a 6-week time course of treatment with minocycline or placebo. Elucidating a role for RA-Homeostasis in the pathogenesis and treatment of major depression will be an important step in the development of more targeted interventions to treat depressed patients, particularly those not responding to standard treatments.

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› Atherosclerosis
› Inflammation
› Interventional Cardiology

IRhom2 in Atherosclerosis

Tumor necrosis factor (TNF)-alpha is a potent inflammatory mediator that plays an important role in the development of atherosclerosis. It is expressed as a precursor transmembrane protein and subsequently converted into its soluble, bioactive form by TNF-alpha converting enzyme (TACE) mediated shedding. Recently discovered inactive rhomboid protein 2 (iRhom2) is essential for maturation of TACE in immune cells. A genetic knock-out or knock-down of iRhom2 results in a loss of TACE activity and, consequently, in a markedly reduced shedding of TNF-alpha in cells involved in atherosclerosis such as macrophages. iRhom2-deficient mice exhibit reduced serum levels of TNF-alpha in response to inflammatory stimuli, survive otherwise lethal doses of LPS and are protected from the development of inflammatory arthritis. These findings strongly suggest that the iRhom2/TACE/TNF-alpha signaling axis may contribute to atherosclerosis. However, to date, this hypothesis has not been tested experimentally. Therefore, our group evaluates the impact of iRhom2 on atherosclerotic plaque development and on phenotypic and functional characteristics of macrophages as well as the pathophysiological role of iRhom2 in patients with coronary artery disease. Taken together, this project aims at characterizing the role of iRhom2 in atherosclerosis and thus contributes to better understanding of inflammatory processes in atherosclerosis and the development of novel therapeutic strategies for the treatment of this disease.

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› Spatial transcriptomics
› Single-nuclei transcriptomics

Transcriptional Regulation in Healthy and Diseased Kidney Tissue

Kidneys of higher mammals comprise a complex ensemble of many different T-cell types including renal tubules, immune and interstitial cells, to mention but a few. Renal tubules are again subdivided into distinct tubular segments serving the excretion of toxins and participating in body water and electrolyte homeostasis. The renal collecting ducts constitute the most distal part of the renal tubules and are responsible for urine finetuning including electrolyte and water reabsorption. We were recently able to uncover the role of a collecting duct-expressed transcription factor, grainyhead-like 2 (GRHL2), which mediates collecting duct tightness and barrier function (Aue, Hinze et al., JASN, 2015; Hinze et al., JASN, 2018). Lack of collecting duct GRHL2 led to a constant loss of electrolytes and free water and a susceptibility to prerenal acute kidney injury. We could show that GRHL2 orchestrates a set of genes involved in cell-cell junction formation and maintenance in renal collecting ducts. However, the vast heterogeneity of cells forming the kidney drastically complicates the analysis of physiological and pathological renal processes. Each cell type has a distinct role in health and can become an outcome-determining population in disease. Cell type behavior and functions are mainly determined by distinct transcriptional gene expression programs. So far, researchers used a combination of microdissection followed by RNA sequencing to uncover renal transcriptional programs in various settings. We were recently able to establish single-cell RNA sequencing in our lab. This technology facilitates the investigation of gene expression in individual cells and cell populations. With it, we want to deepen our understanding of GRHL2 function in the kidney but also apply it to clinical questions such as in polycystic kidney disease.

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› Inflammation After Stroke

Influence of Endothelial IL6/Stat3 Signaling on Angiogenesis, ECM Remodeling and Neuro-Plasticity After Stroke

Stroke is the second leading cause of death and the leading cause of disability worldwide. Treatment is limited to a narrow time window of 4.5 h, but fewer than 10% of patients benefit from this, and many are left with severe, lasting disabilities. A treatment focused on improving regeneration and functional recovery in the long term would be of great benefit, indeed, the brain harbors endogenous mechanisms to improve neuronal network rewiring. Interleukin 6 (IL6) is associated with higher risk for atherosclerosis and stroke and increased blood IL6 levels correlate with worse outcome. However, other studies have reported IL6 in the acute phase of stroke is able to reduce lesion size. The pleiotropic effects of IL6 might be explained by complex signaling mechanisms that differ according to the cell type involved and the condition of the tissue microenvironment. We have shown that downstream IL6 signaling of endothelial Signal transducer and activator of transcription 3 (Stat3) is of high importance for remodeling of the extracellular matrix (ECM), promotion of angiogenesis and functional recovery. We hypothesize that paracrine IL6 signaling within the neurovascular niche can improve neuronal network rewiring and functional recovery. We generated a mouse model for cell-specific and inducible expression of IL6 (FLEX-IL6). The secreted IL6 is subsequently detectable by a fused myc-tag. IL6 secretion will be induced 2 days after stroke to focus on regenerative mechanisms, rather than preventing acute cell death. We will analyze the effects on functional recovery, angiogenesis, and ECM remodeling. IL6 acts on the CST (tracible by the fused myc-tag), when it is secreted by astrocytes. We will further explore this relationship by using laser capture microdissection to excise IL6 positive CST bundles in order to characterize protein expression. Effects on network rewiring and CST regeneration will be visualized by tract-tracing methods, MRI connectivity analysis, and pharmacogenetic inhibition methods (DREADD).

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› Experimental Cardiology

Electrical and Mechanical Dysfunction in Atrial Cells During Diastolic Heart Failure

Atrial remodeling (enlargement, contractile dysfunction) and atrial arrhythmias are often observed in heart failure and are associated with worse clinical outcomes. In heart failure with preserved ejection fraction (HFpEF) atrial remodeling is particularly common for further compromising left ventricular filling. A variety of mechanisms including increased left ventricular diastolic pressure and neuro-humoral activation have been linked to atrial remodeling in HFpEF. However, the cellular mechanisms leading to atrial dysfunction in HFpEF remain elusive. We use echocardiography, MRI, in-vivo hemodynamics and state of the art cellular imaging techniques (e.g. FRET imaging, local photoactivation, ratiometric and non-ratiometric confocal Ca^{2+}/Na^{+} live cell imaging) to study atrial remodeling in HFpEF. Aims of the current project are: 1) to characterize mechanisms that lead to contractile and/or rhythm dysfunction during atrial remodeling in a rat HFpEF-model, caused by metabolic syndrome, as well as in human myocardium with an emphasis on Inositol-1,4,5-triphosphate (IP3)-receptor mediated Ca^{2+} release, and the activity of the Na^{+}/Ca^{2+} exchanger (NCX); 2) to identify pharmacological targets for the treatment of atrial dysfunction in HFpEF.

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› Cognition
› Neurodegeneration
› Pain
› Translational research

Pathomechanisms and Prevention of Chemotherapy Induced Cognitive Impairment

Neurotoxic phenomena are among the most common side effects of chemotherapy and often result in a major limitation for therapy, preventing optimal medical care. Furthermore, they significantly increase the burden of disease for cancer patients by severely affecting the quality of life. Changes of cognitive function associated with chemotherapy (post-chemotherapy cognitive impairment (PCCI) or »chemobrain«) have gained increased scientific interest, as the underlying pathophysiology remains unclear. We have gathered evidence that very low dosages of systemic chemotherapy such as paclitaxel or bortezomib are sufficient to induce cell death in adult neural stem cells via calcium and caspase-mediated pathomechanisms. This results in an impaired hippocampal neurogenesis and distinct cognitive deficits in mice. For paclitaxel, we have identified a molecular target and established an interventional strategy using lithium to inhibit cytotoxicity of adult neural stem cells in vitro and prevent cognitive impairment in vivo. In a translational effort, we are currently testing patients with paclitaxel chemotherapy for neurocognitive deficits in a prospective longitudinal study (CICARO-study) and comparing the results to non-treated patients. To further elucidate the underlying pathomechanisms of PCCI, we are investigating the role of proinflammatory cytokines in cell culture and animal models as well as patients to establish potential biomarkers. Furthermore, we are characterizing the functional outcome of newly identified molecular targets and evaluating novel therapeutics in the prevention of PCCI in animal models, gathering information for a potential clinical use.

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› Regeneration
› Cardiomyocytes
› High-Throughput Screening

Identification of Pro-Proliferative MicroRNAs in Human Cardiomyocytes Using a Functional High-Throughput Screening

The project aims to detect microRNAs (miRNAs) with the ability to induce and enhance proliferation in human cardiomyocytes (CM) by using high-throughput screenings and high-content imaging techniques. MiRNAs are small non-coding RNAs, which profoundly alter protein output by interfering with messenger RNAs (mRNA) at the post-transcriptional level. In humans, CM withdrawal from cell cycle is observed early after birth. The marginal number of adult CMs (approx. 1%) undergoing cell cycle and stem/progenitor cells supporting myocardial regenerative processes cannot compensate for a myocardial loss after cardiac injury. Therefore, the project aims to improve cardiac regeneration in patients with myocardial infarction/ischemic cardiomyopathy by targeting miRNAs significantly involved in cardiomyocyte pro-proliferative pathways. High-throughput-screenings using a miRNA-library were performed in CMs derived from human induced pluripotent stem cells (hiPSC-CMs). Proliferative capacity of miRNA-transfected hiPSC-CMs was analyzed using a high-content imaging system. Significant miRNAs will be validated in vitro and in vivo. The project is performed in collaboration with the screening unit of Dr. J. P. von Kries (FMP, Berlin-Buch) and the stem cell group of Dr. K. Streckfuß-Bömeke (Universitätsmedizin Göttingen) and is supported by German Centre for Cardiovascular Research (DZHK) and Deutsche Stiftung für Herzforschung (DSHF).

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Fields of Research
› Obesity and Energy Balance Regulation
› Human Gut Microbiota
› Glucose Metabolism

Plasticity of the Human Gut Microbiota During Weight Loss and its Consequences in Humanized Gnotobiotic Mice

This project is geared towards understanding the complex constitution of commensal gut microbes in patients with metabolic diseases and their plasticity during weight loss. During the last years, we collected stool samples from overweight and obese individuals during a randomized weight loss intervention trial. To investigate gut microbial communities we performed 16 S sequencing and whole genome sequencing of the gut microbiota. We found substantial plasticity in the weight loss group with profound changes in the relative abundances of specific microbial clades that have been linked to metabolic health. These changes go along with gene content variation indicating a shift in the metabolic propensity of the of ›obese-type‹ microbiota. To test whether these changes themselves are relevant in body weight regulation we performed humanization experiments in germfree mice. For this, we chose to transplant the gut microbiota of obese individuals before and after severe weight loss. Out preliminary data suggest that humanized mice receiving the gut microbiota from individuals after/during severe weight loss develop a dramatic weight loss within a very short period after transplantation, a phenomenon which is not seen in mice receiving the microbiota of the same individuals before weight loss. Additionally, just looking at the gut microbiota we were able to develop a machine learning algorithm that predicts weight loss during a weight loss program only based on the gut microbial composition at baseline. In a next step, we want to find the top microbial candidates that may promote negative energy balance and initiate the translation into a first human intervention trial.

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› Chemoresistance
› Aggressive B-Cell Lymphomas
› Transgenic Mouse Models

A Pan-Omics Approach to Treatment Failure in a Transgenic Mouse Model of Aggressive B-Cell Lymphomas

Treatment failure is the key determinant of poor outcome in lymphoma therapy. Unveiling the underlying molecular mechanisms is critical to overcome drug insensitivity and may direct the development of novel therapies. Since patient samples are rarely available as matched pairs at diagnosis and at a resistant state, and cannot be further drugchallenged or subjected to functional validation experiments, we considered transgenic mouse models of cancer as valuable tools for the molecular dissection of treatment responsiveness. We utilize transcriptomics, proteomics, metabolomics, kinomics, whole exome sequencing and copy number analysis in a »panomics« approach to decipher mechanisms of treatment resistance in a Myc-driven lymphoma mouse model with previously documented cross-species predictability for human diffuse large B-cell lymphomas.Immunocompetent recipient mice were transplanted with primary Eμ-myc transgenic mouse B-cell lymphomas, and exposed to cyclophosphamide (CTX) upon tumor manifestation. Mass spectrometry-based proteomics, metabolomics as well as array-based transcriptomics, genomics, kinomics and copy number alteration analysis were applied, and the data subjected to bioinformatics processing to unveil mechanisms of treatment resistance.After treatment of lymphoma-bearing mice, lasting remissions (reflecting cure) were observed in about half of them. Repetitive treatments of mice harboring relapse lymphomas resulted in progressively shortened remission times and finally led to full-blown resistance, thereby recapitulating clinical courses of patients with drug-insensitive aggressive lymphomas. Gene-, RNA-, protein- and metabolite-analyzing omics technologies were applied to compare curable vs. relapse-prone and resistant lymphomas, all with or without an additional short-term exposure to CTX to acutely challenge drug-specific response programs. Eμ-myc lymphoma-bearing mice treated in a clinical trial-like fashion were established as a versatile model of clinical chemoresistance. Going beyond a transcriptome-restricted investigation, our pan-omics strategy aims to dissect underlying mechanisms that will be further exploited as targets on their own for novel lesion-based therapies in future cancer precision medicine.

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Fields of Research
› Bone Metabolism
› Fracture Healing
› Posttraumatic Inflammation

Cellular and Molecular Characterization of Fracture Healing in Traumatic Brain Injury

Impaired fracture healing including malunions still represents an ongoing clinical challenge as treatment options remain limited. This is surprising, since bone is one of two organs that is capable to completely restore structure and function without scar tissue formation. In contrast to healing impairments, the clinical phenomenon of traumatic brain injury (TBI) positively affecting fracture healing is of utmost importance from a basic science and clinical point of view. Using an experimental approach, we could previously demonstrate that callus formation is increased in a mouse model combining surgically induced TBI and fracture of the femur. As the underlying mechanisms remain unclear, we are currently investigating the cellular and molecular basis for the observed phenomenon. First, based on our own preliminary experiments and observations made by other investigators, we test the mechanistic involvement of leptin and alpha calcitonin gene-related peptide, both of which are elevated in polytraumatized patients, in the increased callus formation following brain injury. In parallel, extensive gene expression profiling, histological and FACS analyses as well as serum and urine measurements are applied to further dissect and identify crucial target organs, cells and signaling events involved in accelerated fracture healing during TBI. Promising candidates and signaling pathways are further investigated using primary cell cultures and cell lines. Finally, pharmacologic and genetic proof-of-principle experiments are performed to verify the influence of established candidates in vivo. The cellular and molecular characterization of accelerated fracture healing-complementing research on delayed healing is basis for a fundamental understanding of bone healing and its challenges, and backbone to any development of new therapeutic strategies for affected patients.

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› Vascularized Composite Tissue
› Allotransplantation
› Transplant Immunology

Novel Treatment and Diagnostic Approaches Utilizing the Role of Dendritic Cells in Immune Responsiveness

Vascularized composite tissue allotransplantation (VCA) including hand, upper extremity, face, and abdominal wall transplants have emerged from a visionary therapy option in the past to become an innovative reconstructive treatment modality for patients with devastating tissue defects that are not amendable for conventional treatment protocols (Swearingen et al, Transplantation 2008). However, patients must undergo life-long immunosuppression with unwanted effects such as infection, renal toxicity, and cancer. Therefore, it is crucial to understand the underlying mechanisms of skin rejection as the most immunogenic fraction of VCAs to improve existing immunosuppressive therapeutic approaches in VCAs. Our overall objective is, therefore, to critically examine the immunogenicity of mature and immature DCs. Of note, studies of DCs in VCA have also the potential to provide novel treatment approaches for skin and, ultimately, solid organ transplantation. Extremity transplants are currently challenged by two main unsolved problems: the speed of nerve regeneration to regain full motor and sensory function, and most importantly, the application of immunosuppressants with a myriad of unwanted and life-threatening complications for a non-life saving procedure (Shores et al, J Am Acad Orthop Surg, 20100. Dendritic cells (DC) are known to play a key role in T-cell activation via presenting antigenic peptides in the context of MHC molecules to the T-cell receptor (TCR), as well as by providing co-stimulatory signals required for T-cell proliferation and differentiation (Benichou et al, IImmunotherapy 2011). We hypothesize that intragraft DC composition plays a critical role in the potent immunogenicity observed in VCA.

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› Endocrine Cancers
› Adrenals

Androgen-Dependent Regulation of Whole Body Sodium Metabolism, Blood Pressure and Cardiovascular Function

Nowadays, cardiovascular diseases greatly determine morbidity and mortality in industrialized countries. Epidemiological findings demonstrate sex differences in cardiovascular risk: In industrialized countries, men suffer from cardiovascular diseases more often and at a younger age than women [Gos-Wald A et al. Bundesgesundheitsblatt, Gesundheitsforschung Gesundheitsschutz 2013]. Men also have a higher blood pressure than women [Stamler J et al. JAMA 1976]. These observations suggest that androgens contribute to this sexual dimorphism. Sodium intake influences the development of arterial hypertension, as well [Elliott P et al. BMJ 1996]. However, the exact mechanisms responsible for salt-sensitive hypertension and the relationship between sex, salt intake and endogenous regulation of sodium metabolism are widely unknown. Experimental data provided compelling evidence that macrophages are key elements in the regulation of sodium accumulation in the skin [Machnik A et al. Nature Medicine 2009]. High sodium intake promoted lymph hyperplasia in rats. This effect was mediated via the tonicity-responsive enhancer binding protein (TonEBP) in mononuclear phagocyte system (MPS) cells. TonEBP works as a transcription factor and enhances vascular endothelial growth factor C (VEGF-C) secretion. Interference with this system might contribute considerably to the development of sex-specific differences in blood pressure control. The androgen receptor (AR) is expressed in macrophages [Ikeda Y et al. J Endocrinol 2012]. In sum, the role of androgens in the regulation of whole-body sodium metabolism is only poorly understood. We generated macrophage/monocyte-specific androgen receptor knockout mice to investigate macrophage-mediated androgen action. Since macrophages also play a role in the development of obesity, glucose and lipid metabolism will be explored in this mouse model, as well.

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› Head & Neck Cancer
› Preclincial Models
› Biomarker Research
› Target Identification

Development of Novel Treatment Strategies for Head and Neck Cancer Employing Patient-Derived Xenografts

Even though therapeutical options have recently improved, the treatment of recurrent and metastatic head and neck cancer (HNSCC) remains a challange. So far there is only Cetuximab as the single approved compound with a targeted approach in this disease and predictive biomarkers allowing a treatment stratification a largely missing. The current research project is based on a steadily growing platform of patient derived xenografts from head and neck cancer. Starting in 2012, we meanwhile successfully established more than 60 models from various locations and disease stages of HNSCC, which display the heterogeneity of this disease. Established tumor models are characterized on a molecular level for whole gene expression, mutational profile and morphology through FFPE section staining. Further, the models are treated with different compounds, which are used in clinical routine in the treatment of head and neck cancer. Treatment responses are correlated with clinical courses of patients. Through the correlation of response to a given compound with tumor biology we aim to identify predictive biomarkers. Through the knowledge of tumor characteristics of the models were are able to select models for novel research projects. Especially with the advent of novel compounds, that have a specific target and only function under certain conditions, e.g. a mutation of the target, we are able to perform biomarker research driven studies. Positive results may create the rationale for clinical trials

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› Chronic Depression
› Psychotherapy Research

Neurobiology of Chronic Depression: Alterations in Emotion Regulation and Influence of Psychotherapy

About 20% to 30% of patients with a major depressive disorder (MDD) have a chronic disease course (MDD lasting for at least two years). Chronic depression (CD) is a specific subtype of MDD, however, it is barely characterized and demonstrates with high rates of treatment resistance. In contrast to episodic depression, CD often has an »early onset« even in adolescence. The development and persistence of CD are often related to adversity and maltreatment experienced during childhood as emotional neglect for example. Patients with CD often demonstrate a »lack of social empathy«, interpersonal challenges, global and prelogical thinking processes and additionally a reduced affective control. Furthermore, there is growing evidence for a disturbed emotion regulation in patients with depression, however, the results are inconsistent. Especially early childhood trauma seems to be associated with an altered activity of emotion-regulating brain regions (increased amygdala activity, reduced activity of prefrontal cortex). In our project, we want to evaluate, if emotion regulation (reappraisal) is altered in CD in contrast to episodic depression in a fMRI paradigm. Furthermore, we want to investigate, if emotion regulation is depending on specific emotional activation and if there is an altered regulation of the amygdala and the prefrontal cortex. The influence of a specific psychotherapy on emotion regulation in CD is part of a third project.

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› GPI-Anchor Deficiencies
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› Interpretation of Whole Genome Sequences

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Systematic Analysis of Genotype-Phenotype Correlations in GPI-Anchor Deficiencies

In all eukaryotes, there is a complex in the plasma membrane with the key task of anchoring glycoproteins on the cell surface, called the glycosylphosphatidylinositol anchor (GPI-anchor). GPI-anchored proteins (GPI-APs) play a central role in signal transduction, cell adhesion, and antigen presentation. Defects in the synthesis and maturation of the GPI-anchor and their consequences for GPI-APs represent a class of congenital disorders of glycosylation (CDG) that can cause congenital as well as acquired disorders. Among the inherited forms is Mabry syndrome, a recessive disorder that is characterized by intellectual disability, epilepsies, an elevated alkaline phosphatase and a distinct facial gestalt. Paroxysmal nocturnal hemoglobinuria, PNH, is an acquired GPI-anchor deficiency, due to somatic loss of function mutations in cells of the myeloid lineage. Currently, about 30 genes are known to play a role in the GPI-anchor synthesis and maturation. In several of these genes, disease-causing mutations could be identified over the recent years. We found pathogenic mutations in the genes PIGV, PIGO, PGAP2 and PGAP3 in patients with Mabry syndrome and mutations in PIGT in patients with atypical PNH for the first time. In our project, we aim at identifying novel genes that are involved in the GPI pathway as well as regulatory mutations. For this purpose, we use exome sequencing and whole genome sequencing to find pathogenic mutations in patients with suspected GPI-anchor deficiencies of the unknown molecular cause. Flow cytometric analyses play a key role in the assessment of suspected GPI-anchor deficiencies and bioinformatics are an essential part of the data evaluation.

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New Regulators of Liver Regeneration

Primary and secondary malignancies of the liver represent the second most common cause of cancer deaths worldwide. It is well established that liver surgery is oncologically superior to systemic therapy and loco-regional treatment alternatives in primary liver malignancies. Evolving evidence even suggests liver resection increase survival rates in patients with localized tumor spread. Thus, extended liver resections are increasingly applied to a broader spectrum of patients, e.g. patients at a high age or with impaired regeneration capacities due to underlying chronic liver disease, e.g. non-alcoholic fatty liver disease (NASH). Preoperative possibilities to dissect patients who benefit from liver surgery from patients who will face serious complications, e.g. post-operative liver failure, are still limited. Therefore, a better understanding of liver regeneration and non-invasive diagnostic are urgently needed, as it would help to increase the safety of liver surgery and to offer liver resection to a higher number of critically ill patients.

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› Metabolism
› Monogenic obesity
› Rare endocrine diseases

Rare Endocrine Diseases

The development of obesity in industrial and also in low- and middle income countries is a severe burden for health care systems, because obesity is a major risk factor for the development of cardiovascular diseases and type 2 diabetes mellitus. The leptin melanocortin signaling pathway is playing a pivotal role for the regulation of satiety. Gene mutations within this pathway are leading to hyperphagia and early onset obesity. Here, the activation of neurons expressing the gene pro-opiomelanocortin (POMC) via leptin receptors (LEPR) is stimulating to the production of melanocyte-stimulating hormone (MSH), which in turn activates the G-protein coupled receptor melanocortin-4 receptor (MC4R). This is leading to satiety and modification of energy expenditure. Within the CSP project, I have started an investigator-initiated phase 2 proof of concept trial, in which patients with mutation in the gene pro-opiomelanocortin (POMC) and leptin receptor gene (LEPR) have been treated with a MC4R agonist 1, 2, 3. This study drug led to restoration of the impaired pathway and reduction of body weight. Based on this study-data, phase 3 trials have been performed and this MC4R agonist has been approved by the FDA in 2020 as the first drug for the treatment of genetic obesity.

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› CAR-T-cell Therapy
› Neuroblastoma

A CAR-T-Cell Approach for Solid Tumor Attack Using Neuroblastoma as a Model

Targeting tumors by adoptive T-cell therapy is a promising innovative approach that hijacks the immune system to direct effector mechanisms against metastatic and resistant tumor cells. One form uses chimeric antigen receptors (CARs) to target tumor-associated antigens, which while successful against leukemia and lymphomas has not yet made strides against solid tumors. I am interested in optimizing CAR-T-cell therapy for solid tumors to remove the current difficulties that the solid tumor environment presents for this innovative harnessing of immune potential against cancer cells. During my postdoc time in Seattle, I developed a CAR specific for CD171, an antigen expressed in several solid tumors including neuroblastoma, the most common extracranial tumor in childhood with an overall survival of less than 50% in high-risk patients. My current research interest is to increase the persistence and efficacy of CAR-T-cell-based immunotherapy for children with neuroblastoma using the CD171-CAR. I will focus on a) a 3D neuroblastoma cell culture model to investigate which CAR constructs enable T-cells to invade solid tumors, b) structurally CAR construct optimization to regulate activation and target binding, and c) an analysis of the influence of oncogenic MYCN activity on the tumor microenvironment and CAR-T-cell effector function, which also tests the efficacy of combining drugs targeting MYCN with CAR-T-cell therapy. In order to dissect the mechanisms leading to either tumor eradication or relapse, I will use a syngeneic mouse model for the transferred T-cells and the host. The CD171-CAR will be introduced into CD8+ T-cells derived from a mouse expressing a single TCR with tumor unrelated specificity (OT1/Rag-/-). This way T-cell-derived species-specific cytokines such as interferon gamma can only act on the tumor stroma and cancer cell recognition by T-cells occur exclusively through the CD171-CAR.

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› Parasitology
› Malariology

Delayed Haemolysis Following Artemisinin Therapy of Malaria

Malaria remains the most important vector-borne infectious disease in humans. Its importance has been recognized also recently by the award of the 2015 Nobel Prize in medicine to the malariologist Tu Youyou. Artemisinins have become the most important class of antimalarials during the last decade. They are superior to all other antimalarials in terms of efficacy, safety, and tolerability. Episodes of severely delayed hemolysis have recently been observed in non-immune patients treated with Artemisinins for severe malaria. More than 80% of these patients required red blood cell transfusion and re-hospitalization. Post-Artemisinin delayed hemolysis (PADH) has also been reported in a cohort of African children with severe malaria. The pathophysiological background, exact incidence and risk factors of PADH are still poorly understood. The research program aims at addressing these open questions within the following sub-projects: The epidemiology and clinical presentation of PADH will be assessed in a clinical study in cooperation with the European network for tropical medicine and travel health (Tropnet). Thereby the incidence and possible risk factors of PADH will be identified. Primary human hepatocytes will be used to metabolize artemisinins in an In-vitro model. Metabolites with the potential to induce auto-immune mediated hemolysis will thereby be identified. Simultaneous analysis of the cytochrome-profile of the employed hepatocytes will allow assessing inter-individual differences in the pharmacokinetic properties of Artemisinins with respect to different cytochrome-isoenzymes. Changes in membrane properties of red blood cells after malaria will be analyzed using flow cytometry. Results will be used to decipher the underlying mechanism of erythrocyte loss in PADH. Results of this integrative multi-pronged research project shall help to improve the drug safety of Artemisinins as the most important class of antimalarials.

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› Hemophagocytic Lymphohistiocytosis in critically ill patients
› Immune dysfunction in critically ill patients
› Immune stimulation during immune suppression

Biomarkers for Adult Hemophagocytic Lymphohistiocytosis in Critically Ill Patients

Hemophagocytic Lymphohistiocytosis (HLH) is a rare life-threatening hyperinflammatory syndrome with a mortality rate of 68%. It often remains undiagnosed due to sepsis-like symptoms. Early and reliable diagnosis of HLH in the intensive care unit (ICU) is pivotal for patient outcome. It is known that adult HLH is triggered mainly by infectious diseases, malignancies, immune deficiency and autoimmune diseases, leading to an impaired function of cytotoxic T lymphocytes and natural killer cells. This results in an excessive immune activation of macrophages and T-cells with extreme cytokine production of interferon γ (IFN-γ), and tumor necrosis factor α (TNF-α) – the so-called cytokine storm. These highly activated macrophages and the »cytokine storm« infiltrate lymphoid and non-lymphatic tissues and lead to hemophagocytosis and multiple organ failures. Within this project, we plan to build up a biobank and systematically investigate this life-threatening hyperinflammatory syndrome in the ICU in order to detect biomarkers for an early diagnosis. The project aims to find a highly sensitive and highly specific biomarker panel to significantly improve the currently available diagnostic possibilities, to get further insights into its pathophysiology, and subsequently to reduce mortality. In particular and driven by previous studies, we analyze CRP, PCT, IL-1β, IL-6, IL-8, IL-10, TNF-α, IFN-γ, SIL-2R, ferritin, glyco-sylated ferritin, EBV and CMV viral load, the microRNAs miR-205-5p, miR-194-5p and miR-30c-5p, perforin and CD107a.

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› Endothelial function
› Neuroepidemiology

Biomarkers of Endothelial Function in Stroke – the Prospective Cohort with Incident Stroke Study Berlin (PROSCIS-B)

Endothelial dysfunction (ED) is an early component of atherosclerosis, which plays a major role in the development of cardiovascular and cerebrovascular diseases. ED is an established independent predictor for the occurrence of cardiovascular disease, such as myocardial infarction or cardiovascular death, but whether ED also plays a role in cardiovascular risk after first ischemic stroke, is currently unclear. Endothelial dysfunction also play a causal and integral role in the development of a vascular diseases of the small cerebral arteries, so-called »small vessel disease« that is associated with poor outcome after stroke. Novel biomarkers of endothelial dysfunction should be investigated in a good-characterized prospective stroke cohort study (»PROSCIS-B«; clinicaltrials.org NCT01363856). The following aims are defined within the CS program: Determination of novel biomarkers of endothelial dysfunction as stromal- derived factor 1 (SDF-1), antiendothelial autoantibodies and endothelial microparticles (EMP) in the acute phase of ischemic stroke within the »Prospective Cohort with Incident Stroke Study Berlin (PROSCIS-B) and correlation with stroke severity and stroke volume. Evaluation of cerebral MRI markers for cerebral small vessel disease (»white matter lesion«) with visual rating scales and volumetric analyzes in correlation with the above-mentioned biomarkers of endothelial dysfunction. To test the hypothesis whether biomarkers mentioned above are independent risk factors for poor functional and cardiovascular outcomes at one to three years after first stroke.

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› Neurophysiology
› Neurometabolism

Impact of Anesthetics on Cerebral Energy Metabolism During Light and Deep Anesthesia: Possible Implications for Postoper

Anesthesia is a state of pharmacologically induced unconsciousness, amnesia, and analgesia that allows surgery and intensive care treatment – undoubtedly a key element of modern medicine. However, deep anesthesia is associated with postoperative delirium and lasting cognitive decline. The underlying mechanisms of these postoperative complications are largely unknown. The depth of anesthesia can be classified by typical EEG patterns. Burst suppression (BS) and isoelectricity characterize deep anesthesia and correlate with hypometabolism in the brain. Similar EEG-patterns also occur during situations with energy mismatch such as hypoxia or traumatic brain injury, suggesting similar but reversible effects of anesthetics on cerebral metabolism. In the clinical routine, the use of deep anesthesia to reduce metabolism and evoke neuroprotection is controversial as anesthetics impair mitochondrial function. Importantly, the relationship between mitochondrial dysfunction and depth of anesthesia was not yet systematically studied. We aim to characterize the effects of anesthetics on the oxidative phosphorylation and function of neurons during different anesthetic regimes in vitro (i.e. brain slices) and in vivo in rats. Combining oxygen-measurements, electrophysiology and flavin adenine dinucleotide (FAD)-imaging with computational modeling, we want to predict possible targets of anesthetics in the mitochondrial enzymatic system. Understanding mitochondrial function during deep anesthesia will increase our knowledge on the pathophysiology of postoperative neurological complications. Furthermore, comparing gaseous and intravenous anesthetics has clinical relevance for appropriate therapeutic choice. Last, the use of multiparametric measurements and computational modeling could lead to find new biomarkers and improve monitoring during surgery and clinical situations in which deep anesthesia is performed such as status epilepticus or high intracranial pressure.

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› Sleep medicine
› Chronobiology

Prevention of Delirium in Critically Ill Patients

Delirium is the most frequent psychiatric syndrome in the intensive care unit (ICU). The development of delirium in critically ill patients is independently associated with a 3-fold increase in risk of death within six months after ICU admission. Moreover, up to 40% of patients suffer from long-term cognitive impairment after critical illness (similar to scores for patients with mild Alzheimer's disease). Within an interdisciplinary project, supported by the Federal Ministry of Economy, 2 ICU rooms were completely redesigned. The major goal of the redesigning process was to create an ICU bedroom that produces measurable improvements in the physical and psychological states of patients, visitors and staff. Beside interventions aimed at noise reduction, workflow optimization and infection control, we conducted modifications to improve lighting conditions in the room. The first part of the Clinical Scientist project compares acoustic and photobiological characteristics of the modified as well as the standard ICU rooms and evaluates the potential effects of these modifications on patients' outcome. Within the second part of the project, a prospective observational cohort study will investigate the incidence of delirium in patients treated in one of the modified ICU rooms and patients in the standard rooms on the same ICU. We will further evaluate the impact on sleep quality (polysomnography), circadian rhythm (cortisol, melatonin, »clock genes), global cognitive function and general outcome parameters.

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› Posterior Lamellar Keratoplasty
› Intraocular Pressure Elevation
› Corneal Angiogenesis and Lymphangionesis

Evaluation of Surgical Technique of Posterior Lamellar Keratoplasty and Postoperative Complications

Corneal endothelial disorders like Fuchs endothelial dystrophy and bullous keratopathy were treated by penetrating keratoplasty (PKP) since years. Prolonged visual rehabilitation of over a year, high astigmatism, suture-related complications and graft rejection are common complications after PKP. Alternative surgical techniques like Descemet Stripping endothelial keratoplasty (DSEK) or Descemet membrane endothelial keratoplasty (DMEK) have been developed over the last decade and allow the transplantation of posterior corneal layers instead of the complete cornea. Whereas in the DSAEK procedure the technique with graft preparation and graft unfolding is well standardized and reproducible, the technique of DMEK surgery remains challenging. Especially, the main step of the surgical technique of DMEK, the unfolding of the lamella to attach the graft to the posterior stroma, poses difficulties. During this step, the most manipulations to the graft occur. We investigated if the more difficult unfolding correlates to donor characteristics and to the final outcomes (Maier et al., Graefes, 2015). Additionally, we evaluated, if the localization of the surgical approach influences the postoperative outcomes (Maier et al., Am J Ophthalmol, 2015). Postoperative complications like graft detachment, graft rejection, and postoperative intraocular pressure elevation occur also after DMEK. We analyzed the rate and localization of graft detachment (Maier et al., Cornea, 2016). Additionally, we investigated the incidence of postoperative intraocular pressure elevation and analyzed causes and risk factors (Maier et al., Graefes, 2014, Maier et al., J of Glaucoma, 2017). Corneal angiogenesis and lymphangiogenesis are associated with a higher risk of graft rejection after corneal transplantation. We study the role of different factors like ECM molecules in the development of these blood and lymphatic vessels (Maier et al., IOVS, 2017).

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› Metabolic Phenotyping
› Electrophysiology

Probing and Manipulating Neuronal Circuits in Obesity

The prevalence of obesity and type 2 diabetes (T2DM) has reached epidemic proportions worldwide. Primarily reward-related overconsumption of highly palatable, energy-dense foods beyond homeostatic needs is considered a central aspect in the multifactorial pathogenesis of obesity and the accompanying metabolic distortions. Recent cumulative evidence indicates that dysfunctional information flow cortico-striatal networks involved in metabolic regulation, as well as reward processing, may be of primary importance for the pathophysiology of obesity. Progress in the exploration of functional anatomy in a number of neuropsychiatric disorders revealed dysfunctional neuronal processing within cortico-striatal circuits. This aspect and the emergence of deep brain stimulation as a suitable approach to probe and manipulated neuronal activity prompted the concept of circuit disorders for diseases as for example Parkinson's disease, obsessive-compulsive disorder, addiction, and depression. Due to multiple similarities of the neuronal information processing with respect to obesity and recent advances in dissecting the neurocircuitry involved in the regulation of food intake and metabolism by optogenetic studies, cumulating evidence suggests that obesity might be understood in a similar way as the circuit disorder involving malfunctioning of the cortico-striato-hypothalamic system. We, therefore, aim in our experimental design to investigate local field potential oscillations within this system characterize information processing and to apply deep brain stimulation (DBS) in order to manipulate neuronal activity as a potential therapeutic approach in obesity.

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› Energy Metabolism
› Regulation of Neuronal Cell Death

Targeting Intravital Protein Interactions in Neuronal Energy Metabolism of Stroke

This project addresses the pressing need to develop novel treatment approaches for acute neuro-degeneration such as it occurs in stroke. Thus, by investigating the pathophysiological basis for acute neurodegeneration on a molecular level, this project will mitigate the future challenges imposed by the care for patients suffering from these diseases. The high energy demand of the brain predisposes it to a variety of diseases if energy supplies are interrupted, such as in stroke. Neurons are particularly intolerant of inadequate energy supply and die or degenerate in either an acutely or chronically disturbed metabolic environment. Therefore, the goal of this project is to unravel the role of the tight connection between glucose metabolism and the regulation of cell death pathways for neuronal viability or acute neuronal degeneration after ischemic injury. I have previously characterized a multiprotein complex centered around the mitochondrial glycolytic enzyme hexokinase II (HKII), which acts as a sensor of the metabolic state of neurons (Mergenthaler et al., Proc Natl Acad Sci USA 2012) and provides a prototypic mechanistic example of the interdependence of these major cellular pathways (Mergenthaler et al., Trends Neurosci 2013). The main hypothesis of this project is that regulation of the interaction of HKII and its associated multiprotein complex links metabolism to programmed cell death in neurons. Protein:protein interactions can be highly dependent on the physiological context and may be regulated differently in different T-cells. Therefore, in addition to verifying the HKII protein interactions in living cells, I am using live human induced pluripotent stem cell (hiPSC)-derived neurons and human brain organoids to express HKII and its putative interactors with fluorescent protein tags at near-endogenous levels. In vitro differentiation of hiPSCs will permit examining these interactions in human neurons.

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› Machine Learning
› Data Science in Medicine
› Medical Computer Science

Big Data Analytics in Health Care – Medical Data Science to Improve Patient Safety During Intensive Care

Machine learning applications have become ubiquitously popular – from smart mobile phone applications via smart homes to entire smart industries. This family of data-driven methods thrives especially in settings where a large number of concurrent signals go well beyond the capacity of human reasoning. Critical care units are a highly challenging environment that confronts physicians with a demanding caseload and requires rapid decision-making. The handling of a continuous stream of massive amounts of noisy data, such as laboratory results, clinical and physiological measurements as well as imaging and increasingly »omics« information can easily go beyond the information processing capacity of the human operator (intensive care physician) and may lead to treatment delays or clinical errors. Our work applies deep machine learning methods in a critical care scenario to provide timely and highly accurate decision support to clinical staff. We aim to push the translation into the clinical routine by performing rigorous clinical validation.

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› Lymphomagenesis
› Clonal Hematopoiesis and Preleukemia

Genetic Characterization of Primary Mediastinal B-Cell Lymphoma

Accounting for approximately 10% aggressive lymphomas and ~2% of newly diagnosed Non-Hodgkin lymphoma (B-NHL) cases, primary mediastinal B cell lymphoma (PMBL) is a relatively rare disease. It mainly affects young and otherwise healthy women. Although important treatment improvements could be achieved in the last years, a significant proportion of patients remain refractory to standard immunochemotherapy or relapse within a short time period. As PMBL has previously not been distinguished from DLBCL, there is a large knowledge gap regarding its underlying genetic alterations and the prognostic and predictive importance of recurrent gene mutations. As shown by our recent work, unraveling genetic aberrations underlying PMBL lymphomagenesis has the potential to identify new targets for tailored therapy approaches. A thorough description of the mutational spectrum in PMBL and the identification of key oncogenic drivers will thus facilitate rational therapeutic approaches. Until now, we have collected the world's largest PMBL cohort (n>350) through national and international collaborations comprising clinically well-annotated patients. Using a combination of whole-exome, targeted deep resequencing, and gene expression analysis, we aim to identify key oncogenic drivers and deregulated signaling pathways in PMBL. Based on the previous molecular analyses, functional consequences of candidate driver mutations will be analyzed in PMBL cell lines using the CRISPR/Cas technology.

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Development of High Affinity T-Cell Receptors Against Cyclin A1 for the Elimination of Stem Cells in AML

In analogy to healthy hematopoesis, the population of leukemic blasts in acute myeloid leukemia (AML) is based on leukemic stem cells (LSC), which are characterized by unlimited proliferative capacity and resistance to conventional tumor therapies. In many cases, elimination of LSC can only be achieved by cell-mediated toxicity after allogenic stem cell transplantation (HSCT). A potential alternative to HSCT is the transfer of LSC-specific T-cells. We have recently described Cyclin A1 as cancer-testis- antigen, which is selectively expressed in LSC. Aim of the actual project is the development of vectors for the expression of high affinity T-cell receptors (TCR) against Cyclin A1 in autologous patient T-cells. T-cell clones are generated by repetitive stimulation in vitro with a HLA A2-restricted epitop of Cyclin A1. Main problem for the isolation of high affinity TCR against selfantigens is the potential negative selection in the thymus. The latter can be circumvented by isolating T-cell clones against a HLA A2- restricted epitope from T-cells of HLA A2-negative donors because thymal selection is HLA-dependent. Alloreactive T-cell clones reactive against HLA A2 independent of the presented epitope are excluded on clonal level. The intrinsic affinity of the TCR is quantified by tetramer titration using extrapolation of the saturation curve. Functional avidity of the clones (peptide concentration associated with half maximal effector function, EC50) is determined by peptide titration. The TCR originating from the clones with the highest functionality are cloned in a retroviral vector system (MP71) in TCR-P2A-TCR configuration. Miss pairing with endogenous TCR chains is omitted by partial murinization of the constant region and the addition of a second cysteine bridge. Expression of the transgenic TCR is enhanced by codon- optimization of the construct. All constructs, which induce specific functionality against endogenously processed Cyclin A1 in the target cells, are potential candidates for a therapeutic application in a clinical phase I trial.

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› Hemoglobinopathies
› Microbiota
› Biomarker
› Immunreconstitution

An Immune Reconstitution and Biomarker Platform for Hematopoietic Stem Cell Transplantation in Children

Graft versus host disease (GVHD), infections and graft rejection are major complications following hematopoietic stem cell transplantation (HSCT) in children. Severe GvHD is associated with a high mortality rate and remains one of the main reasons for mortality after allogeneic HSCT. Graft rejection remains an obstacle to successful transplantation for children with non-malignant diseases, such as ß-thalassaemia or sickle cell disease. Within this project, we established a biobank for an enduring asservation of materials including blood, urine, feces, cerebrospinal fluid, bone marrow and tissue biopsies. Our patient cohort consists of all pediatric patients undergoing HSCT in the Department for Pediatric Hematology/Oncology/SCT at the Charité and their family donors (currently included: 70 patients, 20 family donors). To connect clinical courses and experimental results, all data will be collected and saved in our database. During the first two years after HSCT, immune reconstitution is characterized using flow cytometry (NAVIOS, DuraClone technology) allowing a detailed characterization of T-, B, dendritic- and natural killer cells and their subsets. Our project aims at a better prediction, prevention and innovative therapeutic approaches for GvHD. Therefore, we are currently evaluating mesenchymal stromal cell-derived exosomes as a new therapeutic approach for GvHD. Moreover, we will focus on the investigation of the human intestinal microbiota and its significance in GvHD, aiming to find the optimal preparation strategy before HSCT and perform fecal microbiota transplantation in the future. Functional analyses of both projects will be carried out in a minor mismatch GvHD mouse-model (in cooperation with O. Penack). Findings will be validated in multicenter studies including further pediatric and non-pediatric HSCT centers. Comparing impacts of different transplantation settings on the clinical outcome will support transplantation strategy optimization focusing on individualized immunosuppressive drug choice and dosing. Identification of new therapeutic strategies includes the investigation of GvHD pathophysiology and will allow earlier – pre-transplant, if possible – therapeutic options and thereby help to reduce the incidences of GVHD, infections and graft rejection after HSCT.

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› Acute Kidney Injury
› Kidney Transplant Rejection
› Anti-Inflammatory Mediators

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Regulation of Intrinsic Anti-Inflammatory Mediators During the Rejection of Kidney Transplants

Kidney transplantation is the preferred treatment modality for patients with end-stage renal disease and improves quality of life and overall survival. Advances in organ allocation, surgical techniques, and immunosuppressant combination strategies have effectively reduced rejection rates and improved 1-year-graft survival to values above 95%. These advances, however, have not translated into a proportionate increase of long-term graft survival. The etiology of premature allograft deterioration is multi-factorial and includes nephrotoxic effects of immunosuppressive drugs and chronic subclinical rejection. Novel methods for the detection of transplant rejection and the development of immunosuppressant drugs with reduced toxicity are therefore necessary to improve long-term outcome after kidney transplantation. The glucocorticoid-inducible protein annexin A1 has been identified as the central mediator of endogenous anti-inflammatory signaling pathways. It may, therefore, promote the resolution of renal inflammation and foster tissue repair. The regulation of annexin A1 during renal transplant rejection has not been characterized. The aim of the first part of the project is to study the expression of annexin A1 in kidney biopsies from patients with transplant rejection and to identify cellular sources and potential targets for anti-inflammatory annexin A1 signals. The second part of the project will determine the utility of annexin A1 as a biomarker for the detection of renal transplant rejection.

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Fields of Research
› Prostate Cancer
› Quantitative Imaging
› Radiomics/Deep Learning

Prostate Cancer: Large-Scale Radiomics Analysis of Prostate MRI for Non-Invasive Risk Stratification

Prostate cancer is the most common cancer in western men and the third leading cancer cause of death in Germany. One in seven men will be diagnosed with prostate cancer during his lifetime. The imbalance of incidence and mortality illustrates the core dilemma of current approaches in prostate cancer diagnosis: only a few of the diagnosed prostate cancers lead to relevant morbidity and mortality. At the same time, many of the treatment options carry the risk of substantial side effects, preventing a broad treatment regime for this form of cancer. Consequently, there is a need for a – ideally non-invasive – risk stratification method to distinguish successfully between highly aggressive prostate cancers, leading to clinically significant disease and indolent forms, that need no treatment. Multiparametric magnetic resonance imaging (mpMRI) is the most promising modality to that end, especially after the introduction of the PI-RADS reporting system. Although this system proved its usefulness in the subjective assessment and structured reporting of prostate MR examinations, to date no established quantitative method exists to rate prostate mpMRIs. Recently new analysis methods were introduced, that can provide such measures from imaging data: Radiomics, which systematically assesses subjectively or objectively acquired image descriptors or deep learning which creates classifications based on multilayer neural networks. The aim of the project is to investigate if image analysis methods based on radiomics and deep learning can be used to establish new imaging biomarkers to non-invasively determine the aggressiveness of prostate cancers. This would allow for risk stratification and follow-up of prostate cancer patients, avoiding the potential side effects of invasive diagnostic methods and ultimately preventing unnecessary aggressive treatments.

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› Brain Development
› Rare Diseases

Identification and Characterization of »Novel« Microcephaly Genes

Reduced brain volume manifesting as microcephaly (MC) is often associated with intellectual disability (ID) and further comorbidities. With this project, we aim to characterize further genetic causes of MC and ID and to better understand underlying pathomechanisms. In a first part of the project, we aim to identify novel microcephaly genes by a process of clinical screening and genetic analysis of patients with a novel ID/MC phenotype. In a second part of the project, we focus on the functional analysis of novel microcephaly genes identified in our research group. Here, we address the infantile multisystem neurologic, endocrine and pancreatic disease (IMNEPD), recently first described by our research group and linked to homozygous mutations in the peptidyl-tRNA hydrolase 2 (PTRH2) gene. IMNEPD is a multisystem disease with neurological features of intellectual disability, postnatal microcephaly, and cerebellar atrophy. Ptrh2 is an evolutionarily well-conserved protein, which prevents accumulation of peptidyl-tRNAs and thereby maintains protein synthesis. Ptrh2 furthermore has a key role in the regulation of anoikis, a process defined as cell death caused by loss of cell attachment to the extracellular matrix. Our research group also showed that Ptrh2 plays a role in cell size regulation of neurons, skeletal muscle cells, liver and pancreas cells. We have generated Ptrh2 knockout mice and analyzed the role of PTRH2 in brain development in vivo and in vitro.

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› Corneal Surgery
› Oculoplastic Surgery

Femtosecond Laser Assisted Versus Manual Descemetorhexis

Posterior lamellar keratoplasty such as Descemet membrane endothelial keratoplasty (DMEK) and Descemet stripping automated endothelial keratoplasty (DSAEK) has become the standard treatment for conditions like Fuchs` endothelial dystrophy. In DMEK surgery, the patient's dysfunctional endothelial layer is replaced with a donor Descemet membrane (DM). A key step during DMEK surgery is the descemetorhexis (DR), the excision of the recipient's DM. The surgeon penetrates the anterior chamber and makes a circular incision into the patient's DM prior to removing it. Femtosecond laser technology is an important technological advance in ophthalmic surgery. In combination with computer-controlled optical delivery systems, femtosecond lasers are capable of producing precise surgical incisions without damaging surrounding tissues. Thus far, femtosecond lasers have been mainly used in cataract surgery. We have developed a novel method, femtosecond laser-assisted DR, to facilitate DMEK surgery. In a clinical trial, we are investigating possible benefits and the safety of this new procedure in DMEK surgery.

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Fields of Research
› Atherosclerosis
› Inflammation and Glycosaminoglycans
› Nanoparticle Imaging

Glycosaminoglycans as Targets for Non-Invasive Imaging of Unstable Atherosclerotic Plaques

Atherosclerotic plaque ruptures cause life-threatening complications including myocardial infarction and stroke. Methods to identify unstable plaques prior to rupture are therefore highly desirable. Proteoglycans (PG) and their glycosaminoglycan (GAG) chains are key components of the extracellular matrix in atherosclerotic plaques and are involved in disease progression. It is currently unknown whether plaque instability correlates with a specific PG/GAG pattern. This project aims at the identification of instability-associated PG/GAG and their use as targets for non- invasive imaging. We will comparatively analyze PG/GAG composition, GAG structure and their chemical modifications in stable and unstable human atherosclerotic lesions from the coronary and carotid arteries. Glycoanalytical techniques (HPLC, CE-LIF, MALDI-imaging) as well as histological- and expression analyses (RT-PCR, Western Blot, IHC, TEM, FISH) will be applied to identify instability-associated PG/GAG as novel targets for non-invasive imaging of unstable plaques. Previous experiments demonstrated that i.v.-injected citrate-coated very small superparamagnetic iron-oxide nanoparticles (VSOP) are rapidly taken up by atherosclerotic lesions, thereby enabling plaque visualization in the MRI. Experiments in cell culture models and rodents led to the hypothesis that VSOP primarily binds to GAG components of unstable plaques. To prove this hypothesis, we will analyze the potential of VSOP-based MRI to identify unstable atherosclerotic plaques in comparison with established invasive methods including intravascular ultrasound (IVUS) and optical coherence tomography (PCT). These experiments will be performed in Göttingen minipigs under high-fat diet and streptozotocin-induced diabetes.

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› Primary Central Nervous System Lymphoma
› Lymphomagenesis
› Brain Tumors

Molecular Genetic Analysis and Preclinical Modeling of CNS Lymphoma

Despite extensive research, the molecular alterations leading to primary central nervous system lymphoma (PCNSL) and the reasons why PCNSL are confined to the CNS have not been fully elucidated. With regard to the genetic alteration of PCNSL, available data are restricted to whole exome and Sanger sequencing. Our research effort shall gain more insight into the molecular landscape of PCNSL. So far, we assembled a unique collection of 36 CNS lymphoma specimen and used WGS, RNAseq and DNA methylation arrays (850K arrays) to identify important, prognostically relevant genetic and epigenetic alterations and to distinguish between »driver mutations« (e.g. MYD88, CD79B, CARD11, KMT2D, and CDKN2A/B) and kataegis events (e.g. PIM1, BTG2, OSBL10). The results have been compared to the signatures of DLBCL without CNS manifestation (pDLBCL) to identify differences between both entities. Our RNAseq results have already shown separate clustering of PCNSL and pDLBCL and clear differences in terms of expression levels of many different genes involved in e.g. immune escape and response (e.g. HLA-DR, PD-L1, TLRs). Additionally, we seek to elucidate the protein landscape of PCNSL by mass spec. So far, reverse phase protein array (RPPA) revealed high expression of many cancer related (phospho-)proteins in PCSNL, e.g. BTK or MAPK which could be possible targets for tyrosine kinase inhibitors. For further validation, preclinical modeling, and drug target development, we use 3 different diffuse large B-cell lymphomas (DLBCL) cell lines (U2932, OCI-Ly3 and OCI-Ly7) to perform differently in vitro anticancer experiments, e.g. chemical inhibition of MYD88 homodimerization.

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› Liver transplantation
› Ex vivo liver machine perfusion
› Liver regeneration

Defatting of Steatotic Liver Grafts by Ex Vivo Machine Perfusion with DNP

Liver transplantation is the treatment of choice for patients with advanced liver cirrhosis, non-metastatic early hepatocellular carcinoma, and severe metabolic or autoimmune hepatic disorders. While the need for liver grafts is continuously rising, the number of available donor organs is increasingly limited by the scarcity of suitable donor organs. Steatotic liver grafts from donors with fatty liver disease pose a certain risk of primary non-function to the recipient. Defatting by ex vivo machine perfusion has already been proposed as a strategy for conditioning of steatotic liver grafts. A significant reduction of the liver fat could already be achieved by ex vivo perfusion of steatotic rat and pig livers with defatting agents, but successful transplantation of defatted grafts has not yet been shown. This project aims to establish a concept for defatting of steatotic liver grafts by ex vivo machine perfusion with 2,4-Dinitrophenol (DNP) in a rat liver transplantation model. DNP is a mitochondrial protonophore that shuttles protons across biological membranes. It is hypothesized that DNP is a suitable agent for liver defatting by ex vivo machine perfusion under normothermic or sub-normothermic conditions. Liver fat is metabolized by the increased cellular activity that is needed to compensate for the decreased efficiency of the uncoupled respiratory chain. In a first work package, the already established lab-scaled liver perfusion system was be optimized in order to enable liver perfusion over a period of 6 hours without serious damage to the organ at normothermic. In work package 2, a protocol for liver defatting with DNP is currently developed, with optimal DNP concentration and perfusion time. In work package 3, the safety and feasibility of ex vivo liver defatting and the expected superior outcome after transplantation will be proven in rats in comparison to non-treated steatotic grafts.

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› Biomechanics
› Biomaterials
› Mandible Reconstruction

Optimizing Free Flap Mandible Reconstruction

Mandible reconstruction with osseous free flaps is challenging, especially in patients with oral squamous cell carcinoma and osteoradionecrosis. Currently, titanium is the standard material for osteosynthesis in trauma and reconstructive surgery. In head and neck cancer patients, the metallic characteristics and available plate designs with high bone-areas and extreme stiffness are unfavorable, as they cause severe imaging artifacts in tumor aftercare examinations, interference with radiotherapy and high rates of soft tissue complications, e.g., plate removal and thus a second surgery is usually necessary. Despite high precision planning, osseous nonunion in the interosteotomy gaps is a common problem. With the current project, we evaluate various aspects of mandible reconstruction in order to improve patient outcome. Experimental artifact reduction in CT and MRI imaging, biomechanical characteristics in load-bearing situations in vitro and finite element analyses and magnesium degradation in a long-term animal study are performed in order to validate these biomaterials for potential use in craniomaxillofacial surgery. Additionally, mechanobiological optimizations for mandible fixation systems will be performed in future work packages in cooperation with the Julius-Wolff-Institute for Biomechanics and musculoskeletal regeneration.

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› Transplant Immunology
› Immunology of Infection

Adoptive T-Cell Therapy with Enrichment of Central Memory T-Cells in Solid Organ Transplant Recipients with CMV Infection Resistant to Antiviral Therapy

We demonstrated feasibility, efficacy, and safety of adoptive T-cell therapy with CMV-specific cytotoxic T-cells (CMV-CTL) in solid organ transplant recipients with CMV disease. Adoptive T-cell therapy, however, showed not to be long-lasting. We hypothesize that our 2nd generation CMV-specific CTL product enriched for central memory T-cells (TCM) by partial blocking of IL-2R signaling is more long-lasting and effective than our 1st generation product enriched for effector memory T-cells (TEM). This hypothesis will be measured by the ability of these 2 preparations to augment the impaired CMV immune function and decrease high CMV-loads in immunocompromised solid organ transplant with repeated or persistent active CMV-infection resistant to antiviral therapy. CMV seropositive patients will be randomly allocated to two study arms: Arm A: TEM-enriched autologous CMV-CTL product (low proportion of TCM and high numbers of antigen-specific, induced regulatory T-cells). Arm B: TCM-enriched autologous CMV-CTL product (generated in the presence of partial IL-2R inhibition with enrichment of CD4+/CD8+ TCM-like cells). Here, we aim to: (1) start a clinical trial to prove the hypothesis of prolonged efficacy of TCM-enriched autologous CMV-CTL, (2) follow the fate of our adoptively transferred T-cells by monitoring the TCR-repertoire by next-generation sequencing (NGS), (3) understand the mechanisms stabilizing the phenotype of TCM, and (4) extend our studies to other viruses.

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› Diffusion Tensor Imaging
› Neurodegenerative Diseases
› Neuroinflammatory Diseases

Simultaneous FMRI and Cortical EEG – Electrophysiology of the BOLD Effect

Functional MRI and EEG are one of the most used techniques in neuroscientific research today. Basis for most fMRI effects is the Blood-Oxygen-Level-Dependent (BOLD) effect. While extensively used the electrophysiology of the BOLD effect in humans is not well understood. The project »Simultaneous fMRI and cortical EEG – Electrophysiology of the BOLD effect« will further elucidate the electrophysiological basis of the BOLD effect from an EEG point of view.

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› Cardiac Imaging and biomarkers (troponin) in acute stroke
› Takotsubo

Predictors of Acute (Cardiac) Complications after Ischemic Stroke

The main focus of my research group 'Integrative Cardio-Neurology' is to study the mechanisms and long-term consequences of cardiac complications after stroke. In particular, we focus on stroke-associated myocardial injury (troponin elevation). During my CSP period, we have shown that myocardial injury after ischemic stroke 1) occurs in ~50% of patients, 2) is associated with poor functional outcomes and short-term mortality, 3) is linked to a lower frequency of obstructive coronary heart disease than in NSTE-ACS, 4) is linked to stroke lesions within the insular cortex, 5) is associated with the occurence of newly detected atrial fibrillation, and 6) associated cerebral small vessel disease, impaired cognitive function and future MACE. These observations led to the concept of a distinct 'stroke-heart syndrome', a pathophysiological framework for post-stroke cardiac complications. Together with our interdisciplinary partners we apply multimodal brain and cardiac MRI, methods of computational neuroscience, diagnostic measures of autonomic function, and modern epidemiological methods using large-scale clinical cohorts (like BeLOVE) to further advance our knowledge about stroke-associated cardivascular complications.
Recent key publications:
1) Stroke-heart syndrome: clinical presentation and underlying mechanisms. Scheitz JF, Nolte CH, Doehner W, Hachinski V, Endres M. Lancet Neurol. 2018;17:1109-1120.
2) Post-Stroke Cardiovascular Complications and Neurogenic Cardiac Injury: JACC State-of-the-Art Review. Sposato LA, Hilz MJ, Aspberg S, Murthy SB, Bahit MC, Hsieh CY, Sheppard MN, Scheitz JF; World Stroke Organisation Brain & Heart Task Force. J Am Coll Cardiol. 2020;76:2768-2785.

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› Biomarker
› Neuro-Imaging

Routine Laboratory Parameters and Clinical Outcome in Patients with Ischemic Stroke with Unknown Time of Symptom Onset: a Biomarker Study

It is of paramount importance to further improve the clinical care of patients with acute ischemic stroke. Reliable blood biomarkers for the prognosis of clinical outcome after ischemic stroke are highly desirable, but currently lacking. In more than 25 percent of all cases of ischemic stroke, the exact time of symptom cannot be ascertained in the emergency setting. It is suspected that ischemic strokes with unknown time of symptom onset (which often occur during sleep) form a separate sub-entity with regards to etiology, pathogenesis and prognosis. A comprehensive quantitative characterization of the relationship between routine laboratory parameters and clinical outcome has not yet been performed for this stroke subtype. At the moment, the only approved specific therapy for acute ischemic stroke besides thrombectomy consists of intravenous application of tissue-specific plasminogen-activator within 4.5 hours of symptom onset. So far, an unknown time of symptom onset is considered a contraindication for i.v.-thrombolysis. Using the concept of DWI-FLAIR mismatch in magnetic resonance imaging (MRI), one can obtain an accurate estimate of the age of acute ischemic infarcts. For this reason, the prospective clinical trial WAKE-UP was started in 2012 to investigate if patients with acute ischemic stroke with unknown time of symptom onset benefit from an MRI-based decision for, or against, i.v. thrombolysis. We will analyze the relationship between readily available routine laboratory biomarkers and clinical outcome (including hemorrhagic complications) in the WAKE-UP cohort according to treatment status (i.v. thrombolysis yes/no), and evaluate the usefulness of these parameters as prognostic biomarkers. Additionally, we will systematically analyze the currently available scientific data about blood biomarkers and ischemic stroke with unknown time of symptom onset.

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› Visual Perception
› Computational Psychiatry

The Neurobiology of Delusions – Linking Perceptual Inference and Dopamine

Delusions are a core symptom of psychotic diseases such as schizophrenia. They refer to beliefs that are not supported by evidence but are nonetheless held with strong conviction. Delusions can cause great suffering to the affected persons and their environment. For instance, affected persons frequently experience intense fear because they feel persecuted and observed, although outside observers cannot find any indication of such a threat. There is convincing scientific evidence that delusions are associated with excessive signaling of the neurotransmitter dopamine, but it is not well understood how such an excess in dopamine signaling might lead to the formation of delusions. Influential theories postulate alterations in the brain's inferencing machinery that controls perception, such that expected and insignificant stimuli are automatically perceived as surprising and significant and the cognitive effort to make sense out of such aberrant salience results in the formation of delusions. However, the role of dopamine in such perceptual inference has remained unclear. Therefore, the current project is aimed at establishing an empirical link between dopamine, perceptual inference, and delusions. To this end, we will conduct behavioral and functional imaging experiments in individuals with schizophrenia and healthy participants. By the use of mathematical models, we will then the mechanisms underlying perceptual inference. We will test whether these inferential mechanisms are altered in delusions or can be influenced by drugs that stimulate or inhibit dopamine signaling in the brain. If successful, this project will contribute to an understanding of the role of dopamine in perceptual processes that are compromised in delusions.

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› B-mode ultrasound
› RAPD
› Optic neuritis

B-Mode Ultrasound as a Novel Non-Invasive Quantitative Imaging Biomarker for the Functional Assessment of the Afferent Visual Pathway

This project addresses the clinical need of quantifying objectively a relative afferent pupillary defect (RAPD), the pathognomonic clinical sign of optic nerve damage due to optic neuritis (ON). The ultimate goal of this project is to establish ultrasound as a novel non-invasive objective imaging biomarker for the functional and quantitative assessment of afferent visual pathway damage. ON is a common symptom of demyelinating CNS conditions such as multiple sclerosis and neuromyelitis spectrum disorder, leading to severe visual impairment and reduced vision-related quality of life. Early detection and quantification of ON are essential for treatment decisions to improve clinical outcome. Of note, objective quantification of RAPD may also have implications for clinical trials with visual endpoints. Future trials could benefit from a reliable and reproducible RAPD evaluation method such as the B-mode ultrasound approach. In a recent study we performed the first systematic evaluation of B-mode ultrasound for assessment of the pupillary light reflex (PLR) and provided normal values for ultrasound derived PLR parameters for 100 subjects in 4 different age groups (Schmidt et al. PlosOne 2017). PLR assessment with ultrasound in our study was well tolerated, rapidly acquired and had a good test-retest reliability. The goals of this research project are to directly compare the ocular ultrasound approach with infrared video pupillometry for RAPD assessment and to compare B-mode ultrasound with visual evoked potentials and optical coherence tomography, two established methods that measure subclinical damage of the optic nerve. In a longitudinal study, we want to establish the value of B-mode ultrasound for monitoring disease activity and for outcome prediction in patients with ON. As the PLR is influenced by the autonomous nerve system, we also want to collect PLR data from neurological patients with known autonomous nerve dysfunction such as patients with multiple system atrophy.

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› Cancer Stem Cells
› Tumor Associated Stromal Cells
› Pancreatic Cancer

Cancer Stem Cells and Tumor-Associated Stromal Cells in Pancreatic Cancer

Pancreatobiliary carcinomas demonstrate an unfavorable prognosis and a poor response to chemotherapy. Cancer stem cells (CSCs) may define the malignant potential of a neoplasm through tumor initiation and chemotherapy resistance. The aim of the project is the genotypic, phenotypic and functional characterization of the tumor stem cell fraction in pancreato biliary malignoms. Special focus is set on the Notch-signaling pathway as a potential therapeutic target. The hypothesis is then to be evaluated in vitro, in vivo and in a representative cohort of patients with pancreato biliary malignoms. The main focus will be the analysis of patient-derived tumor cell lines and co-culture with tumor-associated stromal cells as better treatment options require a fundamental understanding of the tumor's microenvironment and the complex interaction between tumor and other cell types, especially stromal cells. Furthermore, the question to what extend tumor-associated stromal cells hold a genuine malignant potential or whether those cells act as benign bystander cells remains unanswered. Therefore, the interaction between CAFs and cancer cells is going to be studied in a novel approach by measuring the cell viability of tumor components (cancer cells and CAFs) in direct and indirect co-cultures.

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› Muscle atrophy

Epigenetic Changes and Repair of the DNA Breaks in Skeletal Muscle in Critical Illness Myopathy

Critical illness myopathy (CIM) is a devastating acquired skeletal muscle disease characterized by atrophy, flaccid paralysis and respiratory failure. It develops in very ill patients during the course of critical illness and is a frequent complication of intensive care unit (ICU)-treatment. It is a very peculiar aspect of CIM that skeletal muscle atrophy and weakness last for a prolonged period of time, often life-long, although all identified risk factors like inflammation, hyperglycemia, medications etc. have been removed. We hypothesize that the acute onset of severe critical illness with its dramatic hormonal, metabolic and nutritional disturbances leads to epigenetic changes in skeletal muscle stem cells or early myoblast. The epigenetic changes lead to an impaired ability of the muscle to regenerate and a long-lasting myopathy associated with critical illness that typically extends far beyond the duration of the ICU stay. Furthermore, the epigenetic changes lead to an increase of DNA double breaks in the muscle cells. This project aims to identify and characterize the epigenetic modifications in muscle stem cells derived from severely ill patients within the first days after admission to the ICU. We analyze the epigenome and transcriptome as well as the DNA double-breaks process of activated satellite cells and early myoblasts derived from acute onset CIM patients.

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› Teranostics
› Urogenital imaging
› Hybrid imaging

PSMA Theranostic of Prostate Cancer: Radionuclide Therapy and Functional Molecular Hybrid Imaging by MRI and PET

The aim of this project is to develop new strategies for personalized theranostic management of prostate cancer by using prostate-specific membrane antigen (PSMA). PSMA is a transmembrane protein which can serve as a specific target structure for hybrid imaging of prostate cancer with the new tracer Ga-68 HBED-CC PSMA as well as for new treatments of prostate cancer such as radionuclide therapy using lutetium-177. This project deals with the evaluation of parameter specification such as biodistribution and biokinetics of the new tracer Ga-68 HBED-CC PSMA for imaging prostate cancer. Further, the potential of multimodal functional molecular hybrid imaging such as PET/CT and PET/MRI of prostate cancer and effects on personalized medicine are investigated. New therapeutic strategies in radionuclide therapy of prostate cancer with lutetium-177 are evaluated focusing on the use of radiosynthesizers and radioprotectors to enable higher therapeutic doses of lutetium-177 to be delivered for the treatment of prostate cancer.

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› Pharmacogenetics and -epigenetics
› Functional Neuroimaging

Phenomics and Genomics of Clozapine Pharmacotherapy

Clozapine is generally prescribed if at least two trials of antipsychotic agents have not led to satisfactory clinical improvement, thereby implying that patients on Clozapine generally suffer from more severe and/or persistent symptoms than patients suffering from schizophrenia spectrum disorders (SCZ) on other antipsychotic agents. Unraveling the (functional) genetic variation underlying this severe SCZ phenotype, therefore, has the potential to deepen our understanding of the biological underpinnings of SCZ beyond the boundaries of DSM-based consensus criteria. We here hypothesize that targeting this phenotype in genome-wide association studies and next-generation sequencing studies will signal genetic risk loci implicated in this severe SCZ phenotype. In the future, this may lead to early detection of severe SCZ, which in turn will enable tailoring of pharmacotherapeutic strategies to such SCZ sub-types. Though Clozapine is one of the most effective antipsychotic medications, it goes along with life-threatening adverse drug reactions, such as agranulocytosis, diabetic ketoacidosis, metabolic syndrome or obsessive-compulsive symptoms. Prescribing Clozapine in clinical practice, therefore, requires balancing adverse reactions risk profile likelihoods with clinical response probabilities. This need highly contrasts with the current state of knowledge as it is unknown who will respond to Clozapine and to what degree a specific patient may develop side effects. Based on preclinical studies, we hypothesize that epigenetic and gene expression mechanisms influence treatment outcome after CLZ initiation. We will, therefore, investigate methylation patterns/levels and gene expression profiles before and after initiation of CLZ pharmacotherapy. Furthermore, we will try and identify other predictive factors for treatment outcome following CLZ pharmacotherapy initiation. The overarching goal is to create a prediction model for clozapine response. This model includes genetic, epigenetic and clinical data.

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› Small intestinal enteropathies including celiac disease
› Crohn´s disease
› Development of Colitis-associated carcinoma

Celiac Disease

My project focusses on celiac disease (CD), a polygenetic immune disorder that is triggered by the ingestion of glutens, proteins that occur in wheat, barley and rye. Once initiated a small intestinal immune response against glutens is mounted that leads to intestinal villous atrophy and crypt hyperplasia, resulting in malabsorption of nutrients, weight loss and chronic diarrhea. In terms of basic science I study the impact of the inflammatory environment on polarity of GI epithelia as well as the consecutive defect of the epithelial barrier. We hope to elucidate the mechanism by which gluten uptake is upregulated, since we believe it might be a (presumably reversible) trigger point in the pathophysiology of CD. Another focus is the establishment of methods to visualize barrier defects in epithelial monolayers as well as mucosal tissue specimen. Clinical scientific approaches include the establishment of clinical tests for the diagnosis of celiac disease (including a POCT, point-of-care-testing, for CD) and clinical tests to optimize the classification of treatment-refractory CD, a rare, but severe complication of CD. This includes in collaboration with Professor Michael Hummel (Molecular Pathology, Charité) a molecular pathology technique that evaluates the T-cell diversity in small intestinal samples by means of next-generation sequencing of the variable region of the T-cell receptor. Furthermore we started a register for patients suffering from refractory CD with the help of the German competence network for inflammatory bowel disorders to better understand typical disease courses of refractory CD.

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› Cortical Development
› Hyperoxia-Induced Immature Brain Injury
› Premature Birth and Cognitive Impairment

The Role of Neonatal Hyperoxia in Neonatal Brain Development and Genesis of Neurobehavioral Disorders

Very preterm birth has been associated with an increased risk to develop cognitive and social-emotional disorders. Premature infants are often exposed to supraphysiologic concentrations of oxygen. While arterial oxygen tension in utero is maintained at low levels between 24 and 28 mm Hg, premature birth into room air causes a several-fold increase in arterial oxygen tension in preterm infants to 65 mmHg and higher, even without supplemental oxygen. The exposure to this hyperoxic ex utero environment may affect the immature brain during neuronal differentiation and maturation processes. In humans, the period of fastest brain growth is observed during the last 3 months of a full-term pregnancy. In newborn mice and rats, in contrast, this brain growth spurt occurs between postnatal days 2 and 10. Therefore, rodents have been used as an experimental model to investigate the mechanisms of vulnerability in the developing brain. We are applying an established neonatal hyperoxia model in newborn VGAT–Venus transgenic and in WT mice providing 48 h exposure to fourfold increased oxygen concentration (80% O2) from P5 to P7, followed by recovery in room air until young adult ages. With the current project, we aim to analyze the consequences of neonatal hyperoxia on following aspects of neonatal brain development in immature animal model:1) the neurobiological mechanisms through which hyperoxia affect cortical neurogenesis and may lead to the development of cognitive disorders in preterm children, 2) the neuroprotective effects of erythropoietin on hyperoxia-induced brain injury, with the aim of improving neurobehavioral and cognitive outcomes after preterm birth.

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› Chemotherapy
› Immunotherapy

Evaluation and Integration of Molecular Assays to Address Clinical Problems in Breast Cancer

Greater availability of personalized treatment strategies for breast cancer requires a better prediction of therapy response to select treatment for individual patients. A large number of patients does not respond well to chemotherapy, especially those with hormone receptor- and HER2-negative disease. Many biological determinants of response remain unknown and there are no reliable markers to predict the outcome. In addition to chemotherapy, immunotherapies yield promise in the treatment of breast cancer and reliable measures of tumor-immunological activity are required to select patients. Tissue in pathology is fixed in formalin and embedded in paraffin and numerous annotated clinical trial cohorts are available. The use of high-dimensional techniques like next-generation sequencing can be challenging due to formalin-induced alterations. At the same time, the accessibility of this tissue by modern techniques is crucial for translational research and for the successful translation of gene assays into clinical practice. In this project, we aim to study the mechanisms of sensitivity and resistance to neoadjuvant chemotherapy with or without immune checkpoint inhibition. We will develop robust assays for formalin-fixed paraffin tissue to facilitate the translation into clinical practice. First, we will evaluate the use of RNA sequencing on formalin-fixed paraffin samples. Using paired pre-therapeutic and intermediate biopsies obtained during neoadjuvant therapy, we will then characterize molecular changes that occur under chemotherapy with or without immune checkpoint inhibition. This will allow us to define therapy-induced alterations associated with therapy response. In addition, we will test pre-defined gene signatures of immunological activity as markers for response to immune checkpoint inhibition. We will include the newly discovered markers into customized targeted assays to extend the analysis to a larger number of samples and future clinical trials.

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› Immunoneuropathology
› Autonomic Nervous System

Phosphorylated α-Synuclein in Skin Biopsies: A New Biomarker for Neurodegenerative Parkinson Syndromes

Synucleinopathies are neurodegenerative diseases as Parkinson Syndromes (e.g. Parkinson's Disease (PD) and Multiple System Atrophy (MSA)). Pathological α-Synuclein (SNCA) phosphorylation induce misfolding and deposition of insoluble intracellular pSNCA aggregates. Differential diagnosis of Parkinson Syndromes is based on clinical criteria. However, a definite discrimination can only be assessed post-mortem by means of different cerebral pSNCA aggregate localization (neurons vs. glial cells). In contrast to MSA, PD includes affection of peripheral nervous system. For the first time, our group could discriminate PD and MSA by detection of pSNCA in dermal sympathetic nerve fibers in vivo. All PD patients revealed a positive pSNCA immunoreactivity and all MSA patients were pSNCA negative. However, other groups report on different methods with significantly variable sensitivity and/or specificity that prevent a successful use in a clinical routine so far. Putative reasons are different biopsy locations, diverse staining protocols, pSNCA antibodies and nerve fiber type. In this project, we will implement dermal Serine 129 pSNCA in sympathetic nerve fibers as a new biomarker for early and definite differential diagnosis of PD in clinical routine. We will state a definite, highly sensitive and specific protocol for patients suffering from Parkinson Syndromes, including standardized skin punch biopsy location, the most sensitive pSNCA antibody, and the right target fiber type. Moreover, we will improve the understanding of pSNCA dependent neurodegeneration in the peripheral nervous system (PNS), by correlating functional features of affected nerve fibers types (autonomic vs. somatosensory) with their histopathological pattern to assess differences in morphology, distribution, and quantification of pSNCA in PNS vs. CNS. This project will provide a new in vivo diagnostic tool for PD and will contribute to adjusting the guidelines and diagnostic consensus criteria.

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› Neuroprotection
› Prognostication After Cardiac Arrest
› Cold Shock Protein

Hypothermia and Neuroprotection: A Role for Cold-Shock-Proteins?

The aim of this research study is the investigation of cold-shock protein RNA-binding-motif-protein 3 (RBM3) and its neuroprotective role. The expression of RBM3 is -unlike most other proteins- induced by hypothermia. RBM3 is discussed to be a promotor of global protein synthesis as well as specific proteins with neuroprotective effects of which only a few are known. First described by Derry et al. in 1995 it is expressed ubiquitously in human cells and its pathophysiological function is so far only partially understood. Our goal is to investigate the role of RBM3 and its neuroprotective function during hypothermia using a multimodal approach in cooperation with the research group »Hypothermia and Neuroprotection« at the DHZB, the Department of Neuropathology and the Department of Nephrology and Intensive Care Medicine. Our core projects include the characterization of RBM3 serum concentration in patients treated with mild therapeutic hypothermia after cardiac arrest and resuscitation. Changes in the course of hypothermia could function as a possible marker for neuronal cell damage and/or for the monitoring of hypothermia treatment. Within our study, we also focus on the investigation of RBM3 expression in human brain tissue. Our goal is to quantify and localize RBM3 within the human brain in correlation with pathological quantification/markers of neuronal cell damage giving us insights into possible neuroprotective effects of RBM3 in the adult human brain. In cooperation with the research group »Clinical and experimental Epileptology« we aim to establish human brain slice cultures to analyze RBM3 regulation under hypothermia and hypoxia. The characterization of the RNA expression and RBM3 protein synthesis could provide the groundwork for subsequent studies investigating the optimum neuroprotection through hypothermia.

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› Experimental surgery

Decellularization and Recellularization of Parenchymal Organs

Decellularization removes cells and antigenic material from organs and tissue to obtain the extracellular matrix (ECM). The ECM consists of less or even non-immunogenic proteins (e.g. collagen, fibronectin, laminin etc.) and conserves the three-dimensional micro-architecture of an organ. Furthermore, it contains organ specific growth factors and thus can serve as an ideal biomatrix for the repopulation with cells from a different origin. By applying decellularization of a (xenogeneic) organ and recellularization of this ECM with human cells, the in vitro generation of functional, autologous tissue appears possible. The aim of our project is the implantation of decellularized and recellularized organs (e.g. liver, pancreas, blood vessels etc.) in vivo. To achieve this objective many issues like the re-assembly of an organ-specific micro-anatomy, the re-establishment of a functional endothelial barrier etc. have to be overcome. Furthermore, interactions between cells used for recellularization and the decellularized ECM will be analyzed.

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› Global Mental Health
› Psychiatric Genomic Consortium

Influence of Periphrale Cytochrom P-450 2C19 Activity on Depression: A Functional Study in Two Distinct Ethnic Groups

Various independent findings indicate a direct role of altered Cytochrome P450 activity, especially CYP 2C19 in depression pathogenesis which is independent of pharmacokinetic effects. This involvement is apparently mediated by an impact on the metabolism of endogenous substrates. Translational approaches and initial clinical findings on CYP2C19 showed the presence of a »fast« metabolism (UM) in humans are associated with depressive behavior and reduced hippocampal volumes. Besides drugs lifestyle factors such as smoking, nurture and medicinal herbs can also influence the CYP 2C19 enzyme activity. Interestingly various traditional plantbased drugs, which are widespread in Asia have a strong inhibition effect on CYP2C19 enzyme activity. Such influence factors are entirely neglected by genotyping. In addition to variables such as sex, age, substance consumption and eating habits, there is a high degree of ethnic variability, particularly in the activity of CYP2C19 isozymes. To evaluate the recent findings, the proposed study of an additional Southeast Asian population (Vietnamese) is ideal. Our project investigates for the first time the functional link between the CYP 2C19 enzyme activity and depressive symptoms by the measurement the functional enzyme activity in the peripheral blood in Vietnamese and German patients with depression. The activity measurements on patient-specific cells, in contrast to the exclusive genotyping, is also influenced by epigenetic regulation, induction or inhibition. This functional approach can also provide valuable evidence of potentially usable »druggable targets« which leads to the development of personalized treatment for the patients suffering from depression.

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› Drug Delivery
› Dendritic Cells, Macrophages and MasT-cells
› Skin Immunology

Laser-Assisted Dermal Drug Delivery

Intradermal drug-delivery represents an attractive mode of application because of the skin's easy accessibility and its high and dense network of immune cells. By using a fractionated ER:YAG laser, we can generate micropores of different depth in the skin, which allows the deposition of molecules with high precision. Dermal dendritic cells (DCs) expressing the XCR1 chemokine receptor, also known as CD103+ or CD8α+ DCs, excel in the presentation of extracellular antigens to CD8+ T-cells. By creating laser-generated micropores through the epidermis, we targeted a model protein antigen fused to XCL1, the ligand of XCR1, to dermal XCR1+ DCs and induced antigen-specific CD8+ and CD4+ T-cell responses. In a murine tumor model, we have shown that laser-assisted drug delivery induces a strong local as well as a systemic anti-tumor response, which seems to be superior to classical needle-based drug delivery. We are now aiming to better understand the molecular mechanisms of this enhanced effect of laser-assisted dermal drug delivery. Furthermore, we are planning to apply this method in patients with different skin diseases. The use of this new laser technology, therefore, represents a scientific approach to tackle the clinical challenge of finding the best route of application and optimizing the therapeutic effect.

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› Metastasis
› Therapy prediction

Development of Prognostic and Predictive Biomarkers

Despite radical tumor resection with extended lymphadenectomy, approximately 40% of patients with gastric cancer develop a disease relapse after initial curative treatment. Where in early tumor stage patients are treated only by surgery, patients with local advanced stages get an escalated therapy with chemotherapy and surgery. This additional treatment leads to survival benefit of 10% for these patients. In a retrospective analysis we could show in 76 patients with gastric cancer that 12,8% of the patients had a complete response under the preoperative treatment and 89% of them were alive after 5 years. In contrast to these patients 11.5% had a disease progression under this treatment and a decreased survival of only a few month. To improve the survival of patients with gastric cancer we need on the one hand prognostic biomarkers to identify high-risk tumors in early tumor stages for escalating the therapy. On the other hand we need also predictive biomarkers to identify therapy responder and non-responders for treating patients only with effective chemo-therapy. In this project we analyze the role of the prognostic oncogene MACC1 (metastasis-associated in colon cancer-1) for gastric cancer. On the basis of MACC1 as a model biomarker we are developing an experimental platform to analysis biomarkers on the level celllines in vitro and in orthotopic cellline derived xenograft models (CLDX) in vivo. Furthermore, we are creating patient derived xenografts (PDX) and collecting tumor samples from a large gastric cancer population. In a second step we would like to identify new prognostic makers by performing next generation sequencing in a large gastric cancer cohort. On the base of the experimental platform describe above we would like to prove the quality of these biomarkers. The development of predictive biomarkers is performed in collaboration with the Max Plank Institute for molecular genetic (AG Prof M. Schweiger). In this project we are collecting biopsies of patients with gastric cancer before and after the first cycle of chemotherapy. By analyzing the samples with RNA-Seq and correlating the reaction profils with the histopathologic remission after three cycles of therapy we hope to find specific reaction profils to predict the response to chemotherapy.

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› Pain Research
› Medical Informatics

Investigation of Nociception and Anti-Nociception During Genereal Anesthesia

In current clinical practice, dosing of analgesics during general anesthesia is performed based on the patient's responsiveness to noxious stimulation. If a patient moves or exhibits an increase in blood pressure or heart rate in response to a surgical stimulus, the analgesic dose is increased as the clinical responses are considered signs of a neuronal processing of the painful sensory input, which is termed nociception. Accordingly, if a patient shows no clinical responses to noxious stimulation, the analgesic dose is considered sufficient, as the absence of responses is considered indicative of absent nociception. However, we were able to demonstrate in an experimental setting using functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and spinal pain reflexes (NFR) during general anesthesia that nociception persists in the spinal cord and the brain throughout the common clinical doses of anesthetics (von Dincklage et al., Neuroimage 2018). Furthermore, we showed that the assumption that absence of clinical responses is a sure sign of a sufficient analgesic dose is not valid as we demonstrated a persistence of nociception in spinal cord and brain even though the subjects showed no clinical responses to the stimuli (von Dincklage et al., British Journal of Anaesthesia 2018). Also, we showed in a clinical study that higher analgesic doses during general anesthesia seem to be associated with lower rates of chronic pain, which might be explained by a better suppression of pain sensitization processes that might be triggered through intraoperative nociception (von Dincklage et al., European Journal of Pain 2018). Thus, if future studies confirm this connection between persistent nociception during general anesthesia and triggering of chronic pain, the current clinical practice of dosing analgesics according to clinical responsiveness might have to be changed and alternative surrogate measures for nociception during general anesthesia might be required.

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› NSCLC and Tumor Heterogeneity
› Anaplastic Lymphoma Kinase in NSCLC
› Acne Inversa/Hidradenitis Suppurativa

Comparative Analysis of Tumor Heterogeneity in Non-Small Cell Lung Cancer (NSCLC) by Phosphoproteomics and Next Generation Sequencing (NGS)

Heterogeneity in tumors might have different faces. In general, the role of different clones and sub-clones in different areas of one tumor is discussed. However, different diagnostic test facing the protein level (e.g. immunohistochemistry/IHC) on the one hand and the DNA-level (e.g. Fluorescence in-situ Hybridization/FISH) on the other hand might produce discrepant results. Is this tumor heterogeneity, as well? In a first step, we addressed this question focusing on the Anaplastic Lymphoma Kinase, a treatable target in Lung Cancer. Underlined by our Next Generation Sequencing (NGS) – data, discrepant results by means of IHC and FISH might be due to technical (methodological heterogeneity) or biological (proteo-genomic heterogeneity) reasons. Within the next step, we broaden our view (going away from focusing one target only), as recent data based on NGS, described tumor heterogeneity on the genetic level by Whole Exome Sequencing. However, data on the proteomic level are missing so far. Thus, in this study, we investigate the intratumoral heterogeneity of Non-Small Cell Lung Cancer (NSCLC) on the (phospo)proteomic level in comparison with mutational profiles (NGS-based). Thereby, we focus on the question if future molecular NSCLC-diagnostics should consider (a) aspects of heterogeneity (e.g. biopsies of different tumor regions) and (b) functional relevance of certain mutations (e.g. further investigation on the proteomic level), as the molecular complexity of the mutational landscape is discussed as mechanisms of resistance in targeted (personalized) cancer therapy. In the clinical context (e.g. tumor board) our data might, in perspective, help to identify and predict therapy resistance, as well as propose alternative therapy options.

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› Immunology
› Metabolism

The Role of Mesenteric Fat in Intestinal Inflammation

Creeping fat represents a disease characterizing finding in Crohn's disease (CD) but its impact on intestinal inflammation and epithelial barrier function is unknown. Previous data indicate that bacterial translocation induces a unique immunologic and endocrine milieu within the mesenteric fat of CD patients resulting in immune cell infiltration as well as production of specific cytokines and adipokines thereby influencing intestinal inflammation. The present project aims to define how intestinal barrier defects shape the homeostasis of mesenteric fat, how these alterations confer to an alternative intestinal barrier and how creeping fat modulates epithelial resistance as well as intestinal immune cell composition and immunity. A fat-depleting mouse model will serve to answer these questions and the data will subsequently be correlated with results obtained from a CD patient cohort as well as from a patient with acquired generalized lipodystrophy and combined CD (AGLCD), who lacks mesenteric fat tissue and suffers from severe CD.

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› Immune Reconstitution in Allogeneic Hematopoietic Stem Cell Transplantation
› Clinical Single Cell Sequencing
› Secondary Immune Defects

Mobilization of Donor Immunological Memory and its Fate After Allogeneic Hematopoietic Stem Cell Transplantation

Loss of the adaptive immunological memory and hampered immune reconstitution after allogeneic hematopoietic stem cell transplantation (alloHSCT) substantially increase the risk for severe infections post alloHSCT, which account for significant morbidity and mortality in transplanted patients. Transfer of donor memory cells along with the stem cell graft importantly contributes to the post-transplant immune protection of the recipient. The graft quality with respect to memory cells and the impact of G-CSF on the immune cell distribution in the graft remain insufficiently understood. Especially the role of G-CSF in mobilizing specific memory cells might be relevant, as these cells may possess distinct antigen specificities. In order to gain further insight into the effect of G-CSF on memory cells, we will characterize memory T and B cell subset composition and functionalities in stem cell donors before and after G-CSF treatment. Regarding the fate of the transplanted memory cells, we will analyze memory cell subsets in the corresponding recipients and determine their contribution to immune reconstitution and protection. Modern single cell RNA sequencing (scRNAseq) technologies will enable clonal tracking of immune cells from donor to recipient on single cell level and elucidate immune cell trajectories in reconstitution post alloHSCT. In connection with clinical data, these studies could help to develop treatment strategies such as niche protection or specific adoptive cell therapy to improve post-transplant immune competence.

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› Metabolism in Critically ill Patients

Prevention of Neuromuscular Organ Failure in Critically Ill Patients

My research focus as a Clinician Scientist is the prevention of ICU-acquired muscle weakness via advanced, muscle activating physiotherapy methods. The current therapeutic options allow for the survival of severe diseases. Serious neuromuscular sequelae are an increasing problem that significantly worsens the acute and long-term outcomes in terms of reduced physical functional, reduced quality of life, and increased mortality. We have shown that systemic inflammation and immobilization are major risk factors, inducing pathophysiological processes that lead to an ICU-acquired weakness. Decreased protein synthesis, increased protein degradation, and metabolic dysregulation in the form of a pronounced insulin resistance are detected very early in the course of critical illness. We could recently show that a daily exercise program with electric muscle stimulation can maintain muscle mass, as well as improve glucose metabolism in skeletal muscle. However, these successes are inconsistent and patient-specific, so that a broad application is not yet recommended. From the data of earlier investigations, we could determine the key factors influencing the effectiveness of enhanced physiotherapy options in the prevention of neuromuscular organ failure. Considering these findings, a specific therapy will be further developed under standardized conditions using an established sepsis-mouse-model. Furthermore, recent investigations lead us to the point that neuromuscular failure already occurs during perioperative setting. Therefore, we just initiated an observational trial to confirm these findings of the first description of Perioperative Acquired Weakness (POAW). My work is embedded within the BIH Twinning Research Grant project »Inflammation-induced skeletal muscle atrophy in critically ill patients«. Additional research interests: glucose metabolism, glucose monitoring, insulin therapy, nutritional support, caloric needs, indirect calorimetry, extracorporeal membrane oxygenation.

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Molecular PET/MR-Imaging in Coronary Artery Disease

Atherosclerotic plaque rupture in coronary arteries can lead to myocardial infarction and in some cases to sudden cardiac arrest. Plaques prone to rupture are considered as »vulnerable plaques« and feature distinct characteristics, such as a large necrotic core covered by a thin fibrous cap, macrophage, and positive vascular remodeling. A substantial number of these «high-risk lesions« do not cause flow-limiting stenosis and therefore can detract from common non-invasive diagnostic stress testing and invasive x-ray coronary angiography. Intravascular imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) demonstrated great potential in the assessment of plaque morphology. However, the application is limited due to invasiveness. Cardiac magnetic resonance imaging (MRI) on the other hand is a non-invasive imaging modality that provides excellent soft-tissue contrast. CMR assessment of atherosclerotic altered coronary arteries can depict plaque burden and plaque composition. Positron Emission Tomography (PET), usually combined with computed tomography (PET/CT) for anatomical detail, is a non-invasive imaging modality, which provides molecular information. Dependent on the tracer used, specific pathological processes, such as micro-calcification (18F-fluoride) can be studied. Recently developed PET/MR scanners with the opportunity of simultaneous assessment of structure and biology offer great potential in cardiovascular imaging. The aim of our project is to evaluate the potential of PET/MR imaging in coronary artery disease.

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› Functional Imaging
› Normal Tissue Effects of Radiotherapy
› Tumor Hypoxia

Characterization of the Tumor and its Surrounding Microenvironment During Treatment to Improve Future Cancer Therapies

Radiation therapy combined with chemotherapy (CRT) is the standard of care for locally advanced head and neck squamous cell cancer (HNSCC) and as a preoperative or definitive treatment for esophageal squamous cell carcinoma (ESCC) patients. Metabolic imaging using 18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) is commonly used for staging and re-staging in these patients but the imaging information is not yet routinely used to provide additional prognostic or predictive information during treatment. Therapy-induced FDG uptake of tumor surrounding irradiated normal tissue (INT) has been shown to have a high prognostic impact in both diseases. Additionally, INT cutoff values generated in hypothesis-generating cohorts were able to discriminate patients at high or low risk for local recurrence and death in independent HNSCC and ESCC validation cohorts. When using additional imaging tracers INT showed a strong inverse correlation with tumor hypoxia. Hypoxia is a known adverse prognostic factor in almost all solid tumors, promoting chemo- and radio-resistance and metastasis. The underlying biological mechanisms for the association of INT with patient outcome and tumor hypoxia remain unclear so far. The aim of this research project is to validate INT in combination with tumor parameters in a prospective cohort of ESCC patients undergoing CRT and unravel the biological underpinnings of this phenomenon. For the latter, one patient will receive functional imaging together with analyses of radiation-induced immune response in HNSCC and additionally cell culture of a primary tumor, mucosa and immune cells in ESCC patients. mRNA NanoString analyses will be performed in the already evaluated HNSCC and ESCC cohorts with the aim to identify candidate genes for consecutive cell co-culture experiments.

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› Molecular Diagnostics
› Bioinformatics

Methylation-Based Classification of Cell-Free DNA for AI-Driven Pan- Cancer Diagnostics.

Histopathological examination of tumor tissue is the gold standard for the diagnosis of cancer. Recently, molecular pathological assignment of tumor tissue has also become possible by recognizing the methylation patterns of the tumor genome. This involves the identification and classification of tumor entity-specific hyper- and hypomethylated promoter regions of oncogenes and tumor suppressor genes. This method has reached application maturity as a diagnostic procedure for both brain tumors and non-brain tumors. Specimen extraction (PE) is usually performed by an invasive surgical procedure. Especially in brain tumors, brain stem or tumor diseases with leptomeningeal spread, this is difficult or not possible due to possible cerebral side effects, unjustifiable risks or lack of solid tumor mass. A so-called »liquid biopsy« (LB), the extraction of cell-free tumor DNA (cftDNA) from plasma or cerebrospinal fluid (CSF) provides an alternative to neurosurgical PE. In this project, for the first time, methylation patterns of cftDNA will be determined from CSF and used to classify brain metastases and differentiate meningeosis neoplastica. This is made possible by the use of innovative technologies such as nanopore sequencing and a cancer classifier based on the machine-learning model random forest. Nanopore sequencing allows a cost-effective and time-efficient reading of the base sequence by voltage changes during the transport of DNA through a nanopore. We have already created a first version of the cancer classifier with public methylation data of brain-derived and some first non-cerebral tumors. The goal is to extend this with further public data up to about 150 additional tumor entities. This should enable a minimally invasive, cross-organ, methylation-based classification of cancers.

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› Gastrointestinal Oncology
› Cancer Pathology
› Digital Medicine

Image-Based Prediction of Clinically Actionable Features in Tumor Biopsies of Liver Cancer Using Deep Learning

Artificial intelligence already facilitates many aspects of our daily lives. However, there are comparatively few established applications in clinical medicine so far. As a resident in internal medicine and gastroenterology, I am particularly interested in improving the care of patients with cancer of the digestive tract. Our project focuses on cancer of the liver but is also applicable to other tumor entities. The two most common malignant primary liver tumors are so-called hepatocellular and cholangiocellular carcinomas. These entities represent the second most common cause of cancer related death worldwide. Recent advances in molecular medicine have identified innovate systemic treatments that are specific for certain mutations and should therefore be restricted to patients with these molecular features. However, in certain cases available biopsies do not allow molecular analysis, e.g. due to a lack of material, high costs or missing technological infrastructure. Thus, further analytics tools allowing to improve diagnostic sensitivity and specificity are needed in these patients. In our opinion, this unmet medical need can be addressed by using deep learning-based image analysis of standard histopathological tumor samples. Besides the clinically highly relevant differentiation of the mentioned tumor entities, we are working on the predication of relevant molecular biomarkers, like BRAF, Her2neu, V600E, IDH1/2, FGFR2. In addition, we are developing models to predict clinically relevant information such as response to specific therapy options or recurrence-free survival. In parallel, we are performing laboratory experiments to enrich our database of liver cancer patients with complex molecular features. Our project has the potential to improve clinical workflows of liver cancer diagnosis and treatment. Patients could be preselected according to the machine learning biomarker predications and thus the load of molecular assays and radiological imaging could be reduced. Finally, more patients could benefit from personalized molecular treatment and thus outcomes could be improved.

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Alzheimer's Disease

Identifying Alzheimer's Disease-Relevant Genes at the Intersection of Genomic Risk and Neuronal Lipotoxicity

Complex diseases are caused by an interaction of genetic and environmental risk factors. Large-scale sequencing projects (genome wide association studies, GWAS) continue to illuminate the genetic architecture of complex diseases such as type 2 diabetes (T2D) and Alzheimer's disease (AD); however, it remains challenging to connect the vast number of emerging disease-associated single nucleotide polymorphisms (SNPs) to cellular disease mechanisms. There is a need for systematic strategies that prioritize relevant genes of interest by accounting for environmental risk, especially given scenarios where genetic risk factors are often only revealed by an environmental trigger. An important environmental trigger for a whole array of complex disease including, but not limited to, T2D, coronary artery disease and AD is the overabundance of dietary lipids, predominately in the form of triglycerides (TAGs). This leads to the accumulation of free fatty acids (FFAs) in various tissues, inducing a detrimental cellular state known as lipotoxicity. To date, there is no comprehensive understanding of the contribution across the full spectrum of structurally heterogenous FFAs to disease pathogenesis. AD is one of the most prevalent complex neurological disorders of our time and the contribution of lipids, and FFAs in particular, to disease progression has been recognized before. The identification of the ε4 allele of apolipoprotein E (APOE) gene as the most significant genetic risk factor for AD strongly supports these observations. To specifically address the question how environmentally driven exposure to certain lipids interacts with the genomic risk for AD, we will integrate publicly available GWAS datasets for AD with a novel, transcriptionally derived signature of lipotoxicity in neurons, the primarily implicated neuronal cell type in AD. More specifically, we will expose iPSC derived neurons to a library of 61 biologically relevant but structurally diverse FFAs and perform transcriptomics for each of them. The resulting, unbiased signature of lipotoxicity will then be overlaid with genes ranked by their proximity to SNPs resulting from GWAS for AD. We expect the integration of these two orthogonal lines of evidence to reveal disease relevant genes at the intersection of environmental and genomic risk for AD that constitute prime candidates for further validation studies to investigate their potential as novel drug targets.

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› Deep neural networks
› Navigated transcranial magnetic stimuation
› Brain tumor surgery

Development of Neural Networks for Brain Tumor Patient Imaging Analysis

The gold standard for treatment of intrinsic brain tumors is a complete resection since the extent of resection (EOR) is positively correlated with (progression free) survival. However, the goal of complete tumor removal should always be balanced with preservation of function, because eloquent brain tumors imply the risk of a new functional deficits which not only lead to reduced quality of life, but also to reduced survival. We recently validated our risk stratification model based on regression tree analysis that enables to estimate the risk of postoperative motor deficit based on navigated transcranial magnetic stimulation [nTMS] and diffusion tensor imaging (DTI) data. A tumorous motor cortex infiltration and a distance ≤8mm to the corticospinal tract were risk factors for the development of a new postoperative motor deficit. In these cases, the risk was even higher if we could demonstrate impaired cortical excitability, which is determined by the motor resting threshold. The aim of this project is to combine different modalities such as structural MRI scans (with diffusion tensor imaging), nTMS data and patient characteristics using deep neural networks to further increase the accuracy of motor outcome prediction and identify new correlations where appropriate. In our initial analysis, we built on deep neural networks to predict the patients' postoperative motor status based solely on their preoperative T1 with contrast agent scans. To improve our model performance, we decided to completely revise and adapt the preprocessing of the data and to integrate different modalities in our model as well. After training the model, its performance is further improved by expert validation (supervised learning) and by integrating external data In collaboration with other neurosurgical centers. We plan to develop a freely available web-based decision support tool that can be accessed by any neurosurgeon. In a web-based template, the treating neurosurgeon can enter all relevant patient characteristics and upload the available MRI and nTMS data. The probability of perioperative risk for a new motor deficit is provided, as well as an estimate of the patient's EOR, tumor histology, and survival rate. Relevant risk factors such as tumor motor cortex infiltration or corticospinal tract involvement are reported in a standardized manner.

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› Image based numerical modelling
› Machine learning
› Digital health

Hybrid Modelling: Combining Machine Learning with Physiology Based Models in Cardiovascular Medicine

With increasing affordability of computational power as well as improvements in medical imaging technology, image-based numerical modelling of hemodynamics is gaining increased attention within the medical community. Apart from improving our understanding of the cardiovascular system through in-silico studies, such methods hold the potential to substantially improve treatment decision and outcome prediction capabilities. Using patient-specific 3-dimensional image data combined with computational fluid dynamics (CFD) solver, the ability to non-invasively predict treatment-critical hemodynamic parameters has been demonstrated. However, such methods are time consuming, cost-intensive and require substantial user interaction. As an alternative to CFD, we propose a novel machine-learning (ML) based method that is user friendly and produces results almost instantly. The challenge herein lies in providing a sufficient amount of training data for ML-based methods. Such an amount is not found even in large multicenter studies. To overcome this data gap, available patient-specific data is augmented using a statistical shape model (SSM). With this hybrid approach, we aim to overcome the aforementioned limitations of traditional numerical techniques and to improve clinical feasibility of patient-specific in-silico modelling, thereby facilitating clinical translation. As a proof of concept, this project develops an ML-based non-invasive diagnosis method for patients with aortic stenosis, one of the most common acquired cardiovascular diseases.

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› Next Generation Phenotyping
› High Throughput Sequencing
› Rare Diseases

Computer-Aided Phenotyping of Patient Images in Clinical Genetics

Patients with genetic syndromes often show characteristic facial features and pathognomonic malformations, which can also be recognized on image data. Due to the rarity of specific disease entities and the multitude of different syndromes, it requires special expertise and great experience to assign the particular phenotypes to the correct diagnoses. This process of phenotyping is accordingly lengthy and expensive. It is usually performed at specialized centers, which also have modern DNA sequencing technology to confirm suspected diagnoses by means of molecular genetics. Recently, computer-based diagnostic decision support systems have been developed that can analyze patient portrait images and return a list of suspected diagnoses using machine learning techniques. In my research, I am evaluating the diagnostic value of these systems, try to make them applicable to other image types (photographs and radiographs of the hands and feet), and integrate them into pipelines for interpreting high-throughput sequencing data. This should enable faster and more efficient filtering and prioritization of the huge amounts of data that are generated, for example, during the exome analysis of a patient. The time spent waiting for a diagnosis is supposed to be shortened and the rate of correctly diagnosed cases increased.

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› Automated Insulin Delivery

Open-Source Artificial Pancreas Systems – Translating Experienced-Based Evidence from Patients to Academia and Industry

Despite advances in care, pharmaceuticals and technological developments, type 1 diabetes remains a challenging chronic condition that impacts life expectancy and diminishes quality of life. Technological approaches aim to diminish the decision-making complexity in self-management and alleviate the cognitive and emotional burden on people with diabetes, simultaneously improving glycemic levels and variability. Automated Insulin Delivery (AID) systems combine glucose sensors and insulin pumps with control algorithms to automatically adjust insulin delivery. Despite significant research and commercial interest, a limited number of AID systems are currently licensed for use, and their functionality is limited by regulatory authorities. AID systems are, therefore, not universally available, accessible, affordable, or individually suitable. Given these limitations, a patient community, united under the hashtag #WeAreNotWaiting, has created open-source AID systems to better utilize existing devices and data. Not approved by regulatory bodies, but with code and documentation freely accessible online, the use of open-source AID continues to increase globally, with an estimated ten thousand individuals using them. There are around 25 million hours of real-world data from which has yet to be fully analyzed, leaving the rich vein of expertise, knowledge, and experience that exists within patient communities largely untapped by key stakeholders in healthcare and science. As Digital Clinician Scientist fellow and co-founder of the OPEN project (www.open-diabetes.eu), I am part of an international and intersectoral consortium striving to establish an experienced-based evidence base for open-source AID and identify challenges and possible solutions to enable its wider diffusion. The majority of the team lives with diabetes and is using open-source AID, which makes OPEN a truly patient-led research project. Our research addresses the following questions: Does open-source AID improve clinical outcomes and the quality of life of the users? How can healthcare professionals best support ethical use of open-source AID? What experiences do users have with this technology? How can we further improve and automate predictions and therapeutic adaptations of AID for certain indications? Are there barriers to further dissemination (e.g. age, gender, socio-economic status)? And finally – what can industry, research and other stakeholders learn from the #WeAreNotWaiting movement?

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› Deep Learning in computer vision and natural language processing focussed on radiology

Improving the Generalizability of Radiological Deep Learning Models Through a Prospective Study Infrastructure

Translating deep learning models into clinical practice is a fundamental challenge and is expected to grow in importance. Deep learning models often suffer from low generalizability when applied to new data, which means that the accuracy of the models used is much lower than the accuracy achieved during development under controlled conditions. To prevent this, deep learning models should be clinically tested before they are used. To accelerate this process, I am developing an infrastructure at Charité Universitätsmedizin Berlin to facilitate the prospective evaluation of deep learning models. Together with my team, we aim to integrate deep learning algorithms into the radiological productive system (the Picture Archiving and Communication System – PACS). This will allow us to immediately test and continuously improve developed algorithms until they are highly reliable and can be used in clinical practice.

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› Multi-Omics
› Lymphoma Biology
› Machine Learning
› Novel study design

Anticipation, Rediction and Optimization of the Therapeutic Outcome of Lymphoma Patients Using Digital Model Analysis

In order to improve the long-term survival of high-risk lymphoma patients by personalized medicine, the development of new prediction parameters through a multimodal evaluation approach is necessary. This interdisciplinary project in close cooperation with Prof. Dr. Roland Eils at the BIH Center for Digital Health combines clinical data, basic tumor biology research, and current bioinformatics analysis methods and is thus unique to this point and represents an innovative and conceptual new orientation of tumor precision medicine.

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Mechanisms of Neuronal Dysfunction and Death in Sepsis-Associated Cognitive Impairment

There is compelling evidence that survivors of critical illness that enter medical care with no evidence of cognitive impairment are often discharged with severe de novo neurocognitive decline that is long- lasting and likely permanent. More than one in three patients have profound cognitive impairments for at least one year after release from an intensive care unit (ICU) and as medical care is improving and the number of ICU admissions is increasing worldwide, the number of survivors of critical illness is growing. Sepsis, a potentially life-threatening systemic inflammation, is a leading cause of ICU admission and commonly precipitates severe long-term cognitive impairment. Recent studies aiming to elucidate the neuronal correlate of cognitive demise have found neuroinflammation (i.e. activation of microglia, the immune cells of the central nervous system), and neuronal death to be responsible for diffuse cerebral damage and eventually brain atrophy. However, the underlying pathophysiology remains poorly understood and there is no available treatment. Microglial phagocytosis (i.e. engulfment and degradation of a target) is a crucial process to maintain brain homeostasis during injury as it prevents tissue damage resulting from leakage of toxic intracellular components from dying cells. Thus, it has previously been assumed that microglial phagocytosis of neurons is entirely beneficial and always preceded by a cell's commitment to cell death. However, based on our recent observations indicating that microglia can engulf and thereby eliminate functional neurons and/or synapses during neuroinflammation, it is conceivable that neuronal and/or synaptic loss following sepsis is executed by microglial phagocytosis. The aim of this project is to investigate if phagocytosis of neurons and/or synapses is beneficial or detrimental for cognitive outcome following sepsis and this project will determine whether anti-phagocytic treatment may be a therapeutic option for preventing cognitive deficits in sepsis survivors.

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Fields of Research
› Photoplethysmographic visualization of tissue perfusion
› Kidney transplantation
› Liver transplantation

Intraoperative AR Guided Photoplethysmographic Visualization of Tissue Perfusion

The optimal perfusion of kidney grafts is vital for the long-term outcome after kidney transplantation. Perfusion can be influenced by the placement of the organ in the retroperitoneal space. Using photoplethysmographic visualization tools, minimal changes in colour, that cannot be detected by the human eye, should be made visible and give an idea about the quality of organ perfusion. In a second step this technology should be made available to the surgeon in the operating room via an augmented reality tool, so an optimal placement of the graft can be achieved in less time and with more security concerning optimal perfusion.

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Fields of Research
› Postoperative Neurocognitive Disorders

Multiomics Analysis of Postoperative Neurocognitive Disorders in Older Patients

Postoperative delirium (POD) and postoperative neurocognitive disorder (NCD) are common and severe complications after surgery and are associated with increased morbidity, mortality and loss of autonomy. Both POD and NCD can be regarded as complex diseases, as their development is multifactorial, and only hypotheses are currently available regarding their etiology. It is believed, that no single hypothesis can adequately explain the causal relationships of POD and NCD, and that only pathway interactions can describe the complex phenomena. A systematic approach combining genomic, transcriptomic, proteomic and environmental data using pathway analyses in a patient population has not yet been described. Therefore, the aim of this project is to describe biological pathways involved in the development of POD and NCD using multi-omics analysis in a hypothesis-generating approach. This project is part of the multicenter prospective observational study BioCog – »Biomarker Development for Postoperative Cognitive Impairment in the Elderly« (Clinicaltrials.gov ID: NCT02265263). 1032 patients ≥ 65 years of age undergoing elective surgery were included. Primary endpoints are the occurrence of POD and NCD. Blood samples were obtained from patients preoperatively, on the first postoperative day, and three months after surgery. Genomic, transcriptomic, as well as miRNA profiling data were generated using microarray analysis. In addition, proteomic data on selected parameters are available. These data will be analyzed under consideration of the clinical database in a multi-omics approach. A particular benefit of a multi-omics approach is the possibility of integral (longitudinal) analysis, since data beyond the gene level can also be considered. Another crucial advantage of this project is that omics data from the patient collective of interest are available, that regulatory elements can be taken into account by means of miRNA profiling, and that the clinical database of the study provides comprehensive information on environmental factors. In addition, repeated sampling enables the consideration of temporal factors related to primary endpoints. All DNA, RNA and plasma samples were stored in a biobank, so that further investigations (e.g. methylation patterns, de novo sequencing) are possible. Finally, biological pathways of POD and NCD are to be established. These should provide new hypotheses for follow-up studies on the prevention and treatment of POD and NCD.

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› Congenital Heart Disease
› Cardiovascular Imaging

Decision Support System for Structural Heart Disease

Surgical and catheter-based treatment procedures in acquired and congenital structural heart disease usually focus on normalization of hemodynamics (short term outcome), as well as longer-term goals, including the restoration of normal arterial/myocardial function, exercise tolerance and absence of re-hospitalization. Advances in digital health and biophysical computational modeling allow performing virtual interventions that can predict short term hemodynamic outcome. However, it has remained difficult to predict how these immediate changes translate into mid/long term clinical outcomes. Machine learning that makes use of clinical routine measurements, sensor data and non-invasive imaging data have the potential to overcome this knowledge gap and predict important parameters of long term function, providing a Decision Support System that includes: (1) Virtual treatment procedures, which will be performed and validated against results from the actual clinical outcome in order to provide reliable and scalable solutions for future treatment optimization. (2) Computational biophysical models, in order to simulate immediate hemodynamic outcome (pressure gradients, flow profiles). (3) Machine learning techniques, to predict long term functional parameters (arterial blood pressures and myocardial function) and to provide realistic boundary conditions for longer-term biomedical models and virtual treatment. Non-invasive and imaging-based biomarkers, including internal myocardial power, circulatory efficiency, and aortic distensibility are, furthermore, evaluated to gain new insights into disease pathophysiology and individual disease response.

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› Global Health
› Health economics

mTOMADY – Building Digital Technology to Provide Access to Quality, Affordable Essential Healthcare

Out-of-pocket payments (OPP) remain the predominant mode of healthcare financing in many low and middle-income countries (LMICs). However, the costs for skilled care frequently exceed the savings or assets which can be accessed at one time by a low-income household, leading to medical impoverishment. Today, more than 70% of worldwide mobile phone subscriptions come from LMICs with more than 74 subscriptions per 100 people in Sub-Sahara Africa (SSA) in 2016. In the footsteps of this revolution have followed mobile payment systems, colloquially known as Mobile Money (MM), which commonly utilize low-tech systems to enable financial transactions without the need for a bank account. Making use of this technological development, MM-based hospital insurance or savings mechanisms, which enable low-income households to set aside funds exclusively for healthcare, have been introduced successfully in several SSA countries. However, a substantial knowledge gap remains on the impact, performance, and economic costs of MM-based healthcare financing mechanisms. By building on existing mobile money infrastructure, we have developed and implemented a mobile-phone-based digital savings and payment platform, the Mobile Health Wallet (MHW), for skilled healthcare during pregnancy and delivery. The MHW is a closed loop system enabling expectant mothers to save, send, receive and pay money exclusively for healthcare. We hypothesize that the MHW will improve access to skilled care during pregnancy and childbirth by reducing financial obstacles. To test this hypothesis, we designed a cluster randomized controlled trial, called the Mobile MOney for maTernal HEalthcare Related Spending (4MOTHERS) trial for implementation of the MHW in public health facilities in Antananarivo, the capital of Madagascar. In particular, we will adopt a multidisciplinary, mixed-methods approach to assess three components of the MHW intervention: i) its impact, by measuring usage of public health facilities and health outcomes; ii) its performance, by measuring adoption, usage and user satisfaction; and iii) its economic cost, by measuring incremental costs of the intervention per pregnancy and model the cost-effectiveness of the intervention. We expect the results of our study to guide future initiatives and health policy decisions related to financial risk protection and universal healthcare coverage through digital technology in Madagascar and other low and middle-income countries.

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› Deep Learning
› Viral Pathogenesis
› Explainable Deep Learning
› Human Lung Tissue

Explainable Deep Learning to Investigate Viral Pathogenesis in the Human Lung

Understanding viral pathogenesis is a key field of investigation in emerging respiratory viruses. It is crucial to gain a deep understanding of the molecular and cellular interplay between viruses and their host to enable innovative adjunctive therapies beyond pathogen-directed clinical approaches. To understand the pathogenesis of a viral infection, it is pivotal to identify the i.) cell tropism (which cells are infected by the virus), along with ii.) other cell types present in the lung tissue and involved in the immune response. Over the past decade, the field of systems virology has evolved and technologies such as microarrays and single cell sequencing provide detailed information e.g. about gene expression signatures. Although those methods provide insights into global responses, they lack the ability to provide spatial context. The other way round, imaging techniques, such as immunohistochemistry, are giving spatial context by detecting cell types and viruses in infected tissue but are limited by the number of labels per sample. In recent years, advanced microscopy imaging techniques significantly improved our understanding of viral pathogenesis. In parallel, deep learning models in image classification showed ground-breaking success on general images and have successfully contributed to solve classification tasks in medical imaging. However, neural networks act like a black box and do not provide any information about what led to the classification decisions. Yet, understanding the algorithms decisions would help to gain profund information and to ensure reproducibility. Although both technologies show major contributions independently, they have not yet been combined to investigate virus pathogenesis. Thus, we aim to develop deep learning algorithms and apply explainable deep learning to analyze »omics-data« along with spatially resolved high-resolution microscopy images to enhance our understanding of viral pathogenesis in the human lung.

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› Nephrology
› Transplantation
› Immunology
› Telemedicine

T-Box: A Model for Predicting Kidney Transplantation Failure

Marcel Naik started his academic career during his medical school and did his thesis under supervision of Prof. Dr. Klemens Budde investigating immunosuppressive effects in immune cells for individualization of immunosuppressive therapy in renal-transplanted patients. He was introduced into relational databases and statistical analysis. He developed interest in the problems of a clinical routine database with missing values and suboptimal normalization. In his BIH funded project, he pursues to establish a prediction model for clinical use in the nephrology department at Charité to determine patients at high risk for renal transplant failure or death. Despite advances in treatment graft loss occurs in 5% of patients annually, so that 50% are back on dialysis after 10 years. Unfortunately, early detection of patients at high risk is lacking. Patient data from the clinical transplant database »TBase« is retrieved including all patients above 18 years who had undergone only kidney transplantation at Charité, Campus Mitte, after 2000. Data consists of demographic data of recipient, transplant and donor, examination reports from microbiology, pathology and clinical notes, laboratory values and hospitalizations at Charité. All data needs to be refined and cleared from missings or corrupt data. After that step of data preprocessing a training dataset will be defined to train an algorithm predicting patients with permanent renal graft failure or death. Collaborating with the DATEXIS group at Beuth university for applied science text data from examination and pathology reports will be incorporated into the prediction model. Diogo Telmo Neves, a data scientist from the medical informatics department at Charité and former DFKI researcher, is programming and fusing all branches together. As of 04/2021 a baseline prediction model incorporating demographic data is established using KNN- and Random Forest algorithm. To incorporate the individual patient's timeline into the prediction model a time dependent long short-term memory network will be set up. Furthermore, data from newly established home monitoring of vital sign will be included for detecting early signals. All models will be validated using another cohort from Charité Virchow Hospital. The prediction model's risk assessment will be integrated into individual patient record to show the risk to doctors. Ultimately he wants to show the individual risk to the individual patient.

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› Stroke Imaging
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› Quantitative Imaging
› Outcome Prediction

Radiomics Based Machine Learning Prediction of Clinical Outcome on Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is the most severe form of stroke and remains a major cause of morbidity and mortality worldwide. Early detection of high-risk patients remains a key goal in directing the management and treatment course. Cerebral injury secondary to ICH is a known factor to potentiate the risk of a poor outcome. Rapid advances in our understanding of the underlying mechanisms have fueled an interest in identifying novel therapies targeting secondary injury. However, standardized biomarkers for imaging quantification could so far not be established. Emerging data suggest perihematomal edema (PHE) as a promising biomarker as the temporal course of PHE correlates with the manifestation of secondary injury but results remain inconsistent. Edema formation comprises multiple coordinated and complex mechanisms that are known to be disease-specific. In line with this, the applicant's previously published work highlights the promising prognostic value of early edema formation in different forms of ICH. The assumption therefore seems reasonable that perihematomal edema holds additional imaging characteristics that are not visible to the human eye, yet of great prognostic value. Progressive machine learning (ML) algorithms have paved the way for a fully automated radiomics analysis and therefore hold a clear clinical impact. The application of ML algorithms for the prediction of clinical outcome after ICH are still lacking and have not included PHE features. The applicant's previous results demonstrate that radiomic features provide a high discriminatory power in predicting neoplastic ICH on CT, with significantly higher power than human prediction. Quantitative features of PHE in ICH may distill multiple-but-subtle variations such as in thrombin accumulation, influx of inflammatory mediators, and erythrocyte lysis with significant prognostic value. Following this idea, the clinical research project aims at understanding the high-end quantitative imaging characteristics of perihematomal edema (PHE) which may serve as a predictor of poor prognosis and examine the efficacy in predicting patient outcomes after ICH.

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› Patient Monitoring
› Clinical Alarm Management
› Intensive Care Medicine
› Implementation Science

INALO – Intelligent Alarm Optimizer for Intensive Care Units

Patient safety has improved significantly in recent decades due to the monitoring of vital signs in intensive care units (ITS). However, between 72 and 99% of these alarms are described as false positives or »non-actionable«. They can trigger »alarm fatigue«, a desensitization of staff to critical alarms that can even lead to patient harm and even death. The goal of this project is to develop a user-centered platform that will enable research and implementation of alarm optimization approaches for patient monitoring in the ICU by means of patient-specific data and machine learning approaches. In doing so, the perspective is to achieve a reduction of unnecessary alarms. Digital documentation generates several gigabytes of health data every day. This data can already be used as a basis for artificial intelligence (AI) algorithms that support patient care in the ITS. The development of an alarm optimizer could promote a better understanding of the alarm situation, as well as reduce the workload of ICU staff and improve patient care by reducing unnecessary alarms.

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Fields of Research
› Quantitative MRI
› MR Elastography
› Deep Learning
› Inflammation

Quantitative Spatially-Resolved MRI Of Fibrosis and Inflammation in Chronic Liver and Bowel Disease

Purpose: The aim is to determine fibrosis and inflammation in chronic liver and intestinal diseases using quantitative MRI (qMRI) and artificial intelligence. Background: Determination of disease activity of fibrosis (scar tissue) and inflammation is often crucial for therapy, but so far can only be determined with invasive procedures, such as biopsies or endoscopies. This is particularly true for cholestatic liver disease (e.g., primary sclerosing cholangitis), fatty liver disease, and inflammatory bowel disease (Crohn's disease and ulcerative colitis). These diseases share a common diagnostic gap: determining the spatial distribution -or heterogeneity- of fibrosis and inflammation. Methods: Spatially resolved qMRI can measure this heterogeneity using the following sequences: Tomoelastography (shear-wave speed in m/s), T1 and T2 mapping (relaxation times in ms), diffusion imaging (ADC in mm2/s), fat quantification (in %). Image acquisition and image processing of multiple quantitative biomarkers simultaneously creates a system-independent database and provides the basis to train neural networks. This enables identification of the best parameters for classification of fibrosis and inflammation in liver and intestine. Automated diagnosis of the quantitative image data is performed using a 3D Multi-Channel Convolutional Neural Network. In this process, the different biomarkers can be tested separately and in all possible combinations. Clinical benefit: The number of invasive procedures, such as biopsies, endoscopies, and surgeries, could be reduced. In addition, specific biomarkers could be established for stratification of clinical trials and development of new therapies.

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› Machine learning
› Image biomarkers

Machine Learning and Quantitative FDG PET-CT Image Parameters for Diagnostics and Prognosis in Patients with Lung Cancer

This project investigates the additional value of machine learning (ML) and quantitative image parameters from FDG-PET/CT in patients with non-small cell lung cancer (NSCLC). In the current clinical application of FDG-PET/CT, it is usually assessed as an isolated diagnostic tool, and reporting is mostly confined to visual reading. Consequently, the reliability and reproducibility of FDG-PET/CT reports is variable, which currently entails frequent confirmatory invasive diagnostic procedures. Therefore, substantial advances in the clinical impact of FDG-PET/CT in improving patient-relevant outcomes may require new paradigms. In this project, ML is used both to derive the image biomarkers and to integrate image data with clinical information, pathology reports and lab results (so-called integrated diagnostics). Different ML methods are investigated, including decision trees as well as deep learning (artificial neural networks). The first application of this methodology is in pretherapeutic thoracic lymph node staging in patients with NSCLC. Retrospective and prospective clinical data are used to develop and validate ML models that provide a differentiated and individualized estimate of the positive and negative predictive value of FDG-PET/CT. The goal is to equip clinicians with a decision support system that is ready for clinical use and that allows individualized assessment of the reliability of FDG-PET/CT. This would help physicians to spare more patients additional (confirmatory) invasive staging. The second application that is investigated is the use of ML and quantitative image parameters to predict the patient's survival after curatively intended treatment. Presently, the treatment decision is mainly determined by the clinical tumor stage although this is not sufficiently differentiated to allow individualized prediction of the patient's prognosis and the optimal treatment. The current project investigates the additional value of textural features from FDG-PET and CT data to predict the progression-free survival and overall survival in patients with stage I-III NSCLC. These textural features include conventional, mathematically defined features (»radiomics«) as well as classificators derived with deep learning.

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› epilepsy
› MRI
› EEG
› Epilepsy surgery

Using Computational MRI to Automatically Detect Epileptogenic Lesions in Patients Eligible for Epilepsy Surgery

Epilepsy affects about 70 million people worldwide; it is one of the most common neurological disorders in children and adults. Up to one third of patients are drug-resistant, with poorly controlled seizures despite adequate medication. Epilepsy surgery is the most successful treatment option to achieve seizure freedom for patients with focal drug-resistant epilepsy, which on average is achieved in 65% of patients. The absence of an epileptogenic lesion on MRI has been shown to decrease the probability of seizure freedom by more than 20%. The detection of an epileptogenic lesion on MRI in so far assumed non-lesional pre-surgical candidates remains an important challenge to improve surgical targeting and secondarily postsurgical outcome.In this retrospective study, we assess a new approach to detect individualised lesions in patients with epilepsy in a large cohort, two-centre study by applying an outlier lesion detection machine-learning algorithm. Pre- and if available postoperative MRI scans (T1-weighted (T1 MPR) and T2-weighted FLAIR) of all consecutive patients having received a recommendation to undergo epilepsy surgery, between 2015 and 2020 at the Epilepsy centers in Berlin and Bochum, will be analysed. Clinical variables, including the clinical and neurophysiological focus hypothesis consensus from the multidisciplinary meetings (MDM), will be collected for each patient. Additionally, we are comparing this new approach to previously published methods by applying them to the same data set.The primary outcome measure is the outlier lesion concordance with the epileptogenic focus defined by MDM consensus. Concordance is defined by localisation in the same gyrus or lobe (depending on specificity of presurgical lesion-hypothesis). The secondary outcome measure is the overlap between the outlier lesion and surgical resection site.In the long run, we hope, by applying the outlier lesion detection method successfully, to enable more surgeries in non-lesional cases and potentially cut down the use of invasive diagnostics such as intracranial EEG.

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Electronic Patient-Reported Outcomes for Relapse Detection in Cancer Patients and Mitigation of the Novel Coronavirus Pandemic

Electronic Patient-Reported Outcomes (ePROs) promote patient-centered care by collecting and incorporating patient-reported information into clinical settings. At the heart of this digital health project, an open-source ePRO application (app) was developed with the flexibility to be adapted to various clinical situations and a focus on ease-of-use for the patient. Two different use cases are evaluated for this app: 1.) relapse detection for cancer patients, 2.) risk evaluation of users potentially infected with the novel coronavirus (SARS-CoV-2). Regarding use case 1, standard of care for relapse detection in cancer patients usually involves follow-up visits in fixed intervals. This leads to unnecessary prolongation of relapse detection which can have a deleterious effect on the oncological outcome. ePROs facilitate that patients enter symptoms directly into a database that can be evaluated in real-time. Especially, patients with locally advanced head and neck squamous cell carcinoma (HNSCC) may profit from earlier relapse detection which is seen in 15-50% of the cases. HNSCCs are known to proliferate rapidly and deferred treatment can result in stage progression. Recurrent stage is known to be the most important parameter regarding overall survival. A model is built based on ePROs to detect patterns with the goal of earlier relapse detection with a lower recurrent stage. Machine learning methods are used for model creation in collaboration with Stanford University. For use case 2, the app has been published under the name CovApp and could demonstrate the ability of fast deployment during the onset of the novel coronavirus pandemic and scalability to a larger number of users. CovApp provided individualized recommendations based on ePROs regarding laboratory testing, probability of severe covid-19, and guidance for several million users in Germany and internationally. At the hospital, increased efficiency could be achieved by reducing the time necessary for anamnesis by providing the function to scan ePROs directly from the patient's smartphone via QR code. Hereby, it contributed to identify and interrupt infection chains, optimize health care resources and provide crucial information to the general population, especially to high-risk patients. Further development aims to evaluate the project's big data for local outbreak detection and case number prediction.

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› Acute respiratory infection
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› Picornavirus
› Coronavirus

Excellent Junior Research Group Program
› BMBF Research Group

Virus Evolution and Immune Repertoire Sequencing as a New Approach to Predict the Outcome of ARI

Viral acute respiratory infections (VARI) are the most prevalent infectious diseases in humans. Their onset is non-specific and the immediate clinical courses are highly variable, ranging from recovery to fulminant pneumonia within a few days. Outcomes are likely determined by the composition and development of the infecting virus population as well as the patientspecific immune response. The focus of this research group will be to analyze the extent to which novel laboratory tools (virus population analysis, B- and Tcell receptor repertoire sequencing, cytokine profiling) can predict the outcome of individuals with VARI, based on patient samples from the first days after disease onset. The group will have access to unique patient cohorts, drawn from the largest clinical virology service in academic medicine in Germany.

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› Breast cancer – Systems Biology – RNAseq – Multiplexed immunofluorescence

Excellent Junior Research Group Program
› BMBF Research Group

Discovery of Biomarkers Through Multilevel Measurement of Tumor Heterogeneity in Triple Negative Breast Cancer (TNBC)

Disentangling the diverse composition of tumors is essential to understanding how they emerge, develop and react to therapy, and thus of utmost importance for the development of effective therapies. However, in TNBC, so far, studies in this direction have been limited to either a low number of gene loci or a low number of patients. Moreover, genetic tumor heterogeneity represents only a subset of the variability that can be observed within a tumor. Cells with the same genetic information vary in their epigenetic profiles, transcriptome, proteome and morphology and can adopt different states of differentiation, cell cycle, or circadian rhythm. The goal of this project is to generate high-throughput imaging and -omics data that characterize tumors from TNBC patients before and after therapy at several levels and to provide a comprehensive, multidimensional representation of tumor response to therapy over time. We will use multiplexed immunofluorescence protocols, combined with DNA and RNA sequencing of selected cell populations isolated from tissue sections to characterize patient collectives with TNBC before and after they receive therapy in order to better understand which factors best predict therapeutic outcome and how therapy resistant clones emerge. This integrated dataset will be analyzed in collaboration with the groups of Adrián Granada (CCCC, Charité-Universitätsmedizin Berlin) and Dr. Katarzyna Bozek (CMMC Köln) through iterative combination of histopathological diagnostic algorithms, machine learning based computer vision, sequence analysis, and dynamic models of cell behavior over time in response to therapy. Specifically, we will try to find correlations between the changes in tumor cell composition, expression of groups of markers and prognosis as well as therapy outcome. We hope to develop new precision medicine based biomarkers based on cellular state defined as a complex set of cell properties reaching beyond genomic mutation profiles and including multiple properties of the proteome, transcriptome and cell morphology.

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› Mucosal Immunology, Inflammatory bowel diseases, T cell immunology, Microbiota responses

Excellent Junior Research Group Program
› Lichtenberg Professorship of the Volkswagen Foundation

Microbial and Environmental Factors That Control Gut-Resident Memory T Cells in Human Health and Disease

The human intestine harbours a vast and diverse bacterial community that exerts several beneficial effects on the host. For example, the commensal microbiota harvests energy from otherwise indigestible carbohydrates, synthesises vitamins, and contributes to the maintenance of the epithelial barrier. Furthermore, it is now clear that the commensal microbiota has a profound effect on immune responses. Maladaptation of this host-microbe dialogue can promote inflammatory responses and is implicated in various pathologies including inflammatory bowel disease (IBD). However, the microbial signals and molecular pathways that promote tissue-specific differentiation of gut-resident immune cells are poorly characterized. Deciphering the complex host-microbiota relationship is therefore of great biomedical value.Using cutting-edge technologies, a multidisciplinary approach, well-defined patient cohorts, and mouse models of colitis, I will clarify the interactions between microbial, environmental, and inflammatory factors that promote intestinal inflammation. I will assess mucosal and peripheral CD4+ T cell specificity towards intestinal microbiota under steady state and inflammatory conditions using an experimental approach that combines high throughput culture methods, ex vivo analysis of memory T cells, and in vitro priming of naïve T cells. Furthermore, gut-resident T cells will be profiled at the whole population and single cell levels using transcriptomics, epigenomics, and metabolomics to decipher their molecular signature. The significance and relevance of the identified pathways will be tested in mouse models of colitis, human tissue explants, and novel 3D models using primary human tissue. The overall goal is to utilise the acquired knowledge to identify targetable cytokine signals and pathogenic molecular pathways in microbiota-specific CD4+ T cell populations for therapeutic development in IBD.

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› Pediatric Cancer Genomics
› Personalized Cancer Therapies
› Pediatric Solid Tumor Biology

Excellent Junior Research Group Program
› ERC Starting Grant
› DFG Emmy Noether Program

Understanding the Origin of Complex Structural Variants in Pediatric Cancer Genomes

Significant tumor regression can be achieved in many cancers by induction chemotherapy. The period of remission varies, and is too often followed by regrowth of aggressive, therapy-resistant lesions. Treatment resistance is believed to be partly driven by the pre-existence of resistant phenotypes within the clonal population of the cancer in a single patient. Neuroblastoma is a prototypical example of this phenomenon. Neuroblastomas are the most common tumor in childhood. The majority of high-risk neuroblastomas are sensitive to induction therapy, but quickly recur as chemotherapy-resistant disease that is almost uniformly lethal. Neuroblastoma is characterized by a surprising paucity of gene mutations. However, recurrent chromosomal and complex genomic rearrangements, including chromothrypsis and double minutes, are common in high-risk neuroblastomas. It remains largely unknown what drives neuroblastoma intratumoral heterogeneity, chemotherapy resistance and disease relapse.We have made new discoveries linking DNA recombinases to sequence-specific oncogenic mutations (as published in Nature Genetics and Science Translational Medicine in 2017), which has direct implications for the understanding of genomic structural variation in pediatric tumors. We aim to determine the molecular mechanisms of recombinase-induced genomic plasticity and adaptation to targeted therapies using functional investigation of human tumors and engineered animal models, with the long-term goal of developing rational combination therapy for patients with high-risk, refractory or relapsed pediatric solid tumors. The development and use of functional genomics tools will feature strongly in our group, and work in our lab will focus on investigating the dysregulated organization of cancer cell genomes with the goal of identifying effective targets and therapeutic agents for rationally designed combination therapies.

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› Deep Brain Stimulation
› Movement Disorders
› Brain Connectivity

Excellent Junior Research Group Program
› DFG Emmy Noether Program

Toward a Virtual Patient in Deep Brain Stimulation

Deep Brain Stimulation – a highly efficacious treatment option for movement disorders such as Parkinson's Disease – is currently undergoing a paradigm-shift from stimulating local target regions toward network stimulation, i.e. neuronal modulation of distributed brain networks. Specifically, it was long thought that the procedure exerts its therapeutic potential by local modulation of the target region itself. However, accumulating evidence suggests that effects on distributed brain networks and basal-ganglia-cortical loops are at least equally important. Our group published several articles of general network interactions between DBS electrodes and remote sites using electrophysiology and brain imaging. However, recently, in cooperation with Harvard Medical School, we were able to demonstrate that clinical DBS improvement may be predicted using MRI-based brain connectivity estimates between the site of stimulation and distributed cortical areas. In this study, the structural and functional connectivity profiles of DBS electrodes in 95 Parkinson patients from two DBS centers (Berlin & Würzburg) were highly predictive of clinical motor improvement across patients. Moreover, the study defined effective treatment networks for Parkinson's Disease that may one day be used to guide programming and targeting of deep brain stimulation after further validation. The technique was introduced for Parkinson's Disease but could even be of stronger use in the case of Dystonia, where changes in stimulation parameters often lead to a delayed symptom alleviation and guidance from computer models could be even more helpful in clinical practice. Adopting the technique for treatment in Dystonia is the current focus of our work.

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› Motor Recovery
› Neuroprosthetics
› Stroke Research

Excellent Junior Research Group Program
› Freigeist Fellowship der Volkswagen Foundation

Inducible Neuroplasticity after Stroke Using Neurotransmitter Replacement Strategies

Translating the behavioral output of the nervous system into movement involves interaction between the brain and the spinal cord. The brainstem provides an essential bridge between these two structures. However, the function of this intermediary system in motor recovery after stroke remains poorly understood. In fact, the brainstem is a major source of monoaminergic neurotransmitters that coordinate movement at the level of the spinal cord (Wenger et al. 2016) and mediate plasticity in the central nervous system (Ng et.al 2015). My hypothesis is that motor cortex stroke alters the activity of monoaminergic brainstem nuclei limiting functional recovery after stroke. Using neural tracing experiments and behavioral analysis, I aim to investigate the therapeutic effect of monoaminergic neurotransmitter replacement strategies to engage plasticity of neural networks related to motor production. The translational aim of this project is to investigate neuroanatomical rewiring processes that benefit the restoration of function after stroke.

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› Epithelial Biology
› Gastrointestinal Microbiota
› Gastrointestinal Carcinogenesis

Excellent Junior Research Group Program
› DFG Emmy Noether Program

Mechanisms of Gastric Stem Cell Control Upon Infection and Carcinogenesis

The gastric epithelium is characterized by rapid self-renewal. Long-lived Lgr5-expressing stem cells that are localized in the base of the stomach antral glands constantly regenerate the epithelium. Lineage tracing experiments have shown that stomach glands are regenerated by Lgr5+ stem cells for a year or more, demonstrating the longevity of these cells (Barker et al., 2010). In addition to their physiological relevance, these long-lived cells also appear to be critical in the process of carcinogenesis (Barker et al., 2009). Accordingly, Lgr5+ cells have been reported to expand and show increased evidence of DNA damage in patients with gastric cancer (Uehara et al., 2013). Chronic infection with the gastric pathogen H. pylori is the major known risk factor for the development of gastric cancer (Blaser et al., 1995; Parsonnet et al., 1997). Hypothesizing that H. pylori affects gastric stem cells, we have previously used mice that express GFP under the Lgr5 promoter to show that although they are located at the very base of the gland, H. pylori is able to directly colonize and grow on the intercellular junctions of stem cells (Sigal et al., 2015). Infection induces a two-fold increase in the number of stem cells per gland unit and a significantly higher proliferative activity. Lineage tracing experiments revealed that infection induced a significant increase of the turnover kinetics of stem cells, resulting in the repopulation of entire glands within five instead of ten to 14 days, finally resulting in severe glandular hyperplasia (Sigal et al., 2015). An unresolved question is how stem cell number, their division rate, and fate determination are controlled under physiological conditions as well as upon infection. I plan to characterize the gastric stem cell microenvironment, the so-called stem cell niche, under physiological conditions as well as upon infection to understand how stem cell number, proliferative activity, and fate determination are controlled. I will focus on Wnt signaling, study its cellular organization and unravel how alterations of Wnt signaling affect stem cell and tissue homeostasis. Further, using an unbiased approach I will investigate how the myofibroblasts that surround the stem cells affect stem cell behavior.

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› Intestinal Microbiome
› Host-Microbiome Interaction

Excellent Junior Research Group Program
› ERC Starting Grant

Putative Role for Bacterial Metabolites in Protection from Hypertensive Organ Damage

Hypertension and subsequent damage to the heart and kidneys contribute to cardiovascular morbidity. Besides hemodynamic stress, an important role for the immune system has been uncovered, linking pro-inflammatory T effector cells to the development of hypertension. In particular, interleukin-17A producing TH17 cells promote hypertension and organ damage. Although the deleterious role of inflammation in hypertension has been recognized, current treatments insufficiently address these mechanisms. This project aims to elucidate the role of tryptophan metabolites of bacterial origin in hypertensive renal and cardiac damage. It is based on the recognition that gut bacteria affect host organs and the immune system by virtue of their metabolites. Tryptophan is metabolized by intestinal bacteria to indoles. We have shown that a probiotic Lactobacillus treatment reduces blood pressure and provides beneficial immunomodulation in experimental hypertension, putatively via production of indoles. This project aims to expand on these observations by using cell culture systems, a rat model as well as patient material. Candidate indoles selected in vitro as well as probiotic treatments will be tested for their immunomodulatory and organ-protective potential in hypertensive double-transgenic rats. Tryptophan metabolite analysis will be performed in hypertensive patients, potentially enabling future translation.

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Index

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18 Beyhoff, Niklas (JCSP) CBF
152 Bobbert, Peter (CSP) CBF
57 Dirks, Fabian (JCSP) CBF
103 Friebel, Julian (CSP) CBF
24 Gerhardt, Teresa (JCSP) CBF
61 Girke, Georg (JCSP) CBF
175 Jakob, Philipp (CSP) CBF
231 Wurster, Thomas Heinrich (CSP) CBF

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170 Hewing, Bernd (CSP) CCM
203 Poller, Wolfram (CSP) CCM

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91 Alogna, Alessio (CSP) CVK
173 Hohendanner, Felix (CSP) CVK
122 Oeing, Christian (CSP) CVK
128 Primessnig, Uwe (CSP) CVK
146 Zhang, Kun (CSP) CVK

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134 Rittig, Susanne (CSP) CBF
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210 Schlemm, Ludwig (CSP) CCM
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Page 24, 28, 39, 45, 57, 99, 132, 137, 165, 169, 171, 173, 174, 189, 196, 238, 246, 251

106 Andreas Süß
25, 114 Birgit Formann
33 Center for Stroke Research (CSB)
219, 227, 19 Christoph Weber
184 Kerstin Müller
255 Mediencenter
192 Scharf
87, 229, 80 Simone Baar
118 Stefan Trappe

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194 David Ausserhofer
9 Stefan Zeitz
3, 274, 275 Thomas Raflzyk

Other

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241 Manuel Tennert
50 Memorial Sloan Kettering Cancer Center
244 Michael Gotthardt
200 Peter Johann Kierzkowski
216 Philipp Leu
264 PicturePeople
15 Raphael Hablesreiter
66 Simon Mossburner
261 The Kennedy Institute Of Rheumatology
124, 178 UKE Unternehmenskommunikation
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