BIH CHARITÉ
CLINICIAN SCIENTIST
PROGRAM

BIH | Berlin Institute of Health
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2023

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CHARITÉ
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BIH Academy
Biomedical Innovation Academy

Content

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

2023

With full power and a fresh wind: how we emerge stronger from challenging years

Introduction by Dr. Nathalie Huber[1] and Dr. Iwan Meij[2]

Looking back to the last years, one word probably fits best – namely 'challenging'. But we and our team wouldn't be ourselves if we didn't come out of a challenge even stronger!

From the start of 2023 we have a new director for the Clinician Scientist Program (CSP): Professor Dr. Il-Kang Na. She succeeds Professor Dr. Duška Dragun, who led the program until her much too early death at the end of 2020 and who is still dearly missed. Both passionate Clinician Scientists themselves, Professor Dr. Dragun and Professor Dr. Na knew each other for a long time and worked together within the Clinician Scientist Board. Prof. Na perfectly fits the profile of a new program director: Like Prof. Dragun she acts as a great role model for our fellows, successfully combining research with clinical duties. Furthermore, she has gained a wide range of experience in promoting young scientists, for example as a long-standing CSP board member and as spokesperson for the Berlin School of Integrative Oncology. Welcome on board, Il-Kang – we look very much forward to working together!

The previous program book was published in May 2021 on the occasion of the 10th Anniversary Symposium of the BIH Charité Clinician Scientist Program and memorial ceremony in honor of Prof. Dragun.[3] Against the backdrop of this tragic loss, the jubilee symposium took on an entirely different character then the originally planned as a commemorative event. Accordingly, within the last two years we have done our best to remain dedicated to Duška's mission and all this in times of the corona pandemic…

The pandemic had forced us to switch almost everything to virtual or hybrid formats and now we have to find our way back to face-to-face meetings and events. We had to virtually align our entire program such as the monthly Jour Fixes with our fellows and our curricular offers. Beyond that, our two-stage selection process, meetings with the review panel, and selection colloquia with the applicants were all switched to a virtual format. Also not to be forgotten the target agreement meetings with the fellows, their mentors and clinic directors and the program management at the beginning of the program funding. In January 2022, we hosted our first digital Clinician Scientist Retreat with about 200 participants. The program of the two-day retreat consisted of a panel discussion, scientific lecture sessions as well as strategy, information and networking sessions. We were positively surprised and thrilled by how tangible the 'spirit' of our Clinician Scientist community could be felt and by how the community managed to network in the digital space

1. | 2. Dr. Nathalie Huber and Dr. Iwan Meij are both Heads of the BIH Biomedical Innovation Academy. Dr. Huber is also Head of the Clinician Scientist Office.

3. The current version is the fourth 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 was published in June 2018 for the International Symposium on Translational Medicine in Berlin. In May 2021, the third edition was published for the 10th Anniversary Symposium of the BIH Charité Clinician Scientist Program and Memorial Event in Honor of Professor Duska Dragun.

and discuss intensively in an interdisciplinary way! Still, at some point, we could hardly wait to go back to 'normality' and to switch back from virtual to physical presence. In Summer 2022, after a two-year break we managed to reunite our Clinician Scientist Community with our award ceremony which was once again held in presence with members of the Charité and BIH Board of Directors and the President of the Berlin Chamber of Physicians. The joy of seeing everyone live again and to celebrate together was both emotional and powerful, and a great team spirit came into play!

During the last years, we have also achieved several significant results and successes: On the occasion of the tenth anniversary of the BIH Charité Clinician Scientist Program, we carried out a systematic and large-scale external program evaluation together with the German Centre for Higher Education Research and Science Studies. The comprehensive evaluation report was published in June 2021.[4] The external evaluative perspective identified key points that are not only extremely valuable for the further development of our program in Berlin, but certainly informative as well for Clinician Scientist Programs at other Medical Faculties in Germany. Furthermore, the results of our joint research project with the Institute of Medical Sociology and Rehabilitation Science on »Structural Effects of Clinician Scientist Programs on the Biomedical Research Landscape« was completed. A summary of the study results was published in the *Deutsches Ärzteblatt*.[5] Also of great importance was the extension proposal for our Digital Clinician Scientist Program, which was granted in 2022. Finally, the development of our tailor-made curricula has received a new

boost through a cooperation with the European School of Management and Technology (ESMT) enabling us to offer elective entrepreneurship modules.

We could not have achieved all this without the great and continued support of our Interim Program Directors (2021–2022) Professor Dr. Britta Siegmund and Professor Dr. Dominik N. Müller. Both of them deserve our explicit thanks for the last two years. We are also very happy that both of you have now taken over the Deputy Program Directorate! We would also like to express our gratitude to Professor Dr. Igor Sauer, the Program Director for the Digital Clinician Scientist Program, and his deputy Professor Dr. Robert Gütig – it is so incredibly inspiring to work together with all of you!

4. 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

5. Lange, Ramona; Kusch, Angelika; Hesse, Rüdiger; Huber, Nathalie (2023): Clinician Scientist Programme: Zwischen Individualität und Standard. Deutsches Ärzteblatt, Jg. 120, Heft 3, 20. Januar 2023. https://www.aerzteblatt.de/archiv/229314/Clinician-Scientist-Programme-Zwischen-Individualitaet-und-Standard

Greetings from the new Clinician Scientist Program Director Prof. Dr. Il-Kang Na

Since January of this year, I have started as director of the CSP and I am delighted about this new task.

Clinically, I am a senior physician in the Department of Haematology, Oncology and Tumor Immunology and my research group focuses on therapy-induced changes in the tumor, immune system and their interaction in tumor patients. Together with Dr. Nathalie Huber, Dr. Iwan Meij and the entire team of the BIH Biomedical Innovation Academy, I would like to accompany and support the Clinician Scientist Program and its fellows in the best possible way.

We aim to further develop the program and make it sustainable. For example, it is important to us that they are also well »equipped« for the time after the CS funding so that they can continue to successfully pursue their careers. We are also working on new funding lines, such as an Advanced Track for innovative clinical studies.

## Structural Integration of Clinician Scientist Programs in University Medicine

Clinician Scientist Programs are a modern career path within academic medicine that allow physicians to pursue a structured residency with time set aside for clinical and basic research. They are based on a combination of a competence-oriented clinical education with a translational medicine based curriculum including clearly defined »protected time« for research. The Berlin program is the largest of its kind in Germany and is recognized internationally for its pioneering role. It is considered as a national »best-practice model« and has set nationwide standards in terms of design and quality assurance measures. It has served as a model for position papers by the German Research Foundation[6] (Deutsche Forschungsgemeinschaft, DFG) and the German Science Council[7] (Wissenschaftsrat, WR). We participate in several committees (e.g. German Association of Medical Faculties, MFT) and advise university hospitals in terms of promotion of young talents. 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. In cooperation with the MFT we have taken the central role in the conception of a National Clinician Scientist Cohort. The primary aim is to provide an essential contribution to a consolidated and solid database for health system policy making and Meta Research in order to promote Clinician Scientists the best as possible on their specific career track.

6. 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

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

2021–2022: The Road Back to 'Normality' through the Corona Pandemic
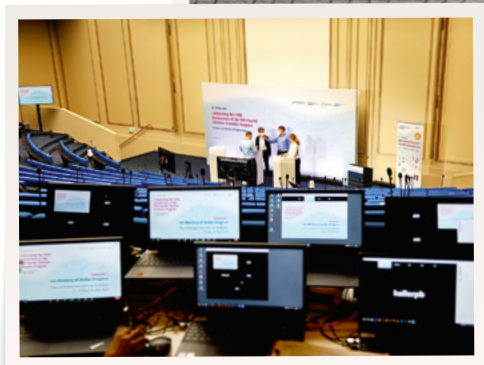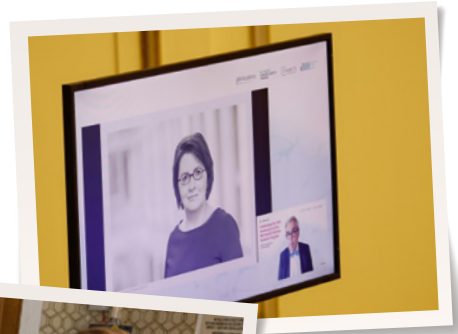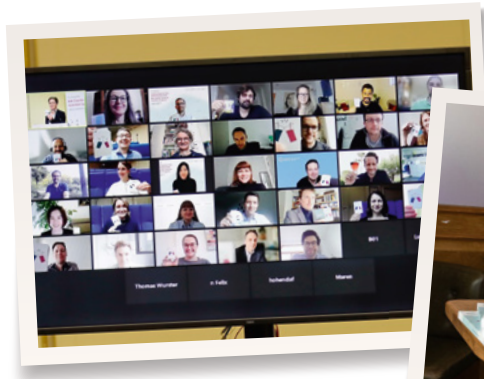
Impressions from program events during and after the Corona Pandemic: From fully digital to hybrid and back to face-to-face.

»... the Excellent Development of Our Program Over the Last Decade Has Not Only Successfully Introduced the Clinician Scientist Track, but Has Furthermore Created an Interdisciplinary Community That Is Shaping the Medicine of Tomorrow ...«

Prof. Dr. Britta Siegmund, Deputy Director of the BIH Charité Clinician Scientist Program
Department of Gastroenterology, Infectious Diseases and Rheumatology (Including Clinical Nutrition), Charité – Universitätsmedizin Berlin

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[8]. 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. Clinician Scientists as researching physicians are thus 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[9]). Evidenced by statistics from the last 12 years demonstrate that program fellows succeed comparably in specialty exams of the Berlin Chamber of Physicians. Our Junior Clinician Scientist Program, implemented in 2014 and meant as a booster program, does not include the mandatory structured training and thus cannot be credited as part of the residency training.

Recently, Prof. Dr. Duška Dragun was posthumously awarded the Georg Klemperer Prize of the Berlin Chamber of Physicians for her pioneering work in establishing a structured Clinician Scientist Program and her significant contribution to building a new generation of young researchers in medicine.[10]

8. 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

9. 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.

10. https://www.aekb.de/kammer/auszeichnungen/georg-klemperer-preis (Zugriff 17.5.2023)

Our different funding lines in a nutshell

BIH Charité (Junior) Clinician Scientist Program

The (Junior) Clinician Scientist Program ((J)CSP) guarantees research-active physicians a competence-based clinical residency training with a contractually regulated »protected time« for research. During specialist training Clinician Scientists and Junior Clinician Scientists are allotted 50 % or 20 % of their working time as »protected time« to exclusively conduct research. A close mentoring by a clinical and a scientific mentor with progress and feedback meetings ensure guidance and support not only for the research project itself but also for the individual career development. Fellows of the CSP are expected to complete their specialist training and their »Habilitation« by the end of the program.

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 a sustainable career support of young scientists.

Fostering the Digital Transformation: the Digital Clinician Scientist Program

Our (Junior) Digital Clinician Scientist Program ((J)DCSP) is an innovative track for physicians during their residency with a special interest in digital medicine. With the rapid advancements in technology within the field of academic medicine, it has become increasingly important for prospective Clinician Scientists to be well-prepared for the challenges associated with advanced computational science approaches. Recognizing this need, we successfully secured additional funding from the German Research Foundation (DFG) in 2018. The (J)DCSP follows a similar structure to the (Junior) Clinician Scientist Program, providing protected time for research. However, what sets it apart is a focus on digital medicine and the inclusion of a digital mentor in addition to the regular mentoring team. This unique feature brings together leading experts in computational sciences with clinicians, allowing fellows in the (J)DCSP to benefit from a comprehensive and interdisciplinary approach. In 2022, we successfully applied for a follow-up funding by the DFG, securing the digital track until at least 2026.

»… Digital Clinician Scientists Have to Shape the Future of Digital Medicine, Create Digital Solutions, and Assess the Significance, Potential, and Possible Dangers of Digital Solutions in Patient Care Through Fundamental Knowledge and Interdisciplinary Exchange.…«

Prof. Dr. Igor Sauer and Prof. Dr. Robert Gütig
Director and Deputy Director of the Digital Clinician Scientist Program
Department of Surgery, Charité – Universitätsmedizin Berlin, Experimental Surgery
NeuroCure Cluster of Excellence, Charité – Universitätsmedizin Berlin

Advanced Clinician Scientist Pilot Program

To close the existing gap in the support of academic career paths after residency, we piloted an Advanced Clinician Scientist Program (AdCSP) in fall 2020. It is designed to support the previously insufficiently considered target group of scientifically active clinicians who have just completed their habilitation and are on their way to leadership positions or professorships. 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 demands of today's highly specialized university medicine. Through this funding line, Charité departments and institutes could apply with up to two qualified candidates. Six departments were promoted with overall ten candidates. Fellows are receiving either 25% or 50% »protected time« for research. The AdCSP includes leadership skills training, peer mentoring, and peer meetings with leading professors from the faculty and academic self-governance. Encouraging, already four of the primarily funded fellows have obtained professorships since program start and fundings could be transferred to further qualified candidates of the same department or upgrading of »protected time«.

Sustainability

Since 2020

Advanced Clinician Scientist Pilot Program
- Completion of specialist training
- Habilitation
- **25 – 50% »protected time« for research**
- **3 – 6 years**

Consolidation

Clinician Scientist Program
- Doctorate with at least cum laude
- Completed 50% of specialist training
- **50% »protected time« for research**
- **Recognition by Berlin Chamber of Physicians**
- **3 years**

Boosting

Since 2019 Digital (J)CSP

Junior Clinician Scientist Program
- Doctorate with at least Magna cum laude
- First 3 years of specialist training
- **20% »protected time« for research**
- **2 years**

| Medical studies | Specialist training | | Specialist certification | Senior physician maturity |

| Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |

Gold Standard · **DFG** Deutsche Forschungsgemeinschaft German Research Foundation · »best practice model« · **WR** WISSENSCHAFTSRAT
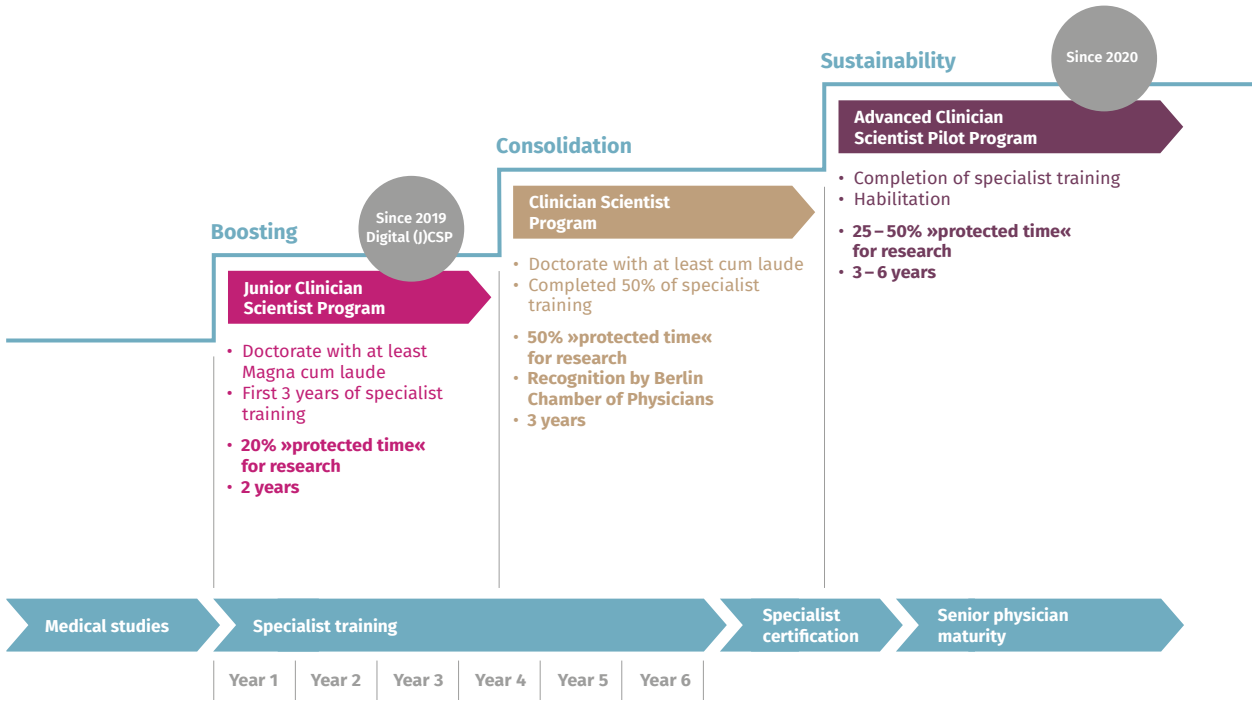
Figure 1. Structured career paths for Junior (Digital) Clinician Scientists, (Digital) Clinician Scientists and Advanced Clinician Scientists spanning different stages of career beginning from medical school.

CSP »Excellence Track«

An increasing number of program fellows have successfully applied for excellent junior research group programs (e.g. ERC Starting Grants Program, DFG Emmy Noether Program, Freigeist Fellowships or Lichtenberg Professorship of the Volkswagen Foundation or BMBF Research Group). This has led to the formation of an »Excellence Track« in 2018. Fellows of this »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. Rather, upon application, they are presented directly to the board to be enrolled. Fellows of the »Excellence Track« have the same rights and obligations as regular program participants. The only difference is that they are not funded by program funds. We currently have 4 members in the CSP »Excellence Track«.

»…the (Junior) (Digital) Clinician Scientist Program Offers a Unique Opportunity for Clinician Scientists from All Disciplines and All Career Stages to form a Diverse Community, Which Is Dedicated to Patient's Interests and Science…«

Prof. Dr. Dominik N. Müller, Deputy Director of the BIH Charité Clinician Scientist Program
Max-Delbrück-Centrum für Molekulare Medizin (MDC)

Measures for Equal Opportunities and Family Friendliness

As a general policy, we actively encourage women to apply and to provide them with the best possible support throughout the whole application process. Among other things, we offer application and presentation coaching as well as information events specifically for potential female applicants. In 2021, we have implemented a gender-segregated evaluation and selection process (using identical quality standards). Furthermore, our programs offer flexible working options enabling parental leave and part-time work within the program period through flexible budgeting. Not least, we offer on-site childcare for our monthly Jour Fixes and for all our program events.

	Percentage of Women
JCSP	45 %
CSP	36 %
JDCSP	35 %
DCSP	39 %
AdCSP	45 %

Table: Percentage of women fellows and alumni across the different funding lines, cumulatively since the start of the program.

Interdepartmental Community Building

The CSP promotes lively networking and acts as an integrative force within the BIH Charité ecosystem. Within the CSP community, interdisciplinarity is not just a phrase but is actually lived through various community-building measures: monthly Jour Fixes for (Junior) (Digital) Clinician Scientists take place, where they present their research projects to the other fellows and the program management. It is also a great opportunity for discussing new program developments and cooperations. Each year, a two-day retreat is held for all (Junior) (Digital) Clinician Scientists and their mentors and clinical or institutional directors. The overall aim of the retreat is to provide a communication platform to discuss both scientific and strategic topics relevant to Charité, BIH and beyond. In addition, a two-day Clinician Scientist Symposium on Translational Medicine is held every two years in Berlin, to which the fellows can invite internationally renowned

scientists as speakers. This gives the fellows the opportunity to discuss their project in person with leading personalities from their own field of research and to take a big step towards expanding their own scientific and professional networks.

The CSP is an important model for building a community of young scientists who are open to translational and innovative biomedical research. The BIH Charité (Junior) (Digital) Clinician Scientist Program fellows come from a wide variety of clinical and diagnostic disciplines, creating a new translational ecosystem, and fostering transdisciplinary collaboration (see Dragun/Huber 2017). The number of participants has grown impressively from eight participants in 2011 to 175 active participants in 04/2023. Currently, 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 shows a graphical representation of all program participants across disciplines.
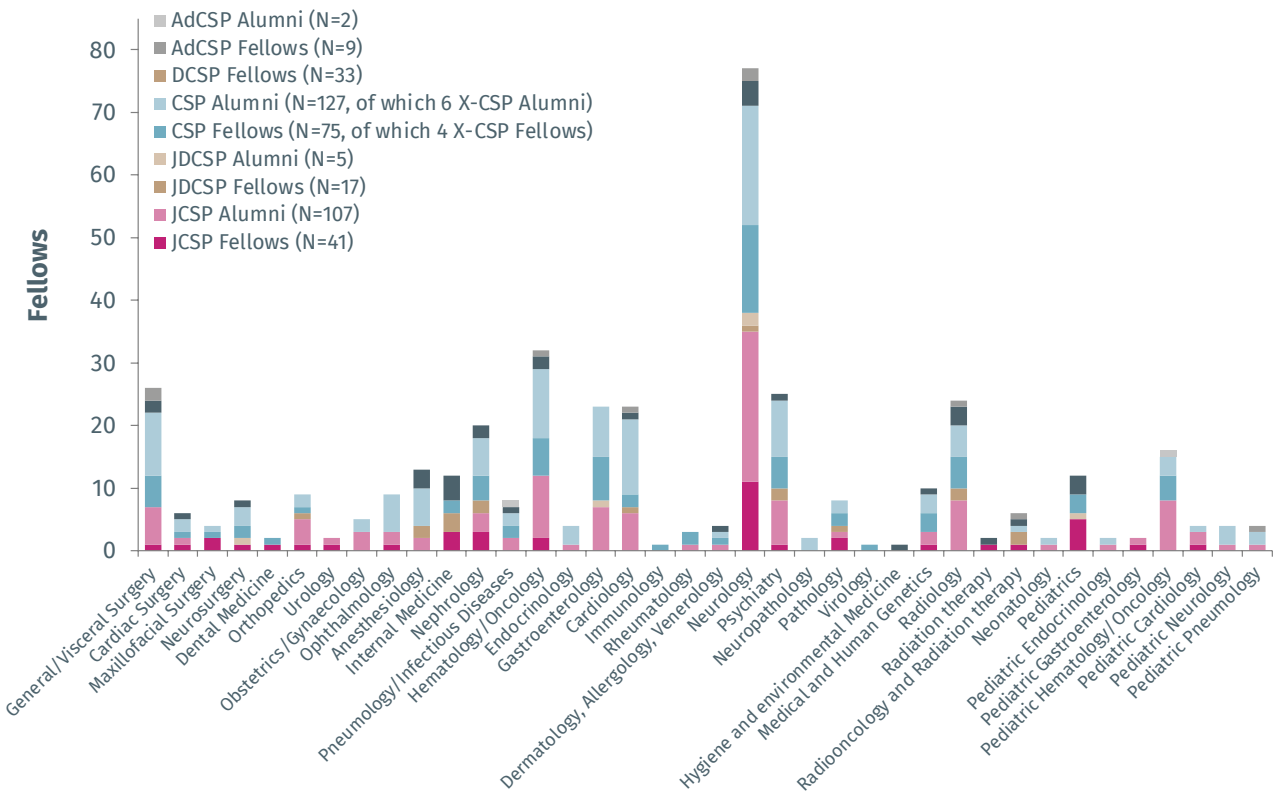

Figure 2: Broad distribution of (J)(D)CSP fellows and alumni over the clinical disciplines at Charité – Universitätsmedizin Berlin.
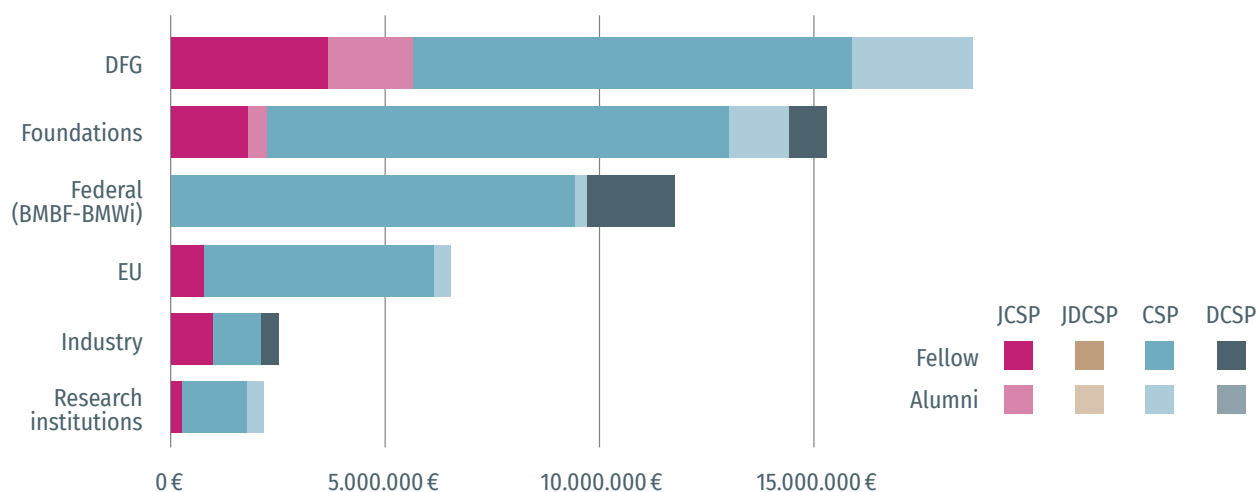
Figure 3: Third-party funding raised in € by BIH Charité (Junior) (Digital) Clinician Scientists fellows and alumni up to 04/2023

On the occasion of the tenth anniversary of the BIH Charité Clinician Scientist Program, the first systematic empirical program evaluation was published by the Deutsches Zentrum für Hochschul- und Wissenschaftsforschung (DZHW[11 | 12]). Standardized online surveys and guideline-structured interviews were used to investigate the extent to which the integration of research into residency training succeeds through the structured program and what opportunities and challenges arise in practice. During the period of June 2019 till March 2021 experiences and perspectives of overall 90 active program fellows and alumni were analyzed and compared with those of 145 scientifically active physicians at the Charité who had not received any Clinician Scientist Program funding. Major attractivity factors for the program were the »protected time« for research, manuscript writings and grant acquisitions, family-friendliness of the program and recognition of research time as part of the medical specialty training by the Berlin Chamber of Physicians. Based on the empirical results, the DZHW formulated general recommendations for the development of Clinician Scientist Programs for medical faculties in Germany.

analysis of the track records, and pre-selection meetings of the candidates by the (Digital) Clinician Scientist Board. In case of a positive vote candidates present themselves and their project during the selection colloquium followed by a board meeting for the final funding decision. Since 2018, we have implemented a semi-automated track record analysis which supports the Clinician Scientist Board during the selection process. After an initial evaluation of this system in 2020, a full-scale evaluation of the scoring weights used for the different career tracking aspects was carried out in 2022. Based on the results of a comprehensive online survey conducted among the board members in summer 2022 and the decisions of the subsequent strategy board meeting, most weightings of the system could be confirmed as accurate. Slight modifications of the weightings of the evaluation categories were applied to allow for a greater impact of excellent project reviews.

Adjustments to the Weighting of Selection Criteria for (J)(D)CSP Candidates
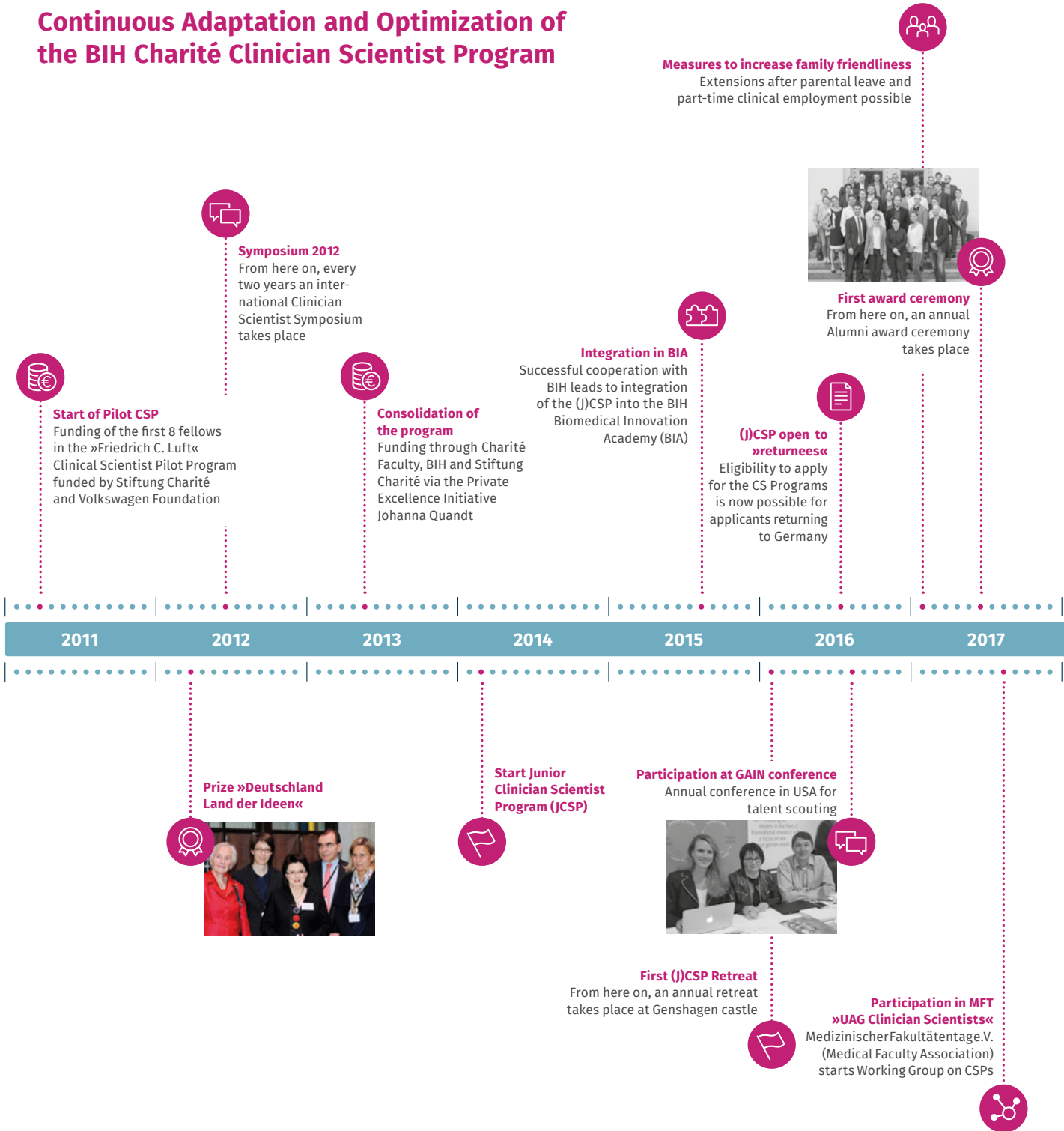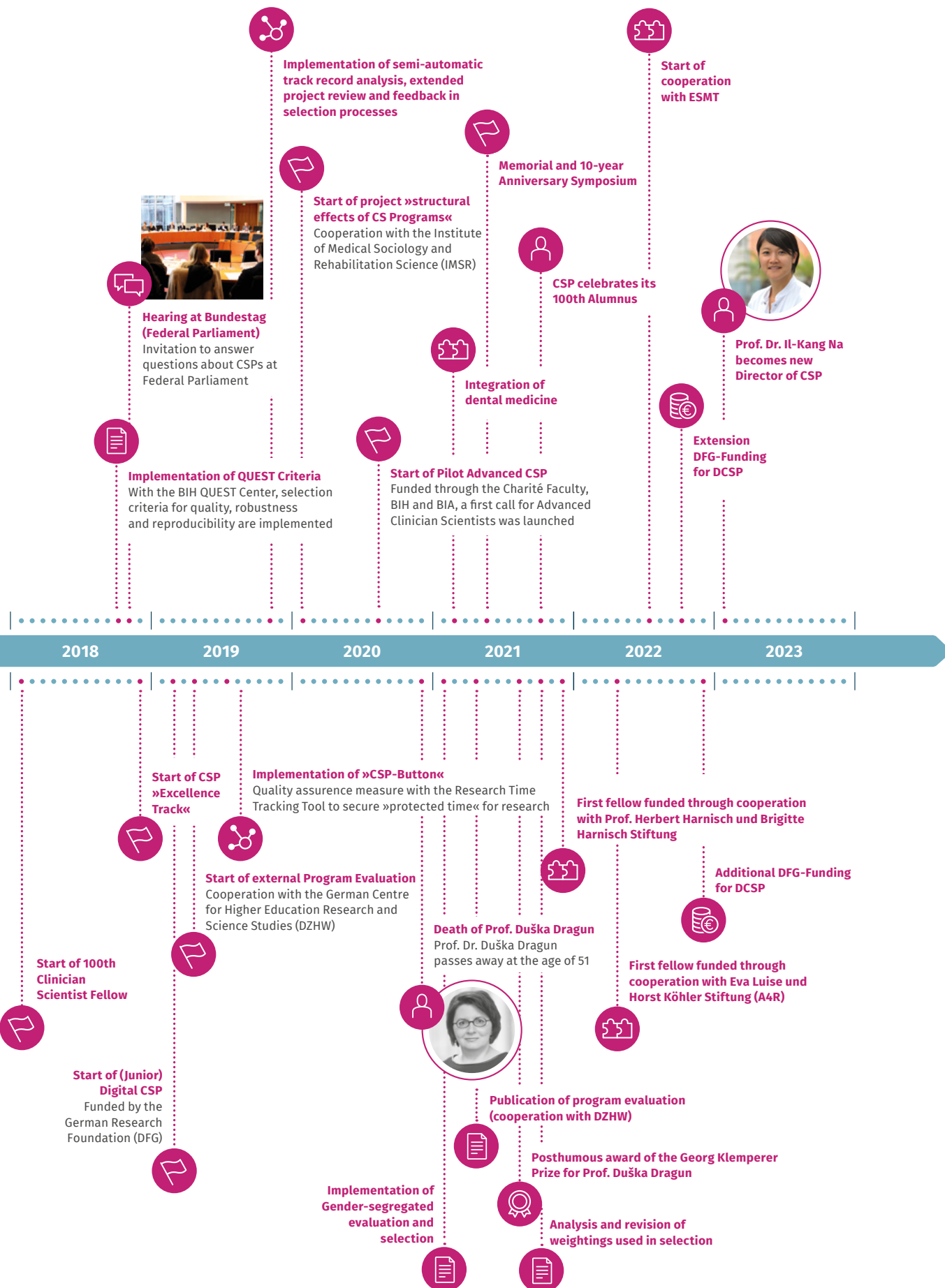
Generally, there are two selection rounds for the different Clinician Scientist funding lines per year whereby each selection round implicates a two-stage selection process. This two-stage selection process includes formalized reviews of the projects by our board members,

11. Hendriks, Barbara; Schendzielorz, Cornelia; Heger, Christophe; Reinhart, Martin (2021): Kritische Bestandsaufnahme des BIH Charité (Junior) Clinician Scientist Programms: Untersuchungen einer integrierten Forschungsund 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

12. https://www.bihealth.org/fileadmin/akademie/bilder/PE___Evaluation/BIH_Charite_CSP_Bibliometrie_Report.pdf

Continuous Adaptation and Optimization of the BIH Charité Clinician Scientist Program

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

Symposium 2012
From here on, every two years an inter-national Clinician Scientist Symposium takes place

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

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

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

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

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

| 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |

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

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

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

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

Memorial and 10-year Anniversary Symposium

Start of cooperation with ESMT

CSP celebrates its 100th Alumnus

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

Prof. Dr. Il-Kang Na becomes new Director of CSP

Integration of dental medicine

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

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

Extension DFG-Funding for DCSP

2018	2019	2020	2021	2022	2023

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

Start of CSP »Excellence Track«

First fellow funded through cooperation with Prof. Herbert Harnisch und Brigitte Harnisch Stiftung

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

Additional DFG-Funding for DCSP

Death of Prof. Duška Dragun
Prof. Dr. Duška Dragun passes away at the age of 51

Start of 100th Clinician Scientist Fellow

First fellow funded through cooperation with Eva Luise und Horst Köhler Stiftung (A4R)

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

Publication of program evaluation (cooperation with DZHW)

Posthumous award of the Georg Klemperer Prize for Prof. Duška Dragun

Implementation of Gender-segregated evaluation and selection

Analysis and revision of weightings used in selection

Clinical and academic achievements of program fellows and alumni

Our fellows and alumni (04/2023) show excellent career progression: 49 % of our alumni became medical specialists, 32.5 % completed their habilitation, and 31 % secured leading positions. Our alumni are not only successful Clinician Scientists themselves, but they also become the mentors and supervisors of a new generation of fellows, further ingraining the Clinician Scientist culture. A significant proportion of our fellows obtain professorships – some of them already during their (J)(D) CSP funding. Overall, we can currently pride ourselves on 24 professors among our fellows and alumni (14 W2 professorships and 10 W3 professorships).

Acquisition of Third Party Funding

Another impressive program outcome result is the cumulative amount of third-party funding raised by alumni and (Junior) (Digital) Clinician Scientists of 52 million Euros (see Figure 3). This roughly corresponds to a »return on investment« of two to one underlining once again the effectiveness of the program and the excellence of its fellows.

Career Tracking and the CSP Alumni Network

What began as a project to develop a reliable, unbiased, semi-automated track-record analysis system to support the selection processes of our Clinician Scientist programs has now evolved into the beginnings of a full-fledged career tracking tool that can be used in meta-research analysis. We hope to use it to better map typical career paths and the hurdles that our fellows must overcome. It will allow the analysis of correlations between the careers of young scientists at Charité and the study of correlations leading to successful careers in academic medicine. It is also possible to find out when and why young scientists most often leave academic careers and what alternative career paths they take. With this deeper understanding of the different archetypes of Clinician Scientist career paths, on the one hand, the individual funding lines can be further refined. On the other hand, it will provide us with a scientific basis for recommendations to policy makers and funding agencies for the development of innovative career support structures.

The development of the career tracking system has also prompted us to increase our efforts in the area of our alumni network, in the hopes of following previous fellows and their careers even beyond their time within our program. As you will notice in this edition of our Program Book, we have now grown so much that we are only listing the profiles of our current fellows in this book. Instead of alumni profile pages, we now provide an index with all our alumni over the different funding lines so far, and an online link to previous editions of this book, where you can find their profiles in more detail. In addition, we have increased the visibility of alumni on our website through the »fellows and alumni finder[13]«.

Furthermore, we have recently connected with the Charité alumni portal, where there is now a dedicated area for (former) Clinician Scientists.

Search for members

| Name | Fields of Research |

| Select state... ⌄ | Select program... ⌄ |

PD Dr. med. Güliz Acker

Charité – Universitätsmedizin Berlin, Department of Neurosurgery with Pediatric Neurosurgery

Email: gueliz.acker@charite.de

Fields of Research
- Moyamoya Disease
- Glioblastoma Multiforme
- Vascular Targeting
- Brain Metastases

Details ⌃

Project Title

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

13. https://www.bihealth.org/de/translation/
innovationstreiber/akademie/fellows-und-alumni

Résumé and Outlook

The BIH Charité Clinician Scientist Program offers a broad spectrum of different funding lines throughout all career phases. Together with our interdisciplinary team we continuously adapt und optimize our programs by both data-driven analyses and by being in close contact with our fellows, clinic directors and board members. Due to the remarkable size of our (J)(D)CSP community, career tracking, monitoring and alumni work become more and more important to systematically address the specific »needs« of young scientists in a continuously changing clinical and academic environment. Through these activities, we are able to apply conclusions of our empirical findings into our funding lines. They also allow us to adapt our running and innovatively developed target group-specific support measures or in the extension of our curriculum respectively – e.g. to address specific competencies in the field of sciencepreneurship through our new cooperation with the ESMT.

The rewards of our efforts and continuous program adaptations are reflected in the high attractiveness and sustained high demand of our BIH Charité Clinician Scientist Program, always having a much higher number of strongly qualified candidates compared to the number of available fellowships. It remains therefore a continuous challenge to secure and acquire additional funding for our programs, both to expand them and to ensure sustainability.

Together with the Program Directorate and our team of the BIH Biomedical Innovation Academy, we are taking on this challenge with full power. As mentioned above: We wouldn't be ourselves if we wouldn't rise to the challenge!

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Fields of Research
› Multi-echo functional magnetic
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› Resting State
› Deep brain stimulation

Individual Functional Resting State Connectivity as a Predictive Biomarker for Deep Brain Stimulation in Parkinson's Disease

Deep brain stimulation (DBS) is an established treatment option in Parkinson's Disease (PD), improving motor symptoms, quality of life and allowing to reduce dopaminergic medication. However, some patients will not reach adequate symptom relief or experience unwanted DBS induced side-effects despite accurate electrode placement. Studies investigating preoperative dopamine response to predict surgical outcome remain inconclusive. To improve the efficacy of neuromodulation for PD patients, fine-tune preoperative selection and allow reliable outcome predictions of DBS candidates, novel personalized biomarkers are needed. Current neuroimaging research, which relies largely on averaging results of many patients, cannot reflect the heterogeneity within PD patients and thus, is not able to provide meaningful outcome predictions.

A novel technology called multi-echo (ME)-fMRI has recently demonstrated the ability to significantly increase reliability and noise suppression, enabling individual mapping of Resting-state function connectivity (RSFC) in 10–15 minutes of healthy adults. Thus, it can capture individual and symptom-specific pathological network changes within a clinically realistic timeframe. As a first confirmatory step towards a clinical application of ME-fMRI, this project will test the hypothesis whether RSFC quantified by ME-fMRI is able to predict the outcome of subthalamic DBS in patients with idiopathic PD.

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› Pediatric oncology
› Differentiated thyroid cancer

Whole-Body 131I Imaging in Children with Thyroid Cancer with Undetectable Thyroglobulin. Benefit or Relict?

In Germany, pediatric patients with differentiated thyroid cancer (DTC) are treated with thyroidectomy followed by adjuvant 131I radioiodine (RAI) treatment with an activity of 25 to 50 MBq per kg body weight in carcinomas larger than 1 cm according to current guidelines. If 6 months after RAI treatment ultrasound and an undetectable tumor marker thyroglobulin (TG) under thyroid hormone replacement indicate absence of remnant persistent disease, the child undergoes diagnostic whole-body 131I imaging (DxWBS) with 5 MBq/kg. This DxWBS is accompanied by measurement of the TSH-stimulated (»true«) TG level. In a 10-year-old boy with 35 kg, DxWBS results in an estimated effective dose of 107 mSv, which is equivalent to approx. 50 years of environmental radiation exposure in Berlin. One might consider measuring the stimulated TG level to confirm absence of disease without administering 131I to perform additional DxWBS. This would obviate the inpatient stay and radiation exposure but is currently not recommended because sufficient evidence to omit the DxWBS is missing.

The aim of my project is to systematically evaluate the value of DxWBS in addition to stimulated TG levels and ultrasound of the neck for determining the presence or absence of tumor disease after RAI therapy that would require further treatment. The working hypothesis is that the diagnostic accuracy of stimulated TG to detect persistent disease that would require therapy is non-inferior to DxWBS. That would mean that DxWBS is not beneficial in children with DTC and undetectable levels of stimulated TG after initial RAI treatment. To thoroughly test this hypothesis, we aim to perform two retrospective studies and subsequently design a prospective confirmatory multicenter trial.

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› Colorectal Cancer
› Clinical trials
› Proteomics

Proteomic Signatures of Response and Resistance to Therapy in Patients with RAS Wild-Type Metastatic Colorectal Cancer from the PanaMa Trial

Systemic treatment strategies for metastatic colorectal cancer (mCRC) focus on efficacy and health related quality of life (HRQOL). Combination chemotherapy plus anti-EGFR antibody is approved for first-line therapy in RAS wild-type (WT) mCRC. However, continuous therapy until tumor progression is limited by accumulating toxicity and consecutively impaired HRQOL, underlining the need for maintenance concepts after intensive induction chemotherapy to maintain HRQOL without substantially decreasing anti-tumor efficacy. The randomized, recently published PanaMa trial investigated panitumumab and 5-FU vs 5-FU alone as maintenance therapy of RAS wild-type tumors after first-line induction treatment with six cycles FOLFOX + panitumumab and established a new treatment option for RAS WT tumors with demonstrated superiority of the combination of 5-FU and panitumumab.

However, treatments with anti-EGFR agents such as panitumumab increase selective pressure and cause secondary RAS mutations and other mechanisms of secondary resistance. The role of proteomics from peripheral blood as means of detection of response and/or resistance mechanisms remains unclear. Sequential characterization of functional proteomic states during induction, maintenance and re-induction will lead to a refined understanding of its role in this setting and help explore novel prognostic biomarkers.

Proteomic platform technologies as developed by our cooperation partner, the Ralser Lab, capture the proteome of peripheral blood in a cost efficient and unbiased fashion. Untargeted proteomic data bear a substantial potential for development of both predictive and prognostic assays: Not only does proteomics efficiently capture human biology, also, one can select individual peptides from the discovery data and translate it rapidly into clinical panel assays.

For the proposed project, >700 sequential serum samples from induction and maintenance treatment of patients from the PanaMa trial will be analyzed using a novel platform to detect proteomic peripheral blood states in mCRC. Proteomics will be conducted using a combined application of new sample preparation technologies, a new mass spectrometric acquisition technique (Scanning SWATH), and specific Deep Neural network based software (DIA-NN). Findings will be correlated with available survival endpoints progression-free survival (PFS, primary endpoint of PanaMa) and overall survival (OS), safety endpoints, as well as other clinical endpoints.

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› Deep brain stimulation
› Parkinson's disease
› Neurophysiology

Multimodal Biomarker Integration to Improve Adaptive Deep Brain Stimulation for Parkinson's Disease

Deep brain stimulation (DBS) is an established treatment option for advanced Parkinson's disease (PD). DBS acts by injecting weak electrical pulses to subcortical target structures, leading to both local and network-wide changes in neuronal functioning. Current DBS technology operates continuously, applying electrical stimulation with fixed parameters over time. While proven effective for alleviating motor symptoms in PD, continuous DBS is unresponsive to fluctuations in the patient's clinical state, potentially leading to side-effects mediated by over- or understimulation. To address this limitation, adaptive DBS (aDBS) systems have been designed, which allow for real-time adjustments to stimulation parameters based on biomarkers informative for the patient's symptom severity. One of these biomarkers is pathologically elevated oscillatory power in the beta frequency range (13-30 Hz) extracted from subthalamic local field potentials, as beta power fluctuations are associated with the current clinical state. However, beta power is also modulated by the patient's behavior. Thus, aDBS solely based on subthalamic beta power may fail to maintain its responsiveness when patients change their behavioral state. In this project, we therefore aim to integrate multiple biomarkers to leverage information from different domains in order to aid the interpretation of beta power fluctuations. We hypothesize that this will allow for more efficacious adaptive stimulation under varying behavioral contexts. In a first working step, an experimental aDBS platform that has been developed by our group will be augmented. The aDBS system will be adapted to use data from a motion tracking system to track the patient's behavioral state. This information will be used to continuously adjust the beta power threshold that triggers stimulation. In a second working step, the updated aDBS algorithm will be tested against the current algorithm with a fixed threshold in a randomized, single-blinded, cross-over study. The results of the project will provide a trajectory for further improvement of commercially available aDBS systems and will provide a means for further investigations on multi-biomarker integration for adaptive stimulation.

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Fields of Research
› Multiple Sclerosis
› Translational research
› Immune profiling

In Depth Analysis of Lymphocyte Subsets in Multiple Sclerosis

The pathogenesis of early Multiple Sclerosis (MS) is still incompletely understood. Current treatments are broadly immunomodulatory or even immunosuppressive, which impedes also beneficial immune functions. A deeper understanding of pathogenic immune cell subsets is needed to design personalized treatment approaches instead of broad cell ablation. To define pathogenic subset patterns, we want to verify a previously defined marker subset (EAE model) in the human disease. In this study, we aim to: 1.1) recruit MS and control patients for the multiplexed FACS analysis of CSF and blood cellularity embedded in routine clinical diagnostics; 1.2) compare results between MS/controls and to validate pathophysiologic immune cell characteristics as identified in our previous work in the animal model; 2) correlate experimental data to clinical diagnostics (MRI and CSF) 3) include the MS patients to an established large prospective cohort for longitudinal observation and follow ups (BERLImmun cohort by PD Dr. med. Tanja Schmitz-Hübsch). Our approach is cutting-edge as it uses a state-of-the-art spectral FACS method in blood and CSF next to routine diagnostics in newly diagnosed, treatment naïve MS patients. Our selected subset of markers may help to identify critical cell subsets involved in human MS and to discriminate at highest risk for disability progression. This may aid early effective and personalized treatment.

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Fields of Research
› Movement Disorders
› Genetic Parkinson's Disease
› Deep Brain Stimulation

Electrophysiological Signatures of Genetic Versus Sporadic Parkinson's Disease: Insights from Deep Brain Recordings

Research into the genetic basis of neurodegenerative diseases is expanding as the potential for preventative or curative measures to combat these widespread and debilitating progressive diseases is recognised. In Parkinson's disease (PD), the past three decades have produced more than twenty genetic variants associated with a higher risk for developing the disease, often at a younger age and sometimes with characteristic disease course. In deep brain stimulation (DBS), an increasingly common treatment for medically resistant PD, electrodes are implanted into the basal ganglia, most often the subthalamic nucleus (STN). By applying electrical current, DBS is effective at modulating the pathological network activity and improving symptoms. Conversely, it allows unprecedented insights into subcortical brain activity by measuring so-called local field potentials around the electrodes. Pathologically synchronised activity in the beta frequency range (13-30 Hz) measured by these electrodes is known to correlate with symptom load. To this day, it remains unclear how exactly this reflects the pathology of PD, at which stage in disease progression it appears and where it falls on the spectrum of hallmark to epiphenomenon of disease pathology.

Research into genetic PD, including whether beta activity is present in these types has important consequences for both pathophysiological understanding and for treatment options regarding DBS and, more specifically, adaptive DBS. Still in development, current strategy often relies on STN beta-activity as the physiomarker for triggering stimulation. For patients with genetic PD, who are often younger at disease onset and stand to profit from the advantages, namely reduction of side effects and sparing of battery life, it is therefore crucial to discover whether this marker is reliable. With the time allocated to me by the Junior Clinician Scientist program, I aim to gather both retrospective and prospective deep brain recordings from genetic and sporadic PD patients undergoing STN-DBS in order to compare the electrophysiological profiles and most notably the presence or absence of characteristically enhanced beta activity. This research will facilitate pathophysiological understanding of this physiomarker and be an important guide to patients with genetic Parkinson's disease considering treatment with deep brain stimulation.

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› 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 peri-natally 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 hypothesize 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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› Thymus and T cell immunology
› Developmental biology
› Gene editing

Differentiation of IPSCs to Thymic Epithelial Progenitor Cells as a Model for Genetic Thymic Aplasia

Background

Thymic aplasia with severe combined immunodeficiency is a rare and fatal disease we screen for, but cannot treat in every fourth patient. Thymic epithelial cells (TECs) are essential for hematopoietic progenitor proliferation and differentiation. Thus, genetic mutations affecting TEC development result in impaired T cell development. However, disease mechanisms in humans remain largely unresolved.

Objectives

To describe mechanisms of intrinsic thymic defects, I perform differentiation of pluripotent stem cell lines (iPSCs) from patients carrying TEC-intrinsic gene defects, genetically modified lines, and healthy controls to thymic epithelial progenitor cells (TEPs). In the long term, this bears the potential for personalized cell-based therapies.

Methods

I generated iPSCs from healthy controls and an athymic patient carrying a newly discovered mutation in the transcription factor HOXA3. I apply base editing to generate control lines and to study associated transcription factors. During differentiation of iPSCs to TEPs I collect cells at four different time points: iPSCs, definitive endoderm, ventral pharyngeal endoderm and TEPs. For characterization of these, immunofluorescence, flow cytometry, ATACseq and gene expression analysis, using qPCR and scRNAseq, are underway. Furthermore, I use an artificial thymic organoid system with patient hematopoietic progenitors for functional validation of the T cell intrinsic development.

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› Tumors of the ovary
› Mucinous tumors
› DNA methylation

Using DNA Methylation Profiling for Differential Diagnosis and for Determining the Origin of Ovarian Mucinous Carcinomas

Primary mucinous ovarian carcinoma (PMOC) is a rare subtype of ovarian cancer with an unfavorable outcome. It is estimated that POMC account for 3 to 4 % of all primary ovarian carcinomas. PMOCs, if not diagnosed at an early stage have an unfavorable response to chemo- and radiotherapy and most patients with extra-ovarian involvement die of the disease. The ovary is also the site of frequent metastases of other mucinous tumors. These tumors are termed secondary mucinous ovarian carcinoma (SMOC) and account for approximately 10 % of the malignant neoplasms of the ovary. SMOCs originate from diverse extra-ovarian sites such as the stomach, the colon, the appendix, the pancreas, and the uterus. The histopathological differentiation of PMOC from SMOC is difficult and represents an unmet medical need. Current clinical practice differential diagnosis is rudimentary and is based on clinical features, histopathology and immunohistochemistry. Hence, in order to distinguish PMOC from SMOC in a reliable and rapid way, new diagnostic tools need to be developed which improve current methods. Additionally, it is important to mention that often SMOCs are identified without knowing the location of the primary.

DNA methylation patterns are highly tissue specific, hence are an ideal method for performing differential diagnosis of POMC versus SMOC. Hence, my aim is to use DNA methylation profiling to develop machine learning algorithms for differential diagnosis of PMOC from SMOC, and that are able to indicate the tissue of origin of SMOCs.

This can lead to the development of a new technology that addresses an unmet medical need – the timely and precise diagnosis of mucinous carcinoma of the ovary. It is important to emphasize that the current diagnosis for these tumors is slow, delaying the therapy and unprecise. According to most international guidelines, the first line of therapy should be based on the tissue of origin, hence a precise differential diagnosis is essential.

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Fields of Research
› Cancer genomics
› Extrachromosomal DNA (ecDNA)
  amplicons
› Epigenetics

Essential Regulatory Elements of High-Level Amplicons

Genomic amplification is the most common genetic gain-of-function variant in cancer. How the extra oncogene copies are active in a different regulatory context than the original remains unclear. We hypothesize that they exploit either tissue-specific or oncogene-specific enhancers and transcription factors. Discovering the factors that drive oncogenic transcription has the potential to reveal cancer-specific dependencies. Indeed, transcription factors (TFs) binding enhancers on high-level MYCN amplicons in neuroblastoma are part of its core regulatory circuit and represent lineage-specific growth dependencies. However, which TFs bind to the enhancers on amplicons of oncogenes in other tumor types remains unknown. We will therefore test the following specific hypotheses in breast and lung cancer samples:

(I) Enhancers on high-level amplicons are cancer-type or oncogene specific. To test this hypothesis, we will compare the enhancers that correlate with expression between amplicons of the same oncogene in different cancer types and between different oncogenes in the same cancer type.

(II) The enhancers contain (tissue or oncogene) specific TF binding motifs to allow oncogene expression. We will scan for known TF binding motifs in the enhancer peaks and test for enrichment by cancer type and oncogene.

(III) These TFs and their binding to amplicons are necessary for tumor growth. We will test the TFs for lineage-specific dependency in existing CRISPR-ko data, providing hypotheses for subsequent validation. We will integrate the largest publicly available datasets of WGS, RNAseq, ATAC/ChIPseq, and standardized genome-scale CRISPR screens. Our findings will be a valuable resource to understand the regulation of oncogenes in breast and lung cancer and our workflows can serve as templates to extend this analysis to other cancer types or new datasets. Our approach to focus on the regulatory units of the high-level amplicons of oncogenes instead of comparing genome-scale epigenetic profiles has only become possible with the recent availability of large WGS cohorts. Public data from genome-scale CRISPR screens across cell lines from multiple lineages now also allows us to see if the TFs we identify based on the tumor samples show growth phenotypes when knocked out in cell lines. Using this integrated approach, we aim to identify cancer-specific vulnerabilities that arise from the regulatory machinery necessary to drive expression of oncogenes.

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› Autoimmune Encephalitis

Characterization of Patient-Derived IgLON5 Monoclonal Antibody Pathogenicity in Anti-IgLON5 Disease

Anti-IgLON5 disease is a progressive neurological disorder presenting with multifaceted sleep and movement disorders, cognitive impairment, and bulbar dysfunction that can progress to respiratory failure and death. What is unique about anti-IgLON5 disease is that it shares features of both neuronal autoimmunity and neurodegeneration. While the presence of antibodies against the surface antigen IgLON5 suggests neuroinflammation, the detection of hyperphosphorylated tau and neuronal loss, proposes a neurodegenerative tauopathy. Whether IgLON5 antibodies primarily induce neurodegeneration or rather present a sequalae of the neurodegenerative processes needs to be solved. Previous studies with polyclonal serum and cerebrospinal fluid (CSF) from patients suggest a down-regulation of IgLON5 protein and disruption of the neurofilament architecture in cultured neurons. However, it is unclear whether the observed structural and functional effects exclusively relate to IgLON5 antibodies or are confounded by the presence of other clinically relevant autoantibodies in the polyclonal patient sample. Studies are necessary for detailed insights into the antibody repertoire of patients with anti-IgLON5 disease and the potential disease-driving pathogenic effects of IgLON5 antibodies. Using established methods in the recombinant generation of disease-specific monoclonal antibodies (mAbs) from patients' CSF or serum, this project aims to characterize the pathogenic mechanisms underlying anti-IgLON5 disease. These patient-derived mAbs will allow the detailed and systematic characterization of the functional role of IgLON5 antibodies, thereby specifically addressing the following questions: 1. From where do pathogenic IgLON5 antibodies originate? 2. Are CSF-derived IgLON5 antibodies pathogenic? 3. Are IgLON5 mAbs the primary drivers of neurodegeneration in anti-IgLON5 disease? Evidence of antibody pathogenicity in anti-IgLON5 disease will provide the rationale for immunomodulatory measures and enable the development of highly specific antibody-selective immunotherapies, potentially improving patient outcome as most patients remain refractory to the current therapeutic measures that comprise unspecific immunotherapies. Further, this study will foster the understanding of neuroinflammation at the pivot of neurodegeneration with implications extending to post-stroke dementia or cognitive impairment in patients with cancer-associated autoantibodies.

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› Stereotactic Radiosurgery

The Role of Radiotherapy in the Treatment of Atypical Meningiomas – A Methylome- and Genome-Based Analysis

Meningiomas are the most common intracranial tumors of the central nervous system (CNS). With the new WHO classification of tumors of the CNS in 2021, new molecular markers were introduced to further specify and distinguish specific tumor subtypes. The diagnosis of meningiomas, however, is still primarily based on histopathological features. Recently, DNA-methylation-based classifiers have shown to accurately predict and stratify CNS tumors to improve the standardization of tumor diagnostics. The traditional approach of meningioma diagnosis using only light microscopy and immunohistochemistry is prone to interobserver biases and limited regarding risk stratification and personalized treatment decision-making. With approximately 80% of meningiomas showing benign behavior (WHO grade 1) and a favorable outcome after surgical resection, the remaining 20% tend to recur due to their aggressive histopathological characteristics (WHO grade 2 and 3). In the case of atypical meningiomas (WHO grade 2), it is still unknown to which degree adjuvant radiotherapy after surgical resection is required. This knowledge gap is highlighted by various contradictory findings in recent studies and

reviews, which were partly conducted at our institution. A recent study established and validated an integrated molecular-morphologic meningioma classification utilizing DNA-methylation analysis. The classification outperformed the WHO classification concerning clinical outcome prediction. These findings suggest that previous studies of atypical meningiomas may have investigated rather heterogeneous cohorts, including other meningioma subtypes, leading to undetected biases. Ultimately, the risk of bias can only be avoided by implementing the integrated molecular-morphologic classifier to ensure accurate tumor subtype identification. The role of radiotherapy for atypical meningiomas can be specifically and correctly assessed by doing so. Identifying potential subsets of molecularly defined meningiomas that profit from radiotherapy is the primary objective of my project and an important goal to avoid over- and undertreatment.

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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 longterm 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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Fields of Research
› resorbable biomaterials
› magnesium implants
› osteosynthesis

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Magnesium Implants as Therapeutic Agents

Magnesium implants are a promising alternative to established titanium implants for both trauma and reconstructive surgery, due to their biocompatibility and biomechanical properties. The primary purpose of osteosynthesis is the ability to offer sufficient stability to the bone during bone healing. Moreover in the process of bone healing, the successful interplay of osteogenesis, angiogenesis and the immune system also plays a crucial role. The main advantage of magnesium is its resorbability, making a second operation for implant removal redundant. With an elastic modulus closer to the cortical bone than titanium, magnesium offers more favourable biomechanical properties during bone healing. In postoperative imaging, fewer artefacts are produced by magnesium, leading to a facilitated evaluation. Throughout implant resorption, magnesium ions develop, leading to an osteostimulative effect, enhancing angiogenesis and interacting with the immune system.

During magnesium degradation, hydrogen gas becomes vacant with the potential to disturb bone healing if the resorption capacity of the surrounding tissue is exhausted. To control the degradation speed and by that, hydrogen gas formation, coating and surface modification are used to match the implant´s degradation speed with the pace of bone healing. The Mg-Y-RE-Zr-based alloy WE43 which is already approved for application as an implant material in humans, offers a suitable degradation rate during bone healing.

With the current project, we evaluate the use of magnesium-based implants (WE43) in the compromised bone healing situation of pseudarthrosis with a special interest in osteoimmunological properties to support bone healing. In the long term, these findings can be used to shift the environment towards a pro-regenerative milieu, even in challenging situations.

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Fields of Research
› Organoids
› Tumor models
› Prostate cancer

Establishment of Patient-Specific Prostate Cancer Organoids as a Translational Tumor Model

Prostate cancer is the most common type of cancer in men worldwide and exhibits highly variable disease progression among individual patients. While patients with low-risk tumors typically experience gradual progression over several years, those with high-risk tumors often experience rapid progression and a high proportion of cancer-related deaths. The underlying cause of these differences is the genetic tumor profile, which is highly variable among individuals with prostate cancer. In recent years, targeted therapies such as PARP inhibitors and AKT inhibitors have been identified through large-scale sequencing studies, offering promise for more effective treatment. To translate these findings into clinically applicable cancer therapies, it is crucial to test them in preclinical tumor models. One promising new cancer model is the tumor organoid, a patient-derived 3D model that replicates the genetic and cellular properties of the tumor. However, no established protocols exist for generating organoid models in prostate carcinoma. The goal of this project is threefold. First, we aim to establish patient-derived prostate cancer organoids.

Second, we will characterize these organoids at the cellular and genomic level using cell sorting and sequencing techniques. Finally, we will create an organoid biobank containing patient-derived prostate cancer organoids for further research into tumor development and drug testing. This biobank will serve as a valuable resource for advancing our understanding of prostate cancer and developing more effective treatment strategies.

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Fields of Research
› Ex vivo machine perfusion
› Liver transplantation
› Gene modification

Normothermic Extracorporeal Gen Modification of the Rat Liver

Liver transplantation still presents the only curative treatment for end-stage liver disease, but viable donor organs are very limited. Normothermic ex vivo liver perfusion (NEVLP) has been developed as an alternative to static cold storage. NEVLP aims at maintaining the liver metabolism by perfusing the graft with oxygenated medium at 37°C and reducing ischemia time. Gene modification during NEVLP may be a possibility to tackle organ failure through immunogenic injury but may also allow for various novel therapies in liver transplantation medicine. Aim of the proposed project is to develop a method to influence the gene expression of liver grafts via transfection with coding RNA sequences during small animal NEVLP. Three different vectors are evaluated for transfection of ex vivo perfused rat livers with a reporter mRNA as well as a shRNA sequence against the CIITA gene expression for the downregulation of the major histocompatibility antigens in rats. We hypothesis that by masking the donor organ against detection by the recipient immune system after transplantation, the need for immunosuppressive therapy after transplantation is reduced.

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› Advance directives
› Medical ethics

»Palliative Care« for Treatment-Resistant Depression: a Mixed-Methods Study on the Perspectives of Patients, Their Family Members, and Healthcare Providers

Historically, palliative care has been directed towards individuals with life-threatening somatic illnesses like cancer. In contrast, despite the frequently persistent and potentially life-threatening character of psychiatric disorders, an explicit palliative care approach does not yet exist in the field of psychiatry. In recent times, there have been suggestions to explore such an approach for patients diagnosed with severe and persistent mental illness. However, a palliative care approach in psychiatry has sparked debates. While some believe that integrating a palliative strategy into the realm of psychiatry holds promise for enhancing the quality of care for individuals coping with severe and persistent mental illness by focusing on alleviating the suffering, others fear that such an approach is faced with challenges, including difficulties with decision-making capacity and prognostication in severe and persistent mental illness. To date, there has been limited understanding of the perspectives held by patients, family members, and healthcare providers regarding a palliative care approach in psychiatry, particularly for severe and persistent depressive disorder. This research project utilizes both qualitative and quantitative methods to analyse attitudes towards a palliative care approach in psychiatry.

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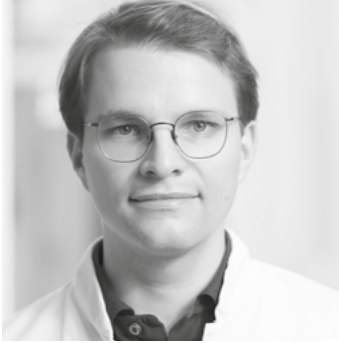
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› Neuromodulation
› Deep brain stimulation
› Brain Connectivity

Multifocal Transcranial Direct Current Stimulation in Patients with Parkinson's Disease

Deep brain stimulation (DBS) is an established and effective invasive treatment option for patients with Parkinson's disease that modulates distributed brain networks. Using electrode localization techniques and functional connectomes, a brain network that leads to symptom improvement in Parkinson's disease patients upon DBS has been identified. In parallel, the concept of multifocal transcranial direct current stimulation (tDCS) as a non-invasive neuromodulation method has been established which can be used to modulate distributed networks on a cortical level. Hence, this could allow modulating the same network that was identified by invasive neuromodulation in a non-invasive fashion. We aim to test whether non-invasive network modulation of the identified network would lead to symptom improvement in Parkinson's disease. In a prospective, cross-over trial, patients undergo both multifocal tDCS and sham stimulation. Standardized motor scores (UPDRS-III) will be assessed before and after stimulation. Significant improvement of motor function in patients with Parkinson's disease could provide proof of principle for successful non-invasive neuromodulation of a previously identified network, with potential applications for further neuropsychiatric disorders.

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› kidney transplantation
› transplant immunology
› biomarker

Next Generation Urine Diagnostics and Monitoring – Urine FACS in Urinary Tract Infection

Kidney transplantation is proven to provide the best therapeutic option for end stage renal disease. Urinary tract infections (UTI) remain a major challenge in kidney transplant patients due to immunosuppression and deviant anatomy. With an incidence up to 98 %, UTI compose a high disease burden to this specific patient group, accompanied by the constantly present risk of transplant deterioration, failure, and higher rejection probability. In previous projects, we were able to establish urine flow cytometry to analyze urine sediments stained by fluorophore-conjugated monoclonal antibodies. Applying urine flow cytometry, we are capable of investigating urinary immune cell populations and kidney cells (proximal tubular epithelial cells, distal tubular epithelial cells, and podocytes) and, thereby, determining urinary cell signatures for specific disorders. The goal of this interdisciplinary project with DRFZ and other partners is (i) to investigate urine cell signature in UTI and (ii) to establish urine bacteria flow cytometry to determine triggering bacterial populations. One key element is to detect urinary immune cell population shifting, indicating occurrence of UTI before patients develop symptoms and before transplant injury develops. With this approach I intend to redefine the diagnostic criteria of UTI, as they are currently defined by appearance of symptoms, and at this time transplant injury is often already present. One of many significant advantages of flow cytometry is the short time frame in which a diagnosis is made. Determination of bacteria populations causing present UTI in a fast manner entails the opportunity to start targeted antibiotic treatment as soon as possible. In comparison, waiting up for microbiological results of urine cultures often takes days in which patients are treated empirically. This project is realized by immune signature and bacteria analysis of urine samples of kidney transplant patients in a longitudinal setting. Patients will separate over the time course into developing UTI (event population) or absence of UTI (control group). With my findings I hope to contribute to enhancing UTI diagnostics, to prevent kidney transplant damage by UTI and to provide a new diagnostic tool to increase kidney transplant survival.

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Fields of Research
› 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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› Oral cancer
› liquid biopsy
› biomarker

Monitoring of Circulating Tumor DNA in Oral Squamous Cell Carcinoma for Detection of Minimal Residual Disease and Recurrence

High risk of recurrence presents one of the challenges in the management of oral squamous cell carcinoma (OSCC). Even patients diagnosed with early stages of OSCC have a significant risk of locoregional relapse, thus indicating occult disease in a subset of patients. Blood-based biomarkers may serve as an additional diagnostic tool in the identification of minimal residual disease (MRD) following tumor resection, as well as in the early detection of recurrence. Promising results from recent studies on the use of blood-based biomarkers in the monitoring of cancer patients have encouraged this study, which aims to investigate the value of liquid biopsy sampling in OSCC.

As part of the cooperation between the Department of Oral and Maxillofacial Surgery and the Department of Radiation Oncology and Radiotherapy, we have successfully established the biobanking of plasma and tumor tissue samples of OSCC patients. The first part of this project explores the use of cell-free circulating tumor DNA (ctDNA) analysis in the monitoring of disease by examining mutations in the promoter region of the telomerase reverse transcriptase (pTERT) gene, which are recurrent somatic mutations associated with an elevated risk of locoregional recurrence in OSCC. Here, pTERT mutation status will be analyzed in sequential ctDNA samples using digital droplet PCR (ddPCR). Results from ctDNA analyses will be correlated with pathohistological results and clinical data on recurrence-free survival and overall survival. The second part of the project aims to establish a patient-specific assays for ctDNA analysis and to demonstrate its clinical feasibility. Briefly, whole exome sequencing (WES) conducted on fresh-frozen tumor tissue (FFPE) samples collected at the time of staging or tumor surgery will be performed. Based on the identified single nucleotide variants (SNVs), individualized next generation sequencing (NGS) assays will be designed for each patient. This patient-specific assay will then be applied for sequential ctDNA analysis.

The overall goal is the clinical implementation of sequential monitoring using ctDNA-based liquid biopsy as a reliable and minimally-invasive diagnostic tool in the detection of MRD and the early detection of locoregional recurrence.

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› Cardiovascular Research
› Myocardial Infarction
› Immunology

Identification of a Diagnostic Biomarker for MINOCA in a Porcine Animal Model

Compared to classic obstructive myocardial infarction (cMI), MINOCA is characterized by symptoms consistent with acute coronary syndrome but without demonstrable coronary obstruction. Thus, its diagnosis remains challenging and often hinges on cardiac MRI that is usually performed only days/weeks after the index event leading to delayed diagnosis and therapy initiation. Cardiac micro embolization (CME) has been characterized as a major pathology underlying MINOCA. However, mechanisms of CME remain poorly understood resulting in no available rapid diagnostic tools while specific therapy approaches are missing. Based on the different pathophysiology of cMI and MINOCA, we hypothesize distinct local and systemic molecular patterns, that could be utilized for diagnostic and therapeutic purposes. In this project, we therefore aim to characterize and compare the different local and systemic molecular patterns underlying MINOCA and cMI by performing a broad molecular screening and histology analysis in translational porcine models. Subsequently, we aim to identify discriminatory biomarkers, for early diagnosis of MINOCA and reveal disease driver pathways for therapeutic purposes.

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› Obesity
› Lipidomics

Characterization of Hepatic Immune Cell Infiltrate in Pediatric Patients with Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic pediatric liver disease and is strongly associated with obesity. Patients with NAFLD may present either with benign simple steatosis, which is characterized by lipid accumulation in hepatocytes or with non-alcoholic steatohepatitis (NASH) that is characterized by additional inflammation, which eventually leads to liver fibrosis. Liver fibrosis may then progress to cirrhosis and end-stage liver disease, requiring liver transplantation. While NAFLD is considered a multifactorial disease favored by an unhealthy lifestyle and genetic factors, the pathogenesis is not fully understood so far. Especially the underlying mechanisms that drive the progress from simple steatosis to NASH remain largely unknown. The gold standard for diagnosing NASH is a liver biopsy. Numerous studies showed significant histopathological differences between adult and pediatric NASH in terms of extent and localization of steatosis as well as fibrosis.

The hepatic immune microenvironment including alterations of distinctive patterns of immune cell composition may play a key role in that. However, a comprehensive characterization of the hepatic immune microenvironment including number, size, shape, spatial distribution of involved cell types and associated alterations of parenchymal, inflammatory and fibrotic parameters has not yet been compiled. To resolve this issue, we plan to perform multiplex fluorescence immunostaining (>12 antibodies) of a single formalin-fixed paraffin-embedded tissue section in n=40 pediatric patients with biopsy proven NAFLD. This method combined with machine-learning based digital image analysis at the whole slide scale, will provide new insights into tissue organization and immune-parenchymal cell-to-cell interactions, which will help to further resolve tissue pathophysiology of NASH patients. The aim of this study is to decipher the composition of hepatic immune cell microenvironment in unprecedented detail and quality in an already existing and well-characterized cohort of pediatric patients with biopsy proven NAFLD. Pediatric NASH data will then be compared to findings in an adult NASH cohort. We further want to correlate potential tissue alterations with clinical parameters. The detailed immune phenotyping will only help to better assess and predict the clinical outcome of these patients but will also help to identify new druggable targets for specific pharmacological therapies.

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› Bone Metabolism
› Joint Infection
› Osteitis

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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› Neural/ Endocrine Mediation of Bone
   Regeneration
› Osteology
› Experimental Traumatology

Neuro-Osteogenic Interaction after Neurotrauma in Polytrauma – Systemic and Local Effects Guiding Regeneration?

Trauma is one of the leading causes of death and disability worldwide, especially in younger people. Among polytraumatized patients, traumatic brain injury (TBI) and traumatic spinal cord injury (SCI) are associated with a drastic rise in complications and mortality, and even if survived frequently cause long-term disability. The molecular mechanisms of the whole-body pathophysiology in the acute posttraumatic phase are not well understood. Consequently, targeted therapies to modulate posttraumatic systemic disruptions of homeostasis and prevent complications such as sepsis, cardiovascular dysregulations, multi-organ failure, reduce mortality and optimize the overall outcome are lacking. Furthermore, the molecular base of accompanying skeletal phenomena, such as heterotopic ossifications and enhanced fracture healing in the context of TBI and TSCI on the one hand and reduced overall bone quality of intact bone after neurotrauma on the other, stay elusive. With a murine polytrauma model combining TBI, SCI, femoral fracture and their combinations in an intensive care-setting we aim in cooperation with colleages from the departments of neurosurgery, anesthesiology and the BCRT/JWI to explore their pathophysiological interactions in the acute phase post trauma using multimodal, multi-scale analysis towards mechanistical studies of the systemic and osseous phenomena in polytrauma.

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› Rare epigentic/genetic diseases
› Biased Signaling (GPCRs)

Monogenic Obesity – Phenotyping of MC4R Deficient Patients and Evaluation of MC4R Related Biased Signalling

The worldwide increasing prevalence of severe obesity presents a major challenge for health care systems in industrial as well as low- and middle-income countries. The hypothalamic leptin-melanocortin signaling pathway is playing a pivotal role for the regulation of satiety and body weight. Mutations in one of the related genes are leading to impaired pathway function, severe hyperphagia and weight gain of the affected patients. Our group performed an investigator-initiated phase II proof of concept trial (EudraCT No. 2014-002392-28) and evaluated the MC4R agonist Setmelanotide (RM-493) as a new pharmacological treatment option for patients with LEPR or POMC gene mutations. Based on these results, a phase 3 pivotal trial has been performed and setmelanotide has been recently approved by the U.S. Food & Drug Administration as the first drug for genetic obesity. The following in vitro analyses of ligand induced MC4R signaling revealed that apart from the activation of intracellular cAMP concentrations via Gs activation, setmelanotide induces biased signaling and activates additionally Gq signaling. Furthermore, some MC4R mutations are leading to an impaired Gq signaling, which could be rescued by stimulation with setmelanotide. Based on

these results, we enrolled MC4R deficient patients, with in vitro evidence for altered Gq signaling and potential signaling restoration by setmelanotide, into our investigator-initiated study. Here, treatment led to a significant reduction of hyperphagia and weight loss. So far, all identified MC4R genetic variants have only been characterized regarding Gs signaling to evaluate functional relevance for the patient. In contrast, our results significantly support the hypothesis that the role of MC4R related biased signaling has been underestimated in the past and that it plays a pivotal role for central body weight regulation.

This project aims to establish the first worldwide cohort of patients with in vitro characterized heterozygous MC4R related biased signaling and the corresponding clinical phenotype. By translating these data sets, this project will reveal new insights about the role of biased signaling for body weight regulation. This could lead to new a fundamental understanding of functional relevant MC4R mutations and an improvement of risk stratification as well as identification of potential personalized treatment options for genetic disease of obese patients.

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› Ophthalmology
› Vascular Biology
› Endocrinology

Central Serous Chorioretinopathy (CSCR): Longitudinal Integration of Clinical and Systemic Biomarkers (BIOCHOR)

This project entails a precise classification of the choroidal vascular disease chorioretinopathia centralis Serosa based on clinical and systemic features in a longitudinal design. This disease mainly affects young people and is without recommended therapy according to current guidelines. My hypothesis is that the disease is not a singular entity, but rather a spectrum of diseases with a spectrum of diseases that differ greatly in etiology, clinical course and, most importantly, response to therapy. and, above all, response to therapy. A retrospective screening of data from our ophthalmic clinic ophthalmic clinic suggests this. In a single-cell RNA sequencing analysis performed by me from human cells of the choroid and the retinal pigment epithelium, I found evidence that steroid hormone receptors (especially for androgens) (especially for androgens) may play a crucial role in the pathogenesis of the disease. Accordingly, we collect blood from all patients at each presentation for hormone analysis and other tests. blood, which are then cryopreserved in a biobank. In the end we will highlight differences in hormone levels of selected patient groups. In follow-up projects, the established biobank will be used for further approaches (proteome, genome, immunome and metabolome analyses). As a long-term long-term goal, we will integrate the findings from the hormone panel and from potential further to develop more precise or even personalized prognostic and therapeutic strategies.

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› Pulmonology
› Biomarkers
› Clinical translation

Serum Proteome Profiling in a Novel Mouse Model of Interstitial Lung Disease to Screen for Non-Invasive Diagnostic Biomarkers

Interstitial lung diseases (ILD) are characterized by interstitial inflammation, progressive pulmonary fibrosis and impaired alveolar gas exchange. Despite intensive research, early diagnostic tests for ILD remain elusive, and most patients are not diagnosed until advanced stages, when irreversible lung damage has already occurred. We use a novel mouse model with conditional deletion of Nedd4-2 in the lung epithelium that mimics main features of idiopathic pulmonary fibrosis (IPF) in adults and ILD in children (chILD). This model allows for investigation of early disease development, addressing an unmet medical need for improved diagnosis and treatment of ILD at these understudied disease stages.

This project aims to identify serum biomarkers for early diagnosis and monitoring of ILD. High-throughput proteomic profiling is used to analyze the serum proteome of conditional Nedd4-2 deficient mice at different disease stages and for comparison with serum proteome of adult and pediatric ILD patients. In addition, the effect of anti-fibrotic drugs on the serum proteome will be investigated in both conditional Nedd4-2 deficient mice and IPF patients. Thus, new predictive biomarkers for therapy response could be identified and the understanding of drug effects will be improved which can be used for the further development of these therapies.

The overall goal of this project is to substantially improve the diagnosis of ILD in children and adults before irreversible lung damage dominates the clinical manifestation. This is the prerequisite for novel therapeutic approaches to prevent ILD progression to incurable lung disease and improve the prognosis and quality of patient lives in long term. Finally, the identification of a series of new biomarkers could facilitate personalized medicine and reveal new therapeutic targets for the treatment of ILD.

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› Translational Medicine
› 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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Fields of Research
› Moyamoya Disease
› Cerebrovascular Diseases
› Vascular Neurosurgery

Development and Characterization of a Human Chip-Based Organoid Model of Moyamoya Disease

The Moyamoya Disease (MMD) is a cerebrovascular disease characterized by progressive spontaneous bilateral occlusion of the terminal internal carotid arteries (ICA) and their major branches with compensatory capillary collaterals resembling a »puff of smoke« (Japanese: Moyamoya) on cerebral angiography. Symptoms are attributed to reduction of the blood flow resulting from stenosis of the ICA (ischemia) and the fragility of the compensatory collaterals (hemorrhage) which frequently leads to severe disability or death. Due to the early age of onset, familial cases and the occurrence predominantly in the East Asian population, genetic causes were suggested. Recently, a variant of the *RNF213* gene was shown to be strongly associated with MMD in the East Asian population, but lacks full penetrance. The multifactorial pathophysiology of MMD still remains to be understood. No diagnostic or prognostic biomarkers have been validated yet and no causal therapy to limit the stenotic lesions or the development of the fragile collateral network is available. The lack of knowledge about the pathophysiology and the lack of biomarkers and causal therapy constitute an unmet research and medical need for this severely affected group of patients. Furthermore, no validated animal or in vitro disease model exists for MMD. In compliance with the 3R principles, the primary aim of this project is to develop and characterize a human in vitro MMD model with perfusable vessel-networks on organoid chips for the first time, which could also be adapted to various other vascular diseases. Importantly, the different contribution of blood vessel cells such as endothelial (EC) and mural cells is debated but essential for elucidating the specific pathophysiology of MMD and current animal models of the disease cannot distinguish the influence of different cell types on the phenotype. By using genetically modified, *RNF213* mutated human ECs and mural cells as well as patient-derived human induced pluripotent stem cells (hiPSCs) to develop complex, MMD-specific 3D vessels on a chip we aim to investigate the pathophysiology based on the specific role and dynamic interactions of selected cell types, thereby reducing and replacing animal models. In parallel, we are preparing and sampling for a multi-omic analysis of our European MMD cohort. In a future translational, multi-disciplinary approach, we aim to translate findings of the multi-omic analysis into our organoid model.

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› Liver Transplantation
› Extended Criteria Donor Organs
› Proteomics

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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› Immunotherapy-induced neurological
  immune related adverse events
› Cancer-related neurotoxicity
› Autoimmunity

Deep Immunophenotyping for the Mechanistic Understanding of Immune Checkpoint Inhibitor-Induced Neurological Adverse Events

Immunotherapies have transformed clinical oncology. Above all, immune checkpoint inhibitor treatment (ICI) with monoclonal antibodies targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) has improved survival rates for an increasing number of malignancies. However, the clinical benefits of ICI are often counteracted by autoimmune phenomena, referred to as immune related adverse events (irAEs).

Although rare, neurological irAEs (irAE-n) are particularly severe toxicities with mortality rates up to 30 % and chronic progression in almost 50 % of patients. To date, early diagnosis and treatment are challenging, as clinical presentation is heterogenous, risk factors are unknown, and diagnostic markers are missing.

The aim of this translational and interdisciplinary project at the interface of neurology, immunology, and oncology is to characterize immune signatures of irAE-n and thereby (1) identify potential marker candidates for the diagnosis and prediction of irAE-n and (2) enhance our mechanistic understanding of ICI-related autoimmunity. To that end, I perform deep peripheral blood immunophenotyping using 37-marker cytometry by time of flight (CYTOF) as well as cytokine assays in ICI-treated cancer patients with and without irAE-n. In addition, I will implement MHC dextramer staining and flow cytometry to detect antigen-specific T cells targeting tumor and muscle antigens in patients with ICI-induced myositis, as recent studies proposed T-cell mediated cross-reactivity as a mechanism of irAEs. With the results, I hope to shed some light on the mechanisms of ICI-induced autoimmunity, help to identify patients at risk of irAE-n, and improve ICI safety.

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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 metastasized 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 personalized treatment options. By establishing and analyzing 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 personalized therapeutic approaches can become future clinical practice.

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› Autoimmune Diseases
› Plasma cells
› Nephrology

IgA Nephropathy – Analysis of Tissue and Urine for Novel Biomarkers and Treatment Targets

IgA nephropathy (IgAN) is a kidney disease that is caused by the deposition of IgA immune complexes and the resulting inflammatory response. It is one of the most common causes of kidney failure in younger adults and there are currently only supportive treatments available.

In this project, we aim to analyze kidney tissue and urine of patients with IgA nephropathy to identify pathogenic contributions of local cells of the adaptive immune system. An additional interest is the potential application of these cells within the urine as a biomarker for disease stratification and prognosis.

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› Nutrition
› age-related diseases
› prevention
› metabolic diseases
› cardiovascular diseases

Prevention of Age Related Diseases by a Dietary Intervention Rich in PUFA and Protein: A Detailed Analysis of a 36-Month Randomized Intervention and Further Insights into the Underlying Mechanisms

The European population older than 65 years is expected to rise from 16 % in 2010 to nearly 30 % in 2060 and with it, an increase in cardiovascular diseases, type 2 diabetes and sarcopenia has been observed. The term »healthy aging« is becoming increasingly important in referring to a successful adaption to the changes caused by age-increase. Dietary behavior is a crucial factor potentially affecting age related impairment of human health. In a Mediterranean population, a diet high in unsaturated fatty acids was shown to improve cardiovascular risk and cognitive function.

However, the effect of such a diet in an older German population is currently unknown and especially long-term evidence is not available. This is substantially driven by the failure of most interventions to achieve a sustained modulation of dietary pattern. Therefore a large multicenter randomized clinical trial was performed in our department to explore the long-term effects of a high-protein and high-unsaturated fatty acids diet in healthy-aging in a community-dwelling population aged 50-80y.

The NutriAct is a randomized multicenter controlled trial, which included 502 adults ages 50-80y and investigates the effects of a high-PUFA-high-protein dietary pattern in healthy ageing, including cardiovascular diseases, cognitive function, muscle mass and function and as secondary outcomes insulin sensitivity, type 2 diabetes, fatty liver diseases and many others.

With the present project, we target i) to acquire a deep understanding of the effect of an isoenergetic high-PUFA-high-protein diet in cardiometabolic diseases, physical function and health in adults aged 50-80 years, ii) to investigate potential mechanistic pathways mediating those changes and iii) to study factors related to a higher modulation of the dietary pattern.

Our preliminary results already showed that the adherence to the intervention was high in the 36 months of trial. Additionally, participants who were more adherent to the intervention had an improvement in their liver fat content. Increase in polyunsaturated fatty-acids intake were associated with improvement in liver fat. Furthermore, adherent participants also had beneficial effects on their glucose levels (HbA1c), which reflected in a higher rate of type 2 diabetes remission.

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

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. 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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› 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 16SrRNA V1-V9 variable 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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› Stroke
› Electrophysiology
› Microglia

Microglial Heterogenity Following Stroke

Microglia are the resident immune cells of the central nervous system and react to changes in the homeostasis of the surrounding tissue with various states of activation. This plays an important role in the context of stroke, wherein the heterogeneity of the states of activation varies from neurotoxic to neuroprotective. The underlying mechanisms are insufficiently understood. I further the characterization of these microglia using electrophysiology, histology and molecular genetics. In an animal model of stroke, I investigate the heterogeneity of cells stemming from the same mother cell. In human stroke tissue I seek to translate the findings from animal research to human microglia. This aims to identify potential targeted interventions on microglia in the clinical setting.

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› Tumor Biology & Immunology
› Precision Medicine

Functional Characterization of CtBP2 and Targeted Inhibitor Assays in B-Cell Acute Lymphoblastic Leukemia

The B-cell acute lymphoblastic leukemia (B-ALL) is a neoplasia of immature lymphoid cells and represents the most common malignant disease in childhood. Despite the success of most intensive therapeutic approaches in recent years and decades (high-dose chemotherapy with stem cell transplantation, tyrosine kinase inhibition, CAR-T cell therapy, bispecific and drug-conjugated antibodies), therapy-related toxicity remains high and the disease often leads to death, especially in adulthood. This highlights the need to develop targeted therapeutic strategies based on disease-specific defects to increase the chances of cure after diagnosis of B-ALL. The pathogenesis of B-ALL is multifactorial. In addition to prominent aberrations such as t(9;22) BCR-ABL1 (Philadelphia chromosome), t(1;19) TCF3-PBX1 (E2A-PBX1), and MLL rearrangement (1q23 rearrangement), other molecular defects in B-ALL cells are known at levels of cell cycle regulators, tumor suppressor genes, and components of lymphocytic differentiation. In particular, the deregulation of entire transcription factor networks (RUNX1, IKZF1, TCF3, EBF1, PAX5) interferes strongly with physiological lymphocytic development.

In this research project, we aim to characterize the functional significance of CtBP2 in B-ALL leukemogenesis. Furthermore, we aim to describe the interactome of CtBP2 in B-ALL cells. Thereby, we aim to identify CtBP2 interactors for further functional validation and deciphering of regulated CtBP2-dependent signaling pathways in B-ALL. Furthermore, we will investigate pharmacological therapeutic options of CtBP2 inhibition of B-ALL by targeted CtBP2 inhibition in vitro as well as in vivo using a zebrafish xenograft model.

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Fields of Research
› Rare diseases
› Limb malformations
› Molecular genetics

Identifying and Characterizing Genetic Causes of Limb Malformations

In the study on the »analysis of genetic alterations in limb malformations« (in short: limb study), which has been in course at our institute since 2004, more than 5000 index patients have been included and more than 8000 samples have been analyzed until today. Although numerous cases have been solved and new disease genes have been discovered, the majority of cases in the limb study remain unsolved up to date. Therefore, the aim of my project is to further investigate the already available samples of our limb study with respect to the phenotypic spectrum of known disease patterns and to optimize the current approach to identify novel pathogenic alterations by a) a more accurate phenotyping and formation of subcohorts, b) an optimized bioinformatic filtering strategy, and c) the establishment of in vitro testing procedures to characterize identified variants.

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Functional Characterization of CAKUT-Associated Missense Variants in ROBO1

Congenital anomalies of the kidneys and urinary tract (CAKUT) are the major cause for chronic kidney disease in children and young adults. This disease entity comprises a diverse spectrum of inborn defects of urinary tract development, which can ultimately lead to end-stage renal disease and thus implicate high morbidity and mortality. In the past years, an increasing number of monogenic causes, i.e., specific germline mutations in distinct developmental genes, have been identified for CAKUT. One such gene is ROBO1 (roundabout guidance receptor 1), which encodes for a transmembrane receptor and is part of the SLIT-ROBO signaling pathway, a major pathway implicated in the development of the nervous system and urinary tract, among others. A variety of patients with a multi-organ syndrome, including CAKUT, has been identified to harbor genetic variants in ROBO1. For those with a null/nonsense variant, causing the production of a truncated protein or no gene product, the pathophysiology is explained by abrogated ROBO1 receptor expression. For those with a missense variant, however, the pathophysiology is yet unexplained. In-silico variant prediction indicates impaired receptor homo-dimerization as a potential mechanism for reduced downstream signaling.

However, further evidence from in-vitro studies is missing so far. This project's aim is to generate an in-vitro assay that allows assessment of the functional impact of eight patient-derived ROBO1 missense variants on cellular function, in particular on ROBO1 protein expression, sub-cellular localization, and interaction with ligands from the pathway. The results will help interpret the pathogenicity of ROBO1 missense variants in CAKUT and so provide more evidence on monogenic causes of this disease entity.

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Fields of Research
› 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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› Early Cystic Fibrosis Lung Disease
› Risk Factors in CF
› Proteomic and Metabolomic Profiling

Characterization of Early Cystic Fibrosis Lung Disease and Identification of Biomarkers by Metabolome and Proteome Profiling

Early cystic fibrosis (CF) lung disease is the major cause for morbidity and mortality. The window of opportunity to prevent development and worsening of CF lung disease is extremely small as first structural alterations already occur within the first months of life even in asymptomatic children. So far, a variety of clinical risk factors including meconium ileus, pancreatic insufficiency and infection with pro-inflammatory pathogens have been described with limited predictive value. Bearing in mind the phenotypic variability, the gap between genotypes and clinical phenotypes should be closed to understand their relationship and interaction and to improve standards of care accordingly.

We have set up a comprehensive, prospective, longitudinal observational study cohort of children with CF that has been followed from diagnosis onwards through the first years of life. Multiple-breath washout as measure for ventilation homogeneity and the investigation of morpho-functional alterations by chest magnetic resonance imaging serve to examine the early CF lung disease. Combining these measures with anthropometric, anamnestic and microbiological findings has offered a large and well-defined cohort.

The aim of this project is to determine risk factors and identify therapeutic targets in early CF lung disease using sensitive, quantitative non-invasive methods and high throughput metabolomic and proteomic profiling in a deeply-phenotyped young pediatric cohort. First, we would like to examine longitudinal, intra-individual proteomic and metabolomic profiles to specify alterations in metabolome and proteome concentration and composition with age in stable pulmonary disease. We will then determine the influence of potential risk factors on the metabolomic and proteomic signatures to identify altered metabolites or proteins as biomarkers for an increased risk of pulmonary worsening. Thirdly, we would like to compare mild and severe phenotypes aiming to detect differentially expressed metabolites and proteins. The overall goal is the identification of relevant biological pathways and molecules serving as possible future therapeutic targets.

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› Neurology
› 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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› Oral barrier
› Inflammatory diseases of the oral
  cavity
› Anti-inflammatory therapy

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Expression and Regulation of S100A7/Psoriasin in Oral Lichen Planus

Lichen planus is a chronic inflammatory autoimmune disease. Signs of oral lichen planus (OLP) range from mild inflammation to destruction of the epithelial surface with painful sores and may result in the development of squamous cell carcinoma. Despite the well-characterised clinical manifestations of LP, the pathogenesis is still largely unknown and there is no curative treatment for OLP. This project aims to help elucidate the aetiopathogenesis of OLP by investigating the regulation of mediators of barrier function in order to develop new therapeutic approaches. In this context, the project aims to characterise the expression and regulation of S100A7/psoriasin in human oral epithelium of healthy donors and patients with oral lichen planus. The functional analyses of the tissue samples will include analysis of mRNA expression by reverse transcription quantitative polymerase chain reaction (RT-qPCR) and protein expression by immunohistochemistry (IHC). The data will be validated by in vitro experiments (RT-qPCR, IHC, ELISA). Furthermore, these expected results will be useful to refine three-dimensional inflammatory models of the oral mucosa to provide an ethically acceptable alternative to human biopsies and animal experiments.

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› Oncology
› Patient-reported quality of life

Necessity of Protective Ileostomy in Rectal Resection (NOTE)?

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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› B-cell mediated Disorders

Preclinical Development of Chimeric Autoantibody Receptor (CAAR) T Cells for the Treatment of Myasthenia Gravis

Myasthenia gravis (MG) is an autoantibody-mediated neuromuscular disorder with generalized or localized weakness of skeletal muscles (1). In about 80 % of all cases, autoantibodies directed to the nicotinic acetylcholine receptor (nAChR, in the following referred to as AChR) are present, causing receptor internalization, blockade and complement activation (2). Chimeric antigen receptor (CAR) T cells have been developed for the treatment of hematologic malignancies. An antibody fragment (scFv) expressed on the cell surface of T cells confers detection of tumor cells. Intracellular activation (e.g. CD3z) and co-stimulatory domains (e.g. CD137) of the CAR mediate T cell activation and cytolysis of respective target cells (3). The striking therapeutic success in treating refractory B cell malignancies has led to admission of Tisagenlecleucel (Kymria®) by the US Food and Drug Administration (FDA) in 2017. In our approach, we engineer chimeric autoantibody receptor (CAAR) T cells that deplete specifically AChR-reactive B cells, which express anti-AChR autoantibodies as B cell receptors on their cell surface. A CAAR resembles the CAR in design and functionality, but the scFv is replaced by the autoantigen's ectodomain, thereby enabling the detection of anti-AChR B cells.

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› Non-alcoholic fatty liver disease
  (NAFLD)
› Immunology
› Liver Fibrosis

Characterizing Immune Cell Subpopulations in Non-Alcoholic Fatty Liver Disease to Identify Novel Therapeutic Targets

Worldwide over 25 % of the adult population are affected by non-alcoholic fatty liver disease (NAFLD), and its more advanced form non-alcoholic steatohepatitis (NASH), with a predicted further increase in prevalence. While NAFLD can progress to NASH, NASH fibrosis and finally liver cirrhosis and hepatocellular carcinoma, no pharmacological therapies are available yet. Over the last years several phase III trials were terminated due to inefficacy. This may be related to an incomplete understanding of the pathways and cell-cell interactions that drive the development of human NASH. To date, several immune cell subsets have been shown to play an important role in the development and progression of NAFLD, including macrophages, dendritic cells, and lymphocytes. However, classical experimental methods often allow only limited conclusions in this respect due to their lack of spatial information, which is needed to put cell-cell interactions into a meaningful pathophysiological context, or are rather limited in the number of markers being studied simultaneously, which prevents identification of multiple cell (sub-) populations.

The objective of this study is to better characterize the immune cell (sub-) populations that are driving the development from healthy liver to NAFLD to NASH and their cell-cell interactions. We aim to address this question by using the technology of imaging mass cytometry (IMC). This technique uses antibodies labeled to defined metal isotopes allowing the simultaneous staining of up to 40 markers in one tissue section, which are detected by mass spectrometry after laser ablation. This enables the simultaneous observation of many different cell types in their spatial context. Liver biopsies of patients undergoing bariatric surgery will be analyzed including patients without liver injury, patients with NAFLD and patients with NASH. The identified cell types or cell-cell interactions that are particularly involved in the development and progression of NAFLD and NASH are planned to be further investigated in subsequent studies as possible therapeutic targets.

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› Adipose Tissue
› Epithelial Cells

Fat Signals – Characterizing the Influence of Mesenteric Adipose Tissue on Intestinal Epithelium in Crohn's Disease

Mesenteric adipose tissue is actively involved in the regulation of various physiologic and pathophysiologic processes, including inflammatory bowel disease and here in particular small intestinal Crohn's disease. In this group of patients, mesenteric adipose tissue is characterized by a unique behavior, also known as »creeping fat«: Hyperplastic mesenteric adipose tissue wraps around inflamed small intestinal segments. Accordingly, extensive research has been performed on interactions with the immune system, e.g., demonstrating immuno-modulatory properties of secreted adipokines like leptin and adiponectin. Other data indicate that creeping fat is a reaction to and barrier against translocation of microorganisms. Studies investigating potential inter-actions of creeping fat and intestinal epithelial cells are, however, sparse, use cell lines and animal models with their respective limitations and often focus on specific adipokines. In this project, we therefore aim to elucidate the effects of mesenteric adipose tissue-derived soluble factors on the intestinal epithelium in more depth. In order to use a model that can mimic in-vivo physiology and 3D architecture more closely, we employ patient-derived primary human intestinal organoids to characterize the effects of soluble factors from mesenteric adipose tissue of Crohn's disease patients and controls. Thereby we want to enhance our understanding of creeping fat's role in the pathogenesis of Crohn's disease and hope to identify potential novel therapeutic targets.

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› 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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› 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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› Paediatric Oncology and Haematology
› Fertility Impairment
› Quality of Life

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, longterm 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 psychosocial 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 psychosocial 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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› Acute kidney injury
› Chronic kidney disease
› Single cell transcriptomics/
  epigenomics

Endophenotypes of Kidney Disease Progression at the Single Cell Level

Gaps in our understanding of the transition from acute kidney injury (AKI) to chronic kidney disease (CKD) remain a major unmet medical need due to the lack of effective therapeutics for >850 million people worldwide. Although several events have been identified that lead to progression from AKI to CKD (AKI-to-CKD transition), a key bottleneck is our lack of understanding of what exactly characterizes adaptive and maladaptive repair, respectively. In the 21st century, nephrologists still group kidney disease based on clinical and histopathological classifications developed centuries ago. Single cell technologies have the potential to fundamentally improve our knowledge of kidney disease development because they capture molecular mechanisms that underlie disease drivers. This project aims to uncover cell type-specific »endophenotypes«, signatures characterizing progression (AKI-to-CKD transition), and regeneration (successful repair) alike. Leveraging state-of-the-art single cell technologies in a heterogeneous patient population mapping major etiologies of AKI, and sampling human kidney cells both invasively and non-invasively via urine, this project aims at uncovering potentially paradigm-shifting insights into kidney disease progression that will help us target therapies based on cell states rather than preconceived disease classifications. Patient-individual tubuloids derived from urine kidney cells will serve as validation platform for in silico findings.

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Fields of Research
› Autoimmune Encephalitis
› 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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› Digital Health and Artificial Intelligence
› Cardiac and Prostate Imaging

Advanced Body Composition Imaging in Clinical Routine

Opportunistic screenings in imaging studies provide additional valuable information unrelated to specific clinical indication, but unfortunately have gone largely unused. One of the most relevant incidental imaging information is body composition analysis. Body composition describes the distribution of muscle, bone, and fat in the human body, and is increasingly being used to identify patients who suffer from sarcopenia, cachexia, and/or obesity. We have trained and evaluated an artificial intelligence (AI)-based software tool for rapid and automatic segmentation of CT images acquired without increasing a patient's radiation dose or examination time. The individual metabolic information derived from AI-based body composition analysis can improve individual risk stratification. In several retrospective studies, we have already shown the feasibility and importance of AI-based body composition analysis. The aim of the project is to further improve the AI-based body composition analysis by creating and establishing a 3D-volume tissue segmentation. The possible influence of AI-based body composition parameters on clinical outcomes are going to be compared with conventional measurements like bioimpedance analysis. Automatic opportunistic screenings in imaging will be used in diverse clinical settings and cohorts including patients who are scheduled for organ transplantation. This digital health project has an emphasis on image-based precision medicine and value-added initiatives.

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Fields of Research
› Single-cell RNA sequencing
› Tumor microenvironment
› Lung cancer

Dissecting Tumor Microenvironment Heterogeneity and its Impact on Prognosis and Therapy Response in Non-Small Cell Lung Cancer

Immunotherapy is an important pillar in systemic therapy of lung cancer. Although current patient stratification is based on PD-L1 expression, the predictive value of PD-L1 is limited and biomarkers that are more precise are urgently required.

Immunotherapies modulate interactions between tumor cells and their microenvironment in order to unleash anti-tumor immune responses. Consequently, novel predictive biomarkers taking into account the cellular complexity and heterogeneity of the tumor microenvironment may add predictive precision to patient stratification for immunotherapy.

The comprehensive analysis of the tumor microenvironment has long been complicated by its cellular diversity. In a recent project, we gained unprecedented insights into tumor microenvironment heterogeneity by single-cell RNA sequencing. Now, I will advance this approach in combination with multiplex imaging to identify novel microenvironment-based biomarkers to predict response to immunotherapy.

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Fields of Research
› Multi-organ chip
› Lymphoma immune cell interaction
› Personalized medicine

A Lymphoma-Immune Cell-Liver Multi-Organ Chip as Predictor Platform for Basic Research and Personalized Medicine

The standard of care for diffuse large B-cell lymphoma (DLBCL) has not changed in decades, despite advanced molecular investigations into its pathogenesis.

Although the R-CHOP chemo-immunotherapy regimen has curative potential, one in three patients eventually succumbs to the disease. While early phase clinical trials using targeted therapies (TTs) showed signs of efficacy, recent randomized phase III trials in DLBCL have consistently failed. The precise mechanisms of individual (in)sensitivity to TT remain elusive, but could be related to tumor heterogeneity, intramolecular target alterations, activation of target-bypassing signaling cascades, alterations in drug metabolism or, even less well understood, an altered tumor-immune synapse. In close collaboration with colleagues from the laboratory of Prof. Sina Bartfeld (Department of Medical Biotechnology, TU Berlin), we have established our multi-organ chip with a human lymphoma/immune cell interface and human liver spheroids. A microfluidic circuit connects all organ compartments via a micropump driven heartbeat mimicking perfusion. Based on this multi-organ chip, we aim to investigate activity changes within the cellular immune compartment due to drug-induced altered tumor immunogenicity or drug-induced immune modulation, which collectively affect drug-induced immune-mediated cytolytic capacity.

Our future goal is to further develop our multi-organ chip to assemble primary human lymphoma samples in their same-patient immune context with human liver spheroids for human hepatic drug metabolism. This will help us to address a central tenet of personalized cancer medicine, namely, to predict drug efficacy prior to the actual treatment decision at the bedside. To validate this patient-derived multi-organ chip, the results need to be correlated with the actual clinical treatment outcome of the patient. Patients from whom we collect the material are therefore enrolled in our clinical trials. Co-clinical trials in our multi-organ chip can provide new biological insights and predict the long-term outcome of individual treatment candidates before they are actually administered to patients.

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Genome Sequencing of Hereditary Connective Tissue Disorders

Hereditary connective tissue disorders (HCTDs) are a heterogeneous group of rare diseases that can affect different organ systems. Hereditary thoracic aortopathies (H-TAD) comprise a subgroup that can present as isolated aortic disease or as part of a multisystemic disease such as Marfan syndrome or Ehlers-Danlos syndrome. Approximately 95 % of thoracic aortic dissections occur in relatively young, previously asymptomatic patients without cardiovascular risk factors. Early genetic diagnosis is essential for individual patient management, such as the timing of preventive surgery.

The risk of developing a thoracic aortic aneurysm can often be explained by a sequence variant in one of 11 definitive causative genes. Routine diagnosis (i.e. panel sequencing) leaves more than 70 % of cases unsolved. We hypothesise that genome sequencing and RNAseq will increase this diagnostic yield. To this end, 200 patients with inherited aortic and complex connective tissue diseases will be enrolled in this study over the next two years. We hope to identify 1) new disease genes 2) new intragenic non-coding variants (e.g. deep intronic and UTR variants) and 3) extragenic regulatory variants.

To improve the interpretation of genetic variants, we will perform detailed and standardised phenotyping of the cohort and implement new prediction tools and variant callers into our software. We also plan to generate a map of regulatory elements in disease-relevant tissues for the evaluation of non-coding variants.

The identification of new causative variants will have a direct impact on the clinical care of affected individuals and their families. In addition, the discovery of new disease genes or regulatory variants will allow a better understanding of our genome and the underlying molecular pathomechanisms of thoracic aortic aneurysm and dysregulated ECM homeostasis.

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› Viral Pathogenesis
› Innate Immunity

The Role of Peripheral Immune Cells to Monkeypox Virus Pathogenesis

Monkeypox (MPOX) virus led to a rapidly evolving pandemic in May 2022, with firstly over 80.000 cases reported beyond the African continent. While most infected individuals display a self-limiting disease with singular pox-like lesions, some endure systemic viral spread leading to whole body rash with risk for necrosis, organ loss and death. Since intra-host dissemination and tropism of MPOX virus are largely unexplored in humans, the cause for this clinical variability remains unknown. To elucidate the cellular tropism of MPOX virus, we exposed human peripheral blood mononuclear cells (PBMCs) from healthy donors with a currently circulating MPOX clade 2 virus isolate in absence and presence of interferon-α2a. In kinetic experiments, we identified increasing MPOX virus DNA quantities in cell lysates, but apparently not supernatants, that peaked five to six days post exposure, suggesting susceptibility of PBMCs to infection. IFN-α2a treatment markedly reduced MPOX virus DNA quantities, suggesting that infection is sensitive to type I interferons. Using scRNA-sequencing of MPOX virus-infected PBMCs,

we are currently identifying viral RNA-positive immune cell subsets and characterizing the corresponding gene expression profile at the single cell level. Finally, coinfections with MPOX virus and HIV-1 have been widely reported during the MPOX virus pandemic, as both virus infections affect the same risk group of men who have sex with men (MSM). Clinical observations reported more severe MPOX virus infections in immunocompromised patients compared to immunocompetent individuals. Therefore, we aim to investigate possible interrelations between MPOX virus- and HIV-1-infection at the level of viral replication and infectivity.

Our results have the potential to illuminate aspects of intra-host propagation of MPOX virus that may involve a lymphohematogenic route for replication, and will widen our knowledge on poxvirus pathogenesis, therefore contributing to the global preparedness in times of frequently emerging zoonoses.

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› 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).

In this project, we assessed the occurrence and clinical significance of covert brain infarction and cerebral microbleeds (two cardinal manifestations of silent cerebrovascular disease) in different study populations with cardiovascular diseases (i.a., Braemswig et al. 2022 & 2023). Further, in cooperation with the Department of Cardiology, we are investigating whether sonolysis (continuous transcranial Doppler monitoring) reduces the risk of covert brain infarction during transcatheter edge-to-edge repair of the mitral valve.

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› Neuroscience
› Epidemiology

Effects of Dopamine Modulation on Motivational and Motor Function in Major Depression Characterized by Low-Grade Inflammation

Major depressive disorder (MDD) is a leading cause of disability worldwide and has many adverse mental and somatic health consequences including cardiometabolic diseases. However, about one third of patients do not achieve full remission from depression even after multiple antidepressant treatments – potentially due to its clinical heterogeneity. Chronic low-grade inflammation is present in more than a quarter of patients with MDD, is associated with treatment resistance, and may represent the underlying substrate linking depression and cardiometabolic diseases.

A large body of evidence on depression heterogeneity point to an »immunometabolic« subtype characterized by the clustering of immunometabolic dysregulations with atypical behavioral symptoms related to energy homeostasis. Motivational and motor impairments reflected by symptoms of anhedonia and psychomotor retardation in MDD are closely related to alterations in energy homeostasis, are associated with increased inflammation, and may be a direct consequence of the impact of inflammatory cytokines on mesolimbic dopamine (DA) signaling.

In the proposed project, we will examine the effect of DA stimulation on motivation and motor function in patients with MDD and healthy controls and the role of inflammation using a double-blind, randomized, placebo-controlled, cross-over design. If successful, our study would provide crucial evidence that pharmacologic strategies that increase DA may effectively treat inflammation-related symptoms of anhedonia and psychomotor retardation in MDD. Similar pharmacological strategies may have clinical utility in other neuropsychiatric populations with increased inflammation as well.

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Fields of Research
› Emotional abuse
› Childhood trauma
› Social cognition

Impact of the Oxytocin System on Empathy in Individuals with a History of Childhood Emotional Abuse

Emotional abuse in childhood (CEA) is defined as repeated behaviors by a caregiver that communicate to the child that they are worthless, flawed, unloved, unwanted, dangerous, or only useful for fulfilling the needs of others. CEA is often associated with interpersonal deficits, emotional dysregulation, and somatic and psychiatric disorders in adulthood. It is also the strongest predictor for therapy-resistant depression in adulthood. However, the neurobiological and psychological consequences of CEA are scarcely researched. CEA is associated with changes in the endogenous oxytocin system and in empathy in adulthood. Empathy is an important aspect of social cognition and consists of a cognitive component, i.e. the ability to recognize, understand, and empathize with the feelings, thoughts, and intentions of others, and an emotional component, i.e. the ability to feel the same as other people. The oxytocin (OT) system plays a crucial role in cognitive and emotional empathy. Several meta-analyses have shown improved accuracy in emotion recognition after exogenous OT administration in healthy subjects and patient populations. Initial evidence suggests improved emotion recognition in healthy individuals with heterogeneous childhood trauma after oxytocin administration and increased emotional empathy in healthy individuals and those with borderline personality disorder. The exact mechanism of action of OT and the role of CEA in empathy are poorly understood. Current data on the effects of OT suggest that its effects depend on the current context and individual variables (e.g., CEA). In this planned study, we aim to investigate whether the enhancing effect of OT on empathy is present in healthy female participants with CEA. The hypotheses are that 1) participants with CEA will demonstrate reduced cognitive and emotional empathy (especially reduced emotion recognition) compared to healthy participants (group effect) and that 2) a single dose of 24 IU of synthetic OT nasal spray (Syntocinon®) in healthy participants with CEA will lead to a greater improvement in cognitive and emotional empathy compared to healthy participants without CEA (group × treatment interaction).

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› Neurovascular disorders
› Diffusion-weighted imaging
› Ocular vascular occlusive disorders

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
› Rare genetic disorders
› Lymphovascular diseases
› Lymphatic malformations

A Translational Approach to Improve Healthcare of Patients with Rare Lymphovascular Diseases

Lymphovascular diseases (LVD) represent an underdiagnosed and heterogeneous group of maladies that occur sporadically or as a part of a syndromic disorder (e. g. overgrowth syndromes with vascular involvement). Due to the pathophysiological complexity of LVD, specialized, interdisciplinary care structures are required. Our project represents an innovative patient care concept to provide personalized medicine in LVD: We organize multi-centric, interdisciplinary case conferences to provide a detailed clinical characterization, essential for further phenotype-based evaluation of genetic data. Using Next Generation Sequencing we analyze the protein-coding and non-coding regions of the human genome using DNA from blood, as well as affected tissue samples. Thereby identified genetic variants are then evaluated for pathogenicity utilizing genetic databases, bioinformatic prediction tools as well as functional studies. Using this approach, both the confirmation of a known genetic disorder, as well as the identification of new candidate genes in LVD can be achieved. Identifying disease-asso-ciated genes improves our understanding of LVD pathogenesis and is the first crucial step for the establishment of novel therapeutic approaches. Moreover, our project also aims to assess the use of already available pharmaceuticals in LVD. For this, we establish individual endothelial or fibroblast cell lines for in-vitro testing. Through this process, the efficacy of different FDA-approved drugs is tested, providing important information for the optimization of current patient therapy.

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› B-cell lymphoma
› Immuno-Oncology

Biomarker-Informed SUMO Inhibition for Improved Lymphoma Therapy

Diffuse large B-cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma. Patients achieving remission after first-line immunochemotherapy have a good long-term prognosis, whereas survival is impaired at relapsed or refractory disease. Despite the striking success of immunotherapies in many tumor entities, latest trials on immune checkpoint blockade (ICB) in DLBCL have shown rather disappointing results. The poor response rate of DLBCL to ICB is partly attributed to an immune-cold tumor microenvironment (TME), which is frequently caused by genetic alterations. Within previous studies, we attributed SUMO inhibition (SUMOi) with strong immune-modulatory effects, emphasizing its potential to reactivate the TME. However, it is unclear which patient subgroups (biomarker-defined) would benefit from the addition of SUMOi to ICB and the impact of the most frequent genetic drivers of DLBCL on the TME is poorly understood. Within this project we aim to comprehensively characterize the impact of driver mutations and the SUMO state on the TME in DLBCL patients with

the ultimate goal of pinpointing biomarkers of an immune-cold TME. Furthermore, we will investigate the efficacy of SUMOi to reactivate the TME in these biomarker-defined subgroups aiming to develop biomarker-informed SUMOi-based combination therapies with ICB. In summary, this project will define biomarkers to drive forward translation of SUMOi addition to cancer immunotherapies in biomarker-defined subpopulations of DLBCL.

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› 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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› 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

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 char-

acterised 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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› Pancreatic tumor microenvironment

Personalized Therapy Response of PDAC in Correlation with Presence or Absence of Extrachromosomal DNA (EcDNA)

The complex genomic aberrations of the aggressive Pancreatic Duct Adenocarcinoma (PDAC) have not yet been sufficiently characterized. Chromothripsis has been shown a critical mechanism in the molecular pathogenesis of PDAC and is deemed responsible for accelerated tumor progression. Subsequent chromosomal recombination presumably leads to molecular by-products such as extrachromosomal DNA (ecDNA). Genome wide analyses estimated that ecDNAs are present in around 15–20 % of PDAC patients. The exact clinical relevance of ecDNA structures on PDAC patients are not sufficiently examined. We therefore seek to identify ecDNA signatures in enriched tumor samples. Three-dimensional tumoroid culture will be employed to allow enrichment of the cancer epithelium from 50 resected specimen. We will subsequently perform modern deep sequencing methodologies to identify characteristic ecDNA signatures, also using state-of the-art computational algorithms. In addition, clinical outcome and follow-up of patients will be correlated with detailed genetic information. Ultimately, we conduct cytotoxicity assays with our tumoroid cultures, to directly assess the functional impact on PDAC tumor cells. This study is aimed at expanding our knowledge about the molecular determinants of pancreatic carcinogenesis and may have direct clinical impact on diagnostics and therapies of this aggressive disease.

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Molecular MR Imaging of Extracellular Matrix and Inflammatory Activity for the Early Detection of Osteoarthrosis

Osteoarthritis (OA) is a common degenerative joint disease that affects a significant portion of the population, particularly those over the age of 60. Despite advancements in imaging technology, joint damage is often only detectable in the advanced stages of OA, leaving little room for curative approaches.

Studies have shown that OA is a cytokine-driven process involving low-grade inflammation affecting joint tissue homeostasis, as well as subchondral regions and surrounding structures such as muscles, capsules, and ligaments. Matrix metalloproteases, specifically ADAMTS4, play a crucial role in this process through the degradation of intra-articular aggrecan. Our group has identified a peptide probe in the one bead one compound (OBOC) screen that binds exclusively to ADAMTS4, which can be coupled with an MR-active Gd-DOTA complex or fluorescent dye via a lysine linker.

By using this probe for molecular imaging with MRI, we aim to detect and quantify ADAMTS4 as a molecular target. This could potentially make the pathogenetic low-grade inflammation of early OA clinically detectable for the first time, allowing for earlier diagnosis and more effective treatment strategies. Moreover, this could lead to a better understanding of the pathophysiology of OA and contribute to the development of curative treatments for this chronic disease.

To establish this new methodology, we plan to conduct a longitudinal, exploratory study in the Dunkin-Hartley guinea pig animal model. By doing so, we hope to pave the way for innovative diagnostic and therapeutic approaches that extend beyond traditional radiological imaging techniques. The potential implications of this work are significant, as it could help to address a major public health concern and improve the quality of life for millions of individuals living with OA.

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› Heart failure

Thrombo-Inflammation in Cardiovascular Disease

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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› Gene expression regulation

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 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 biomarkers and druggable targets for high-risk disease.

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› Immunology
› Single cell technologies

Identification and Modulation of Novel Immune Targets in Juvenile Idiopathic Arthritis Using Single-Cell-Sequencing

Juvenile Idiopathic Arthritis (JIA) is the most common chronic inflammatory disease in childhood. JIA is currently considered a single entity divided into 7 subtypes solely based on clinical findings. This diverse clinical presentation and a polymorphic response to conventional and biological treatments suggest its heterogeneity. Currently the choice of treatment is still empirical, different drugs can be administered for the same disease phenotype and the same drug can be used for multiple JIA subsets. JIA can undergo medication-free remission in roughly half of patients for currently unknown reasons, whilst the rest develop a persistent arthritis and need long-term care. The molecular mechanisms differing these two populations remains unclear. This suggests different disease endotypes. For JIA typical therapy involves intraarticular installation of steroids, making the synovial fluid and synovial fluid mononuclear cells equally available as peripheral blood mononuclear cells for in situ analysis of the inflammation.

Due to technical advances, it is now possible to phenotype the immune system with single-cell resolution. Using this advanced immune phenotyping, we have already identified some immune signatures of JIA and immune targets of JIA using paired samples of blood and synovia. This way, we were able to show that the disease relevant cells which are highly prominent in the synovia are also found in the blood even though there are far smaller frequencies. This enables non-invasive diagnostic using high resolution blood analyses. During my Clinician Scientist fellowship I will extend our immune phenotyping of JIA by additinal immune cell types. Furthermore, identified targets will be tested for therapeutical potential. And with a clinical prospective trial, I moreover want to investigate to what extent the molecular signatures identified so far correlate with disease phenotypes, prognosis and treatment response. This will provide the basis for developing new biomarkers that will enable personalized management of JIA.

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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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Generation of Liver Tissue from IPSC to Investigate the Mechanism of SNP in Non-Alcoholic Fatty Liver Disease

NASH is a leading cause of end-stage liver disease (ESLD), often evolving from NAFLD. Despite the high prevalence of NAFLD, only a fraction of individuals develop severe fibrosis. The disease's complexity arises from environmental factors interacting with a polygenic susceptibility background. Studies have showed light on the genetic basis of NAFLD, revealing significant correlations with single nucleotide polymorphisms (SNPs). However, the role of SNPs in progressing from steatosis to NASH remains unclear, and creating appropriate disease models is challenging. Mouse models don't reflect the identified SNPs, and access to human samples with specific genetic backgrounds is limited. Stem cell technology has the possibility to overcome these restrictions. Human-induced pluripotent stem cells (hiPSCs) can differentiate into hepatocytes with specific genetic backgrounds, helping model NAFLD progression in human livers, potentially elucidating the mechanisms behind the disease progression.

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Lightsheet Microscopy-Based 3D-Histology

An improved and detailed understanding of the underlying pathology causing human diseases is key to improve diagnosis and treatment. However, current diagnostic gold standards are time-consuming, have intrinsic limitations and do not provide sufficient information for deep phenotyping and genotyping of the identical tissue sample. Therefore, the Hägerling group develops a fully automated platform focused to help researchers, clinicians and pathologists increase their sample throughput from tissue preparation to analysis and answer the most challenging questions in diagnostics with the combination of tissue conserving spatial 3D information and genomics in daily routine work. The platform allows optical sectioning of the entire tissue samples including downstream genomic analysis in almost every research and routine sample. It enables researchers and pathologists to evaluate multiplexed biomarker staining of tissue samples with cellular 3D spatial resolution in a clinically feasible time and to incorporate new technologies, such as artificial intelligence, on the fly.

Although, the platform is suitable for high throughput analysis, it can also be applied to study and diagnose rare (lympho)vascular diseases – the second research focus of the group. In combination with in vitro tests and state-of-the-art sequencing techniques, the lab establishes an innovative approach to precision medicine for rare (lympho)vascular diseases ed to improve diagnosis and patient care.

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› Oxygen glucose deprivation induced
  cell death

Non-Hematopoietic Erythropoietin Splice Variants as Endogenous Neuroprotective and Neuroproliferative Substance

Erythropoietin (EPO) is a glycoprotein induced by hypoxia, which inhibits apoptosis and promotes differentiation of progenitor cells. Due to its effects on hematopoietic cells, EPO is applied in anemia therapy. Through the same mechanisms, EPO protects neurons from apoptosis and promotes generation of new neurons. However, these endogenous repair mechanisms are not sufficient to compensate damage induced by a stroke for example. Therefore, the therapeutic use of EPO in neurological disease is obvious but limited by hematopoietic side effects such as thromboembolism.

In preliminary studies, we showed that hypoxia-induced paracrine but not hypoxia-induced autocrine neuroprotection is transmitted by EPO. The detection of endogenous EPO splice variants revealed potential candidates transmitting autocrine neuroprotection. Especially one splice variant showed comparable neuroprotective effects without hematopoietic function in the mouse model. We are now testing the neuroprotective effects of this promising variant in the human model using iPSC-derived neurons and oxygen-glucose deprivation (OGD) as in vitro model of stroke. The iPSC model further allows evaluating potential effects on differentiation on neuronal stem cells and therefore additionally acts as a model for adult neurogenesis and regeneration. Moreover, we want to analyze expression of this splice variant in human neuronal disease. Therefore, we apply a new RNA hybridization method named BaseScope in post-mortem human brain. With this method, single mRNA molecules and their splice variants can be detected as single dots next to each other at single-cell resolution. In cooperation with Dr. Anna Zemella, group leader of Cell-free Protein Synthesis at the Fraunhofer Institute for Cell Therapy and Immunology Potsdam, necessary amounts of the splice variant are produced with a highly new and efficient cell-free method, which is a future technology for developing therapeutic proteins.

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› Cardiovascular Imaging

Myocardial Dysfunction and Injury Patterns in Patients with Ischemic Stroke

Cardiac complications after stroke are frequent and of medical relevance as they substantially contribute to stroke-associated disability and death both in the acute and chronic phase after acute ischemic stroke (AIS). About 20 % of all stroke patients are reported to suffer a severe adverse cardiac event, such as acute coronary syndrome, heart failure or cardiac arrythmias within the first few days after the incident stroke. Part of the spectrum of cardiac changes observed early after stroke is elevation of cardiac troponin T (hs-cTnT) which indicates presence of myocardial injury. At the same time, the rate of major adverse cardiovascular events over the course of three years is doubled if patients present this surrogate of myocardial injury in the acute phase after stroke. So far, limited information is available on the assessment of cardiac function or non-ischemic myocardial alterations in patients with AIS. State-of-the-art cardiovascular MRI (CMR) allows to precisely visualize myocardial function and injury patterns. We hypothesize that CMR will reveal myocardial dysfunction and tissue alterations in AIS patients with elevated hs-cTnT. Until now, no study provided in-depth myocardial tissue characterization by using state-of-the art feature tracking sequences to study

myocardial deformation (global longitudinal strain) together with T1 and T2 mapping sequences and late gadolinium enhancement (LGE) imaging. This approach will also allow to study diffuse myocardial fibrosis as well as edema and inflammation in addition to focal fibrosis (LGE). This project is an explorative analysis within the prospective CORONA-IS trial and the pre-specified »heart-brain-vignette« of the prospective BIH BeLOVE study. As CMR is performed at two different time points (5 days and 90 days) after AIS, we face the unique opportunity to study both the acute and chronic phase after AIS. With this approach, we wish to identify the burden of myocardial injury patterns that underly the high cardiovascular risk after AIS. Furthermore, we hope to use this data in correlation with blood-based biomarkers to improve our understanding of heart-brain-interaction as an underlying pathophysiology in the development of post-stroke cardiac dysfunction.

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› Adoptive T cell therapy
› Pancreatic cancer

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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Matrix-Based Colorectal Liver Metastases as a New Approach to Study Tumorbiology and Evaluate Therapeutic Strategies

Modern multimodal therapy strategies have improved the outcome of patients with colorectal liver metastasis (CRLM). Nevertheless, the overall prognosis is still devastating. To further improve patients' therapeutic options, it is necessary to develop and test new targeted therapy approaches. Mouse models are most common to study metastatic colorectal cancer. However, the rate of successful translation from animal models to clinical trials is less than 8 %, illustrating the strong need for alternative models to study metastatic cancer biology. We aim to develop a novel personalized matrix-based in vitro model of human CRLM as a new platform to study the tumor biology and perform personalized drug testings. This newly developed model will be validated against existing data from patient- derived organoids and xenografts. The goal is to show the non-inferiority of our newly developed model compared to mouse-matrix based models. After the validation of the model, we will establish a patient-matched matrix-based in vitro

CRLM and compare it to their native counterpart. The comparison will by based on histology, single-cell RNA-sequencing, and targeted gene sequencing. Afterwards, we will translate our matrix-based in vitro CRLM into a personalized drug screening platform to test drug responses from standard-of-care to novel inhibitor combinations.

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› Neuroregeneration

Promoting Neurovascular Regeneration in Spinal Cord Injury Via the Cell-Specific Regulation of Ephrin-B2 Signaling

Traumatic Spinal Cord Injury (SCI) is one of the leading causes of disability in the world. A complex pathophysiology and insufficient endogenous regeneration of the spinal cord leave this condition not accessible to curative therapy. The overarching goal of our research is to facilitate endogenous regeneration to ameliorate spinal cord regeneration post SCI. Experimental research in ischemic stroke, a condition which in its pathophysiology resembles SCI, could show the guidance molecule Ephrin-B2 to be associated with a stabilization of the neurovascular unit (NVU). In SCI, the role of Ephrin-B2 is not well-known and an inhibitory role through the induction of astrogliosis is assumed. With this project, we aim to examine the cell-specific role of Ephrin-B2 on neurovascular regeneration post SCI. We hypothesize that 1st endothelial Ephrin-B2 plays a significant role in stabilizing the NVU post SCI and its specific knock-out leads to an aggravation of secondary injury in the spinal cord. 2nd Ephrin-B2 in reactive astrocytes inhibits axonal regeneration and its specific knock-out ameliorates spinal cord regeneration. To test these hypotheses, a cell-specific conditional knock-out mouse model is utilized (R. Adams, Münster). The primary endpoint of this project is neurological restitution, and the secondary endpoint is structural regeneration of the spinal cord. Methodically, behavioral analysis using Catwalk® automated gait analysis, magnetic resonance imaging, histological and immunohistochemical analyses, and longitudinal in vivo microscopy will be performed. As the current therapy of spinal cord injury is restricted to supportive therapies, the findings of this study will lead to an enhanced understanding of SCI pathophysiology and spinal cord regeneration with the final goal to develop translational therapies building on this preclinical work in the future. This project is performed at the neurosurgical Spinal Cord Injury laboratory at Charité Berlin in cooperation with the Fehlings Laboratory at the Krembil Neuroscience Center, University Health Network, Toronto, Canada.

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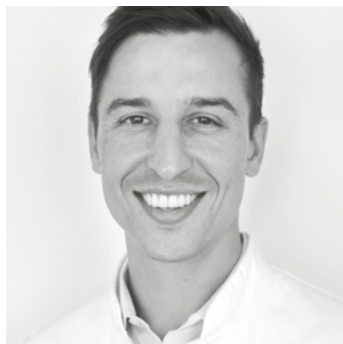
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› 3D printing
› Computed tomography
› Image quality

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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› Cognitive function
› Affective and stress-related disorders
› Psychoendocrinology

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 research focuses on severe psychiatric diseases. I am investigating underlying neurobiological mechanisms that lead to impaired learning and neuro-cognitive processes in neuropsychiatric diseases. We apply a broad range of techniques in order to elucidate the 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), magnetic resonance spectroscopy, 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. However, clinical phenotypes in psychiatric diseases are very heterogeneous and imaging techniques, thus far, only provide a limited explanation for this heterogeneity. Clinical characterization is still the gold standard, Therefore I started a new project evaluating the clinical use of patient-reported outcomes both for clinical and research purposes. The upcoming use of recording patient-reported outcomes longitudinally might inform future studies and thus elucidated the aforementioned neurobiological mechanisms.

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› Monogenic kidney disease
› Genome editing
› Base editing

Genome Editing as a Treatment for Monogenic Atypical Hemolytic Uremic Syndrome

Atypical hemolytic uremic syndrome (aHUS) is a very rare, life-threatening thrombotic microangiopathy mainly caused by uncontrolled complement activation. It is associated with thrombocytopenia, acute kidney injury, and hemolytic anemia. Approximately 50-70 % of aHUS patients have an underlying monogenic cause. Variants in the gene encoding complement factor H (CFH) are the most common cause of aHUS in 20-30 % of the cases and lead to an overall severe disease course, with high risk for relapses and rapid progression to end stage renal disease (ESRD). Once ESRD is reached, patients require either dialysis or transplantation, which represent an enormous health-care burden worldwide. Eculizumab and novel complement inhibitors such as Ravulizumab have entered clinical applications. It is highly effective for treating acute episodes and preventing relapses but still bears major side effects. In addition, it needs to be administered frequently as a life-long treatment. Thus, a »single-shot« »once-and-done« treatment via CRISPR-based genome editing could be a promising novel treatment strategy for patients suffering from aHUS due to CFH variants. CRISPR base editing combines high effi-cacy and easy programmability without requiring double-strand breaks (DSB) or donor templates. Recent in-vivo applications underscore its potential. We will target different CFH variants by in in-vitro base editing in HEK293T reporter cells using different combinations of guide RNAs and base editors. Targeted amplicon sequencing will assess base editing efficiency. The results will be validated in iPSC-derived hepatocytes after introducing the patient variant. Adeno associated virus (AAV) has successfully been used as a vehicle to express base editors in-vivo. Due to the large size of base editors, split inteins must be employed to distribute the payload of base editor and gRNA on two AAVs. Thus, I will test different splice-inteins and splicing positions to generate a split-intein base editor that sufficiently edits the CFH variants. In the long run, we plan to apply base editing in-vivo to explore if pathogenic variant correction can prevent, halt or reverse disease progression. Overall, this project aims to use innovative CRISPR base editing tools that have been successfully applied to correct other genes, to now correct CFH variants causing aHUS.

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› Immunotherapy
› Immunopeptidomics
› TCR mimic CAR T cells

Mass Spectrometry Driven Identification of T Cell Immunotherapy Targets in Head and Neck Squamous Cell Carcinoma

Even if treated with state-of-the-art care, patients diagnosed with metastatic head and neck squamous cell carcinoma (HNSCC) face a devastating 8 months median overall survival highlighting a profound unmet medical need for additional treatment strategies. Over the last years, immunotherapeutic approaches such as antibody-based immune checkpoint blockade have been implemented successfully in clinical care demonstrating responsiveness of HNSCC towards immunotherapy. This effect might be mediated by T cell recognition of the three different sources for highly tumor-specific immunotherapy targets expressed in HNSCC tumors: oncogenic viral antigens, cancer germline antigens and mutation-derived neoantigens.

We aim to identify these tumor-specific targets, which are presented on the cell surface as small peptides in the context of Human Leukocyte Antigen (HLA) complexes. Utilizing immunoprecipitation of these HLA complexes followed by ultrasensitive mass spectrometry of the presented peptides will enable us to determine their exact amino acid sequences. To increase the sensitivity and clinical relevance of this approach, we will first identify all potentially presented HLA ligands in an overexpression system of COS7 cells transfected with HLA complexes (HLA-A*01, -A*02 or -A*03) and antigens (viral, cancer germline or somatically mutated) of interest. Then, we will validate the presence of such bona fide HLA ligands in tumors generated from patient derived xenograft (PDX) models to ensure their biological relevance.

Such well-defined and validated HLA ligands will then form the basis for future studies in which we aim to identify reactive TCRs as wells as TCR mimic CAR T cells to develop and provide effective cellular immunotherapies for patients with HNSCC.

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› Proteomics
› Myositis

Molecular Characterisation of Pathomechanisms in Acquired and Hereditary Myopathies

Idiopathic inflammatory myopathies (IIMs) form a group of autoimmune diseases affecting the skeletal muscle and, to a variable extent, other organ systems (e.g. skin, lungs, heart muscle). While research has shown that the pathogenesis of IIMs is heterogeneous, this fact is not yet reflected by the current classification systems. As a consequence, in many cases the treatment of IIMs follows an »one fits all« approach that does not reflect the complex molecular differences of IIMs. Pilot studies have shown that some subtypes of IIM might even be misclassified in the current diagnostic classifications. In this project, we will perform state-of-the-art untargeted proteomics in a large cohort of patients with IIM to explore the molecular pathogenesis of the different diseases. This data will then be used in the development of a modern, evidence-based classificition system (»Myositis 3.0«) that may hold important implications for future therapy strategies (e.g. targeted therapies) in the context of IIMs.

A second focus of my research is the characterisation of mitochondrial dysfunction in the context of IIMs and hereditary myopathies. Mitochondria may show abnormalities caused by primary genetic defects (e.g., mtDNA mutations and deletions), inflammatiory processes (e.g., in Inclusion body myositis), and/or by post-tranlational/-transcripitional mechanisms (e.g. sequestration of transcription factors, e.g. in Myotonic dystrophy type 2). This interplay and the particular role of mitochondria in the pathophysiology of the individual diseases is only incompletely understood. Unraveling the role of mitochondria, however, may open new opportunities for targeted treatment approaches.

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Fields of Research
› Nephrology
› Single Cell Diagnostics
› Urinalysis

Urine-Derived Regenerative Tubular Epithelial Cells (RegTEC): Biomarker and Therapeutic Target in Acute Kidney Injury

Acute kidney injury (AKI) is a major health problem implying significant morbidity and mortality. The care for AKI patients is merely supportive and our understanding of the pathophysiology is limited. One key to improved treatment of kidney disease is new diagnostic methods that allow assessment of individual regeneration potential or risk of progress to chronic kidney disease after AKI. Recently, dedifferentiated kidney tubular epithelial cells (TECs) have been revealed to be essential in injury and repair processes in AKI.

Usually, urine is devoid of cells. But after AKI, patient's urine contains kidney TECs with regenerative potential (regTECs). These cells, so far only detected by single-cell RNA sequencing, have a molecular makeup which is sufficiently preserved in urine to infer data informative about expression patterns in a patient's kidney without biopsies. My project specifically promotes the rapid translation of these findings to a clinically relevant application in three elementary steps:

1) The dynamics and prerequisites of the damage-associated occurrence of regTECs in urine will be elicited in a temporally resolved manner with single-cell RNA sequencing and validated separately in kidney tissue.

2) The regTEC detection in urine will be made scalable using simplified methodology (flow cytometry), thus enabling the examination of larger cohorts and clinical use of urinary regTECs as a cellular biomarker for AKI recovery.

3) Using cell sorting, regTECs will be isolated from urine and made accessible for the evaluation of their regenerative potential in vitro.

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Fields of Research
› Genetic kidney disease
› ADPKD
› ADPLD

Inhibition of the Ire1α-XBP1 Pathway Using as a Novel Way to Delay Progression of ADPKD

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease, affecting 1:400 to 1:1,000 individuals. It accounts for over 90 % of all hereditary renal cystic diseases and is characterized by the presence of bilateral renal cysts. These cysts typically grow and expand slowly over decades, resulting in significantly increased total kidney volume, progressive renal injury and ultimately end stage renal disease (ESRD) around the sixth decade of life. The most common extrarenal manifestation of ADPKD is polycystic liver disease, which can also occur as an independent genetic entity, autosomal-dominant polycystic liver disease (ADPLD). Previously, it has been demonstrated that ADPLD and ADPKD share a common underlying molecular genetic mechanism centered on the activity of polycystin-1 (PC1) despite differential degree of kidney manifestations. PC1 is the protein product of the primary gene linked to ADPKD, Pkd1. ADPKD appears to be recessive at the cellular level. Therefore, somatic second hits in the normal PC1-allele of cells containing the germline mutation initiate or accelerate the formation of cysts. It became evident that the Ire1α-XBP1 pathway, the most conserved branch of the endoplasmic reticulum (ER) unfolded protein response (UPR), plays a protective role in cyst formation induced by Sec63 deficiency, one of the genes causing ADPLD. This is accomplished by an optimization of the ER-folding environment of misfolded PC1 via upregulation of chaperone proteins dependent on XBP1. Our recent unpublished data has revealed that XBP1 is a direct genetic interactor of Pkd1 and may surprisingly promote the progression of ADPKD via inactivation of PC1. We hypothesize that upregulation of XBP1 protects Pkd1-deficient cyst cells from apoptosis, which in turn promotes cyst growth. Consequently, double inactivation of Pkd1/XBP1 leads to specific apoptosis of cyst lining epithelia without any impact on proliferation. Preliminary data strongly suggests that avenues modulating homeostatic Ire1α-XBP1 signaling in vivo may hold therapeutic potential. This protective effect is accomplished by selectively promoting the apoptosis of cells that have acquired second hits in Pkd1, and which are responsible for the development of cystic lesions that eventually lead to polycystic kidney and liver disease. Based on these studies the aim of this project is to investigate: a) the underlying mechanism of Ire1α-XBP1-double knockout dependent cyst-lining cell apoptosis and the impact of chemical modulation of the Ire1α-XBP1 pathway on cyst progression and b) the effect of XBP1 inactivation on the progression of polycystic liver disease due to Pkd1 or Pkhd1 deletion. We hypothesize that avenues that inhibit Ire1α-XBP1 hold therapeutic potential for a novel treatment of ADPKD.

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› Autoimmune Encephalitis
› Neuroimmunology
› Humoral Immune Responses

Cross-Reactivity of Antiviral Antibodies Against Neuronal Autoantigens as Cause of Autoimmune Encephalitis

Encephalitis is a rare but serious neurological condition in which inflammation of the brain frequently causes irreversible neurological dysfunction and death. Few years ago, it was shown that these disorders can be mediated by antineuronal autoantibodies, most commonly by those that target the NMDA receptor. Some of the affected patients had previously undergone viral brain infections. However, it has so far remained unclear whether these infections might be causatively related to the autoantibody formation and the antineuronal autoimmunity.

This research project will investigate whether antineuronal autoimmunity can occur through specific cross-reactivity of antiviral antibodies or as an unspecific epiphenomenon. Cerebrospinal fluid and serum biosamples from anti-NMDA receptor encephalitis patients have been collected via the German autoimmune encephalitis network (GENERATE). They will be analyzed using VirScan, a recently developed bacteriophage display technology to derive reactivity profiles of antibody binding against all human-pathogenic viruses at the resolution of single viral peptides. These investigations will be performed in a rotation to the lab of VIrScan co-founder Benjamin Larman at the Johns Hopkins University School of Medicine. Afterwards, the binding epitope data will be used to isolate monoclonal antibodies against selected viral peptides from stored cells of autoimmune encephalitis patients with the history of viral encephalitis to further investigate antineuronal cross-binding on the level of monoclonal antibodies.

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Fields of Research
› Parkinson's Disease
› Movement Disorders
› Deep brain stimulation

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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Fields of Research
› Cognition
› Neuropsychiatry
› Parkinson's disease, movement
  disorders

Predictors of Cognitive Decline after Deep Brain Stimulation in Parkinson's Disease

The course and severity of cognition in Parkinson's disease (PD) is of outstanding importance for our patients and their quality of life. When it comes to deep brain (DBS) stimulation surgery and chronic stimulation the cognitive prognosis is even more relevant. In a first retrospective study, I was able to show that the volume of the Ncl. basalis Meynert, the main cholinergic nucleus of the basal forebrain, is a significant predictor of cognition 12 months after DBS surgery. In order to take into the multifaceted etiology of cognitive change after DBS surgery, I set up and executed a prospective study including more possible predictors (https://clinicaltrials.gov/ct2/show /NCT03982953): Detailed preoperative phenotyping regarding non-motor symptoms, imaging, dementia markers and genetics was conducted. An extensive tablet-based test battery specially tailored for and validated in patients of different stages of Parkinson's disease was applied prior to surgery as well as 3 and 12 months after. Additionally, perioperative procedures that can influence cognitive outcomes and the depth of narcosis via an intraoperative EEG were recorded. As postoperative delirium can lead to permanent cognitive deficits, screening for this complication was conducted three times daily. Preliminary results suggest that, in particular, age, dopaminergic dose, but also deficits in specific neuropsychologic domains influence the occurrence and severity of a postoperative delirium which, in turn, has a negative impact on cognition 12 months after DBS surgery. The overarching goal of my research is to gather knowledge on the effects and risks of therapeutic strategies in movement disorders in order to guide patients to their individual personalized treatment with optimal and long-lasting effects.

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› Ischemic stroke
› Magnetic resonance imaging
› Computer tomography

Prediction of Long-Term Outcome in Acute Ischemic Stroke Patients Using Lesion-Network Mapping

Despite the development of successful acute treatments for ischemic stroke, stroke remains a leading cause of lasting disability and permanent functional dependance worldwide. Not only can an ischemic stroke lead to severe motor deficits impeding mobility, there is growing evidence that stroke can lead to more complex and long-term symptoms including chronic depression and progressive cognitive decline; all of which have a substantial impact on the patients' rehabilitation success and quality of life. Due to the frequency and complex course of these post-stroke symptoms, understanding the underlying mechanisms is essential to develop accurate prediction models to identify patients at risk to ultimately introduce targeted treatments. A relatively new methodology, called lesion network mapping (LNM) using the so-called human connectome offers a new and accessible way to evaluate anatomical as well as functional connectivity across lesions using magnetic resonance (MR) sequences acquired in routine clinical diagnostics. The consideration of lesion functional connectivity has the potential to substantially increase the accuracy of our outcome prediction models in the field of stroke and

subsequently allow us to optimize individualized treatment options for stroke patients. Therefore, the current project will pool MR and clinical data of >1500 ischemic stroke patients from several independent large, well-characterized, prospective stroke cohorts to 1) identify the functional networks associated with early motor recovery, as well as the development of post-stroke depression and cognitive impairment – using LNM with the connectome. Furthermore, 2) we aim validate these findings using predictive modelling in a large independent cohort of stroke patients with long-term follow-up. Our main hypothesis is that with a systematic approach using large datasets (including clinical & paraclinical data), we can apply LNM to predict post-stroke outcome, including motor recovery, functional dependence, as well as post-stroke depression and cognitive decline.

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› Solid tumor microenvironment

Personalized CRISPR/Cas9 Gene Therapy to Alter the Tumor Microenvironment and Enhance CAR T Cell Therapy in Solid Tumors

Therapy-resistant solid tumors represent a growing global challenge. Neuroblastomas are examples of solid tumors, and as the most common extracranial solid tumor of childhood, they are responsible for 15 % of childhood cancer-related deaths. The overall survival for high-risk cases still does not exceed 50 %, and treatment options are limited in cases of relapse. One novel approach could be adoptive T cell therapy with chimeric antigen receptor (CAR) T cells. It uses T cells engineered with specific antigen recognition motifs fused to costimulatory and signaling domains to generate a tumor-specific immune response. While this novel form of therapy is successfully used to treat CD19+ B-cell malignancies, response rates in the treatment of solid tumors are not yet sufficient due to a series of hurdles, especially insufficient T cell infiltration and an immunosuppressive tumor microenvironment. To overcome this hurdle, we are developing personalized gene therapy to patient-specifically modify neuroblastoma cells in vivo to express transgenes encoding T cell-attracting and stimulating chemokines and cytokines. Their expression can favorably alter the tumor microenvironment to enhance both CAR T cell activation and tumor infiltration. The approach is demonstrated in

neuroblastoma but is extendable to further solid tumor entities. To achieve the necessary safety and efficiency for in vivo gene therapy, we aim to combine two targeted mechanisms. On the one hand, tumor-specific mutations identified via an established multi-step analysis of genomic and transcriptomic data are targeted using CRISPR/Cas9 technology to achieve tumor cell specificity. On the other hand, we are developing a targeted lipid nanoparticle-based delivery system (tLNP), where gene therapy carrying lipid nanoparticles are modified with neuroblastoma-specific antibodies to preferentially direct the gene therapy to the tumor cells. Gene delivery, gene therapeutic effect, CAR T cell efficacy, safety, and toxicity will be evaluated after targeted gene transfer alone or in combination with CAR T cell therapy in humanized patient-derived (hPDX) mouse models. Our approach is unique in that it aims to engineer the patient's tumor cells to alter the tumor microenvironment to enable T cells to reach the tumor cells within.

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› Movement disorders
› Deep brain stimulation
› Intracerebral recordings

Neurophysiological Network Signature of Delayed DBSeffects in Dystonia

Dystonia is a movement disorder that is characterized by abnormal movements and postures. Pallidal deep brain stimulation (DBS) has proven an effective treatment option for dystonia. To achieve optimal DBS effects, a variety of stimulation parameters must be individually tested. In dystonia, this approach is specifically challenging as many DBS-effects occur with a delay of days to months and symptom severity may vary over time, which favors recall bias of patients when asked to evaluate DBS-settings. Two approaches could help to improve adjustments of DBS-therapy in dystonia: 1) The use of computer-based video processing, so-called »computer vision«, to enable objective symptom evaluation outside the clinical setting and 2) the identification of real-time electrophysiological markers of symptom severity as recorded from DBS-electrodes by sensing-enabled DBS-devices that could be used to adjust DBS-parameters in a closed-loop system. Examples are pallidal low frequency activity (3-12 Hz) and reduced alpha coupling (10-12 Hz) between the pallidum and cerebellum, which have emerged as neurophysiological correlates of dystonic symptoms. So far, the investigation of cortico-subcortical activity patterns was temporally limited to a short perioperative time window in which DBS-electrodes were externalized and could thus not incorporate delayed DBS-effects. Chronic recordings are needed to validate the reliability of known neurophysiological markers and identify markers of delayed DBS-effects. In this project, we will try to advance both the objective assessment of motor symptoms via computer vision as well the characterization of pathophysiological correlates in chronic DBS-recordings. In project 1, I will extract movement traces from the large archival video database of dystonia patients of the movement disorders unit by using computer vision and test their symptom-specific predictive value. In project 2, I will perform chronic recordings via pallidal DBS electrodes to identify symptom-specific oscillatory correlates of symptom severity objectively assessed by networks trained in project 1. In project 3, I will compare cortico-subcortical network activity as recorded by whole-head magnetencephalography before and after chronic DBS to explore DBS-associated plasticity within the network profile as a marker of DBS-effects. Taken together, these findings will help to improve symptom-assessment and guide treatment optimization for patients with dystonia.

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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
› Cartilage
› Bone

Disease Modifying Osteoarthritis Cell Therapy

Osteoarthritis (OA) is the most common form of arthritis worldwide. Chronic low-grade inflammation in the articular environment causes cartilage degeneration at an early disease stage, resulting in chronic pain, disability and loss of independence due to progressive joint destruction. To date, no treatment is available to sustainably combat low-grade inflammation in early-stage OA patients.

PLX-PAD cells, which are adherent mesenchymal stromal-like cells derived from donated human placentas and developed as a cell therapy, demonstrate significant regenerative, immunomodulatory, and anti-oxidative properties. Specifically, through the regulation of SDF-1, IL-1β, and IL-6, PLX-PAD cells have been shown to reduce oxidative stress and the release of pro-inflammatory cytokines while increasing anti-inflammatory IL-11 and CCL5 secretion when challenged by pro-inflammatory signals present in OA. We thus hypothesize that PLX-PAD cells could restore the pathologically altered joint environment, dominated by pro-inflammatory and catabolic signalling cascades. For this project, we follow a combined in vitro and in vivo approach:

1.) Ex vivo / in vitro work will be performed using tibial cartilage samples excised in regular knee arthroplasty surgeries for OA. Obtained OA chondrocyte cultures as well as ex vivo organ culture samples are treated with PLX-PAD, and RT-qPCR, immunohistochemistry, ELISA, and spectrophotometry/DMMB will be conducted to assess cellular and molecular response.

2.) In vivo, we will use the Dunkin Hartley guinea pig model of naturally occurring OA, which is widely established due to a close resemblance to human OA, and which has been used to successfully explore intraarticular therapies for OA. Six-month-old animals will be treated with intraarticular injections of PLX-PAD versus placebo, and compared to healthy controls. Animals receive in vivo MRI scans to detect short- (one month) and long-term (six months) effects of PLX-PAD therapy on cartilage integrity.

Six months following treatment, animals will be euthanized, and among others, histology, immunohistochemistry, and RT-qPCR of knee joints, micro-CT structural analysis of subchondral bone, and serum OA biomarker analysis will be conducted.

Restoring physiological joint homeostasis at an early disease stage may be the key to understanding health to disease progression in OA. Targeting this 'window of opportunity' may fundamentally change the way OA is treated today and in the future.

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› Interventional therapy
› Echocardiography

New Advances in Tricuspid Regurgitation

Tricuspid regurgitation (TR) is one of the most common structural heart diseases and is associated with high morbidity and mortality (Singh et al., Am J Cardiol, 1999; Nath et al., JACC, 2004). In recent years, various interventional therapies for TR, such as percutaneous annuloplasty and transcatheter edge-to-edge repair, have been developed (Praz et al., EuroIntervention, 2021). Particularly, older multimorbid patients who were previously managed symptomatically may benefit from minimally invasive therapies. The accurate quantification of TR using echocardiography is a prerequisite for determining the treatment indication. However, previous echocardiographic measurements of the regurgitation orifice area (EROA) and volume (RegVol) based on the »PISA« method are prone to errors due to the tricuspid valve anatomy and underestimate the TR severity by approximately 50 %. An angle-corrected formula for calculating EROA may address this diagnostic gap (Tomaselli et al., Eur Heart J Cardiovasc Imaging, 2022).

In the current project, titled »New advances in tricuspid regurgitation«, we aim to evaluate (i) the prevalence and prognosis of TR in different heart failure phenotypes, (ii) the outcome of patients after different types of interventional TR therapy, and (iii) the prognostic value of angle-corrected quantification of TR.

To accomplish this, we prospectively enrolled 1000 patients with heart failure who underwent echocardiographic examination to quantify TR. Follow-up telephone visits are conducted at three, six, twelve, and twenty-four months. Additionally, patients who undergo interventional TR therapy are enrolled in the »Berlin Registry of Right Heart Interventions«. Follow-up examinations, including echocardiography, electrocardiograms (ECG), laboratory measurements, and symptom assessments, are performed at two, twelve, and twenty-four months. Offline echocardiographic analysis enables further TR assessment using the angle-corrected formula for calculating EROA, allowing evaluation of the prognostic value of the corrected TR grading in both cohorts.

The overall objective of this project is to enhance the diagnosis and treatment of TR patients.

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› Cognitive Neuroscience
› Psychopharmacology

The Neurocognitive Mechanisms of Serotonergic Antidepressants

Pharmacotherapy of depression targets monoaminergic neurotransmission, with selective serotonin reuptake inhibitors (SSRIs) constituting first-line antidepressant intervention. Serotonergic antidepressants work well for many patients, however, it typically takes multiple weeks before they experience clinical benefit. Clinically, this delayed onset of action is problematic, as it prolongs patients' suffering and complicates therapeutic decision-making. Scientifically, it is puzzling, as SSRIs boost brain serotonin levels within hours of treatment initiation. To date, it remains unknown why neurochemical and therapeutic effects operate on different timescales, with SSRIs impacting neurocognitive function within hours, and clinical benefits only emerging after several weeks. Further, psychiatrists lack early markers that predict who may show a delayed clinical response to antidepressant intervention. Arguably, this arises from a paucity of knowledge about how antidepressants work, as, even 60 years after their serendipitous discovery, the exact neurocognitive mechanisms of their action remain elusive. Thus, the aim of my research is to refine depression treatment by providing a neuroscientifically grounded, mechanistic understanding of antidepressant

drug action. In my prior work, I used a combination of cognitive experiments, computational modelling, and pharmacological neuromodulation to assess how SSRIs impact reward processing, learning, and decision-making in healthy individuals. Further, I developed a neurocomputational framework of how these neurocognitive changes can lead to gradual mood improvement over time. In this BIH Clinician Scientist fellowship, I aim to probe this mechanistic account of antidepressant drug action in a bench-to-bedside translational approach in depressed patients initiating antidepressant treatment. Here, the goal of my fellowship is two-fold: First, I will determine how a serotonergic impact on neurocognitive processes in patients gives rise to mood improvement and a delayed clinical onset of SSRI therapy. Second, I will identify early neurocognitive markers, occurring within hours or days, that may serve to predict who will show a delayed clinical response after weeks of serotonergic intervention.

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› Neuromuscular disease
› Muscular dystrophy
› Protein aggregation

Therapeutic Strategies in Myofibrillar Myopathies – a Model for Protein Aggregation Diseases?

Myofibrillar myopathies are a clinically and genetically heterogeneous group of neuromuscular diseases often leading to progressive skeletal myopathy and cardiomyopathy. The exact molecular pathogenesis of myofibrillar myopathy remains to be fully understood, though most mutations generate myofibrillar structural changes with abnormal intracellular aggregates of the intermediate filament desmin and other proteins.

These protein aggregates have been likened to aggregates and amyloids found in Alzheimer and Parkinson diseases, systemic amyloidosis, amyotrophic lateral sclerosis (ALS), Huntington disease and type II diabetes, but also share properties with prions, as found in Creutzfeldt-Jakob disease. Protein misfolding and the amyloid phenomenon are increasingly being recognized as a major disease driving mechanism, yet no therapies exist to date to cure the associated diseases.

I created and characterized a CRISPR-Cas9 engineered rat with an exchange of arginine to proline at position 349 (R349P) of the desmin gene; orthologous to the most prevalent desmin mutation in humans. This is the first rat model of myofibrillar myopathy. The rats exhibit both skeletal and cardiac myopathies with sarcoplasmic aggregates and signs of injury and remodeling, as well as ventricular arrythmias, a disorganization of the cardiac tissue architecture and fibrosis.

This Clinician Scientist project explores several therapeutic approaches targeted against protein aggregation in a rat model of desminopathy, the most common myofibrillar myopathy, to improve muscle function.

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› Cardiothroacic Surgery
› Myocardial Revascularization
› Cardioprotection

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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› Cancer immunology
› Protein engineering

Mechanisms of Cross-Presentation Assisted Tumor Rejection During T Cell Therapy

T cells are specialized effector cells of the immune system capable of eliminating virus infected and cancer cells. The T cell antigen receptor stands unique among cell surface receptors being able to recognize down to a single specific antigen per target cell and at the same time specific enough to distinguish even a single amino acid substitution. Importantly, TCR recognition of a target does not just lead to a binary (activated / not activated) state of the T cell but can additionally encode information about the quality of the antigen allowing for different functional outcomes, e.g., proliferation vs. exhaustion. T cell targeting of tumors can be achieved with bispecific antibodies, or genetic modification of T cells with new TCRs or chimeric antigen receptors (CARs). Bispecific antibodies and CARs are successfully used to treat hematologic malignancies but show inadequate results in solid

tumors. This is mainly due to a paucity of specific and effective antigen receptors. Even as more solid tumor specific TCRs become available prioritizing individual receptors for clinical development is challenging, because there are no known in vitro parameters that can accurately predict a receptor's performance in vivo.

We are developing tools to better understand how individual antigen-receptor interactions drive specific T cell signaling pathways and phenotypes. In addition, we use protein engineering to fine-tune the receptor-antigen interface in order to better skew signaling towards clinically beneficial outcomes.

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› Heart Failure
› Onco-Cardiology

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. Mammalian (mechanistic) target of rapamycin (mTOR) has been shown to be a key marker of diabetic cardiomyopathy, and inhibiting mTOR has been shown to be beneficial in diabetic hearts. Nevertheless, it is known that broad inhibition of mTOR has major side effect including immunosuppression. Therefore, more targeted fine-tuning of mTOR signaling is necessary. This project determines the mechanisms and therapeutic implications of our new discovery that cGMP-stimulated protein kinase (PKG) suppresses mTOR complex 1 (mTORC1). mTOR is a master regulator of protein and lipid synthesis, metabolism, and autophagy in response to growth factors including insulin, as well as to metabolites, and mechanical load. Its activation favors growth while reducing autophagy, and is thought to play key roles in heart failure, cancer, aging, diabetes, and others. Our data shows that PKG stimulates autophagy by inhibiting mTOR activity, improving heart function and blocking maladaptive responses to hormonal and pressure-overload stress. This requires PKG phosphorylation (activation) of tuberin (TSC2), a principal negative modulator of mTOR. We find PKG blunts mTOR by phosphorylating / activating TSC2 at a Serine 1365, enhancing autophagy and countering pathological stress remodeling in vitro and in vivo. This new mechanism is exciting because its impact is substantial when mTOR is being activated, but not under resting conditions allowing more fine-tuning and a new therapeutic toehold that does not have major side effects seen by broad pharmaceutical mTOR inhibition. We now found another patho-mechanism that we first test in mice and might lead to a novel clinical trial to improve outcome of patients with heart failure under different metabolic stress conditions.

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› Autoimmune liver disorders

Multiomics and Functional Characterization of the Mutational Landscape in Small Intestinal Neuroendocrine Tumors

The intestinal epithelium is characterized by rapid self-renewal, driven by crypt-base stem cells that express the R-spondin receptor Lgr5. Stem cell turnover and differentiation into various intestinal cell types have been recapitulated using organoids and, recently, also growth factor conditions to culture hormone-producing entero-endocrine cells (EECs) have been revealed. Characterized by a high level of complexity, EECs can dedifferentiate and form intestinal neuroendocrine neoplasms (NENs), a set of rare but lethal tumors with a concerning increase in incidence. Small intestine neuroendocrine tumors (siNETs) in most cases already present with metastases at the time of initial diagnosis. Their grading is mainly based on the Ki-67 proliferation index, which determines therapeutic procedure and ultimately patient survival. At present, the development of more effective therapies and prognostic markers has been limited partly by a lack of studies aiming to understand the biology of these rare tumors. In addition to small patient numbers, the absence of in vitro and in vivo models that accurately represent these tumors constitute a limitation in this field. To gain a deeper understanding of siNET biology, our group has launched a multiomics project, in which whole genome sequencing (WGS) and transcriptome analysis has been performed. Our preliminary data hint towards an important role of specific mutations. By using organoid culture system technologies, this study aims to understand the functional impact of specific mutations in siNETs and to explore their role for EEC survival, proliferation and dissemination.

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› Hepatology
› Intravital microscopy

Dynamic Characterization of Resident Kupffer Cells in Liver Disease

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, as seen in most chronic liver diseases, leads to a sustained influx of monocyte-derived macrophages that augment the pool of liver macrophages. These bone marrow-derived cells infiltrate with a specific task – 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 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 at different stages of liver injury and injury resolution. By using multicolor intravital microscopy, we can investigate the function of these subsets further in vivo and with regards to their critical immune function: capturing of blood-borne pathogens and initiating / suppressing immune responses in the liver via crosstalk with other immune 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. Ultimately, by gaining a better understanding of the functional consequences of liver macrophage heterogeneity, we hope to identify novel pathways that can be targeted therapeutically in patients.

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› Cancer immunomodulation

Identification of Targets and Biomarkers for Innovative Uveal Melanoma Immunotherapy

Uveal melanoma (UM) is an aggressive intraocular tumor that in terms of biology and clinical behavior is markedly distinct from its cutaneous counterparts. Despite highly effective eye-preserving radiation therapies such as proton beam therapy (PBT), systemic dissemination occurs in ~50 % of patients through early micrometastases. There is no established (neo)adjuvant therapy to prevent metastatic spread. Although recent immunotherapeutic advancements have been made, prognosis of metastatic UM remains dismal due to a lack of effective therapies for the majority of patients. Various factors have been identified that lead to low immunogenicity and the development of an immunosuppressive tumor microenvironment, however there is a high need for a better understanding of the complex immune-evading mechanisms as a prerequisite for novel therapeutic strategies in UM. Together with the Helmholtz-Zentrum Berlin, the Charité is one of the largest PBT centers worldwide. In this project we will characterize the cellular ecosystem in UM and investigate the immune modulating effects of PBT on the tumor microenvironment and decipher mechanisms of disease progression and immune escape. For this, we will perform single-cell multi-omic mapping of the UM tumor immune contexture using high-dimensional spectral flow cytometry complemented by single-cell transcriptomic and proteomic characterization and spatial profiling in a comparative approach of PBT-pretreated UM tumors (with secondary surgical resection) and treatment-naive UM tumors (obtained through primary enucleation). With this research, we aim to identify immunomodulatory targets and corresponding predictive biomarker candidates for therapeutical interventions in the neoadjuvant/adjuvant setting to develop novel therapeutic strategies to reduce the risk of metastases.

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› Innate Immunity
› Pneumonia
› Signal transduction

The Sweetness of Infection – the Role of a Bacterial Sugar and a Novel Pattern Recognition Receptor in Pulmonary Inflammation

The first line of defence that recognizes a potential pathogen and initiates an inflammatory response is the innate immune system. It depends on a network of specific immune receptors, termed pattern recognition receptors (PRR), that detect bacterial pathogen associated molecular patterns (PAMPs) and initiate a stereotyped immune response. Recently this cellular pathogen recognition apparatus was extended by the discovery of a novel PAMP in Gram-negative bacteria, ADP-heptose (ADP-hep) and its corresponding PRR, Alpha kinase 1 (ALPK1). ADP-hep is a soluble intermediate metabolite in synthesis of the conserved core oligosaccharide of Lipopolysaccharide (LPS) which is an integral component of the outer membrane of Gram-negative bacteria. Binding of ADP-hep to ALPK1 leads to activation of the central immune regulatory transcription factor NF-kB. Involvement of this pathway in initiation of inflammatory responses in vitro could be demonstrated for infections in a growing number of Gram-negative bacteria. The lung is particularly dependent on a tightly regulated innate immune response that effectively clears an infection and simultaneously conserves organ function. Infections of the respiratory track

and especially pneumonia still pose a major medical challenge and are associated with high mortality rates. Especially in hospitalized patients and immunocompromised individuals, infections are frequently caused by Gram-negative bacteria and here antibiotic resistance is becoming more prevalent. So, there is an urgent need to develop novel strategies to improve treatment of infections and to prevent detrimental, de-regulated hyperinflammation. Here, modulation of innate immune responses has been identified as a promising target. Our aim is to understand the (patho-)physiological function of ADP-hep and ALPK1 in inflammatory responses and development of pneumonia in vivo. This will be tested using a lung infection model with the clinically highly relevant pathogen Pseudomonas aeruginosa.

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› Hypothermia

»Of Heart and Mind«: A Longitudinal Neurodevelopmental 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 are patients who had a resuscitation (> 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

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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› Chronic Pain
› Immune System

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

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

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 signaling 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 inter-

ventions 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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› Axial Spondyloarthritis
› Acute Anterior Uveitis
› T Cell Receptor

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 and present in a third of axSpA patients. During my JCSP, 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 total, 56 % of the AAU patients had concomitant spondyloarthritis, mainly axSpA (Rademacher et al, Arthritis&Rheumatology 2023). 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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› Headache
› Sex Hormones

Migraine across the Female Lifespan: Influence of Sex Hormones on Calcitonin Gene-Related Peptide (CGRP) in Tear Fluid and Plasma

Migraine prevalence in women is three times higher than in men. Hormonal fluctuations play a crucial role in the generation of migraine attacks. According to the estrogen-withdrawal-hypothesis, a drop in estrogen concentrations can trigger migraine episodes. In line with this hypothesis, migraine frequency and severity are higher during the perimenstrual phase of the menstrual cycle but also in the perimenopausal period before hormonal stabilization at an older age. The pathophysiological mechanisms leading from hormonal changes to the development of migraine attacks are still widely unknown. The neuropeptide Calcitonin Gene-Related Peptide (CGRP) has a key role in migraine initiation. During a migraine attack, CGRP is released from trigeminal afferents and triggers an inflammatory response. Preliminary preclinical research suggests that sex hormones fluctuations can lead to activation of the trigeminovascular system and release of CGRP, which may explain the high prevalence of migraine in women of childbearing age. One-third of all women of childbearing potential in Europe take oral contraception, most commonly combined oral contraceptives (COC). The regular intake of a COC leads to suppression of the physiological hormonal fluctuations. The effect of COC on migraine is highly variable, with migraine attacks occurring most frequently during the seven-day hormone-free interval. The exact association between COC intake and CGRP release remains to be determined. From a methodological angle, the accurate measurement of CGRP in peripheral blood samples is challenging. CGRP has a short half-life time and is subject to dilution effects after release. The measurement of CGRP in tear fluid has recently been proposed as a non-invasive and more direct method due its spatial proximity to the trigeminal nerve. This research project aims to elucidate the complex relationship between sex hormones and CGRP in different hormonal states across the female lifespan (regular menstrual cycle, COC, postmenopause). Key research questions are: 1) How do different hormone profiles affect CGRP release? 2) Does the impact of sex hormones on CGRP differ between patients with migraine and healthy controls? 3) To what extent is CGRP measurement in tear fluid feasible for clinical practice?

The findings of this project could help to explain the changes in migraine frequency in the course of life of women and specifically during the menstrual cycle and under contraceptive treatment.

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› Autoantibodies
› SARS-CoV-2
› Neurology

Autoantibodies Against the NMDA Receptor

NMDA receptor (NMDAR) encephalitis is the most common autoimmune encephalitis causing psychosis, epileptic seizures and cognitive impairment. The underlying pathogenic autoantibodies target the GluN1 subunit of the NMDAR and lead to internalization of the receptor as well as profound synaptic changes. Although the pathogenic role of NMDAR autoantibodies is undisputed, detailed insights into the pathophysiology of NMDAR antibodies are missing, therefore hindering the progress of disease-specific immunotherapies. One reason for this is the limited availability of patient-derived monoclonal antibodies against the NMDAR. In this project, new antibodies against the NMDAR will be cloned from patients with NMDAR encephalitis. Using these new antibodies, I want to answer the following questions:

1. »What is s the antigenic landscape of the NMDAR?« – Where do the majority NMDAR antibodies bind to the NMDAR? How can different classes of antibodies be grouped, in particular with respect to their overlapping epitopes between GluN1 and other NMDAR subunits?

2. »Where do pathogenic antibodies exert their effect?« – How does the pathogenic potential of NMDAR mAbs correlate with their epitope, their affinity, or other biophysical properties?

3. »Where do the pathogenic antibodies come from?« – Can structural or functional properties of NMDAR mAbs be correlated with their antibody sequence features?

4. »What is the difference between pathogenic and beneficial or neutral NMDAR mAbs?« – How do NMDAR mAbs from different compartments in patients (CSF, teratoma, blood), or different disease stages (acute phase, remission) compare with NMDAR mAbs from healthy people?

5. »Are there public NMDAR clonotypes, similar to what has been found in the SARS-CoV-2 antibody response«? – Do certain combination of germline antibody sequences predispose to NMDAR binding?

Answering these questions will provide important insights into the pathophysiology of the most common form of autoimmune encephalitis and related pathological processes including autoimmune dementia and autoimmune psychosis.

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› Precision Medicine
› Immune Therapy
› Head and Neck Cancer

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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› Multiple Myeloma
› Dendritic Cell

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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› Tumor Microenvironment

Non-Invasive Imaging Biomarkers for the Immuno-Metabolic Crosstalk in Liver Cancer

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide with the majority of cases being diagnosed at intermediate or advanced stages. In unresectable HCC, loco-regional therapies (LRT) including tumor ablation and embolotherapies represent guideline-approved treatments. While systemic approaches have largely failed to elicit significant prognostic advantages, this negative trend has recently been challenged by the emerging concept of immune-checkpoint inhibitors (ICI). Specifically, combination treatments with ICIs resulted in improved survival compared to standard treatment in advanced disease (Imbrave-150, HIMALAYA trial) but only in a subset of patients, calling for further strategies to improve tumor susceptibility to therapy. While a variety of resistance mechanisms are under investigation, the immuno-metabolic crosstalk as an organizing principle of tumoral immune evasion has gained significant interest. One postulated underlying factor is the acidification of the tumor-surrounding microenvironment (TSE) driven by hyperglycolytic tumor metabolism (»Warburg effect«). This acidic TSE contributes to exhaustion and quiescence of local immune cells in an oftentimes anyway inherently tolerogenic, chronically inflamed cirrhotic liver. Additionally, the metabolic state of the tumor plays a pivotal role in shaping the extracellular matrix (ECM), which may facilitate the creation of a biophysical barrier for an immuno-compromised, pro-tumorigenic niche. Currently, no technique other than invasive tissue biopsy can reliably provide insight into the molecular tumor characteristics. Thus, novel methodologies are urgently needed to non-invasively characterize the mechanisms of immunosuppression mediated by the immuno-metabolic crosstalk in HCC in vivo. Such tools may further allow for the visualization of LRT-induced alterations to design strategies to convert tumor habitats from being resistant towards being susceptible to LRT and immuno-oncological treatments. Therefore, this project is focused on developing novel MRI techniques for non-invasive in vivo profiling of liver tumors in a translational rabbit model including the assessment of tumor vascularity, cellularity, acidity, ECM components, and immune cells. If implemented in patient care, the findings may promote a paradigm shift away from a »one-size-fits-all« indication and transform LRT and immunotherapies for HCC into personalized, TSE-directed treatments.

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› Neurology
› Omics
› Stem cells

Modelling Chemotherapy Induced Neurotoxicity with Patient-Specific Induced Pluripotent Stem Cell-Derived Sensory Neurons

Chemotherapy-induced neuropathy (CIN) is a highly prevalent, potentially irreversible adverse effect of cytotoxic chemotherapy characterized by altered sensation, sensory loss and neuropathic pain. At present, its underlying molecular mechanisms are incompletely understood and it is not possible to predict individual CIN susceptibility in patients. As therapeutic options are still limited to unsatisfactory symptomatic treatments, chemotherapy-induced neurotoxicity represents an immense unmet medical need. With the generation of stem cells from adult human cells and their further differentiation into sensory neurons, otherwise inaccessible human tissue has become available to model disease. We apply patient-specific neurons with high-throughput multi-omic approaches, bioinformatic pathway analyses and the functional integration of the results in relation to the clinical phenotype. Combining these tools enables a potent human in-vitro model to discover meaningful molecular mechanisms of toxic neurodegeneration, biomarker discovery and the development of preventive treatment strategies.

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› Stroke
› Intracerebral hemorrhage
› Hematoma expansion

Investigation of Hematoma Growth in Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is a disease with a very high short-term mortality of 40 % and a high post-incident morbidity. One major reason for this high mortality is that a third of patients develop significant hematoma expansion during hospitalization, and this number is doubled in patients taking oral anticoagulation. However, while hematoma expansion is a reason for poor outcome it also provides the opportunity of a therapeutic intervention. Non traumatic ICH starts with the burst of a single vessel, giving rise to an initial hematoma. In 1971 Fisher introduced the idea that the mass effect of the initial hematoma ruptures surrounding vessels by shearing, causing secondary bleeding. He believed that at least parts of the final hematoma volume are explained by this »avalanche« theory. In our group we recently developed a novel animal model, which provides the first direct experimental proof of the »avalanche theory«, i.e. the concept for secondary vessel rupture and bleeding as a potential mechanism for intracerebral hematoma growth. I now want to transfer knowledge from the animal model into the clinical setting. Follow-up imaging in patients with ICH is not standardized in the clinical setting. We are used to look only at snapshots of specific time-points. Follow-up imaging is typically undertaken if the patient worsens, after 24 hours or not at all. It remains therefore difficult to understand the dynamics of the process and clinical decision making might be substantially delayed. However, one would expect a rather fast expansion rate in the beginning causing sudden »stroke-like« symptoms when counter pressure from the surrounding tissue is minimal. Therefore we will investigate repeated CT imaging in acute ICH at the Charité in order to define ultraearly hematoma growth and to streamline early clinical decision making. With the »Stroke-Einsatzmobil« (STEMO) Berlin offers the possibility to investigate the hyperacute phase of ICH in a unique patient population.

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› Acute myeloid leukemia
› Multiple Myeloma
› Drug resistance

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 acti-

vation 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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› Nephrology
› Vaccine response

Epigenetic Regulation of Plasma Cell Differentiation in Systemic Lupus Erythematosus

B cell-directed therapies have improved prognosis for some autoimmune kidney diseases like PLA2R+ membranous glomerulonephritis and minimal change disease. However, other diseases like SLE are refractory to B cell-depletion and even plasma cells-directed therapy may not work for alloantibody production in kidney transplant patients. In Nephrology, we can study various ways of B and plasma cell induction and maintenance, from transient B cell-autoimmunity to persistent auto/allo-immunity mediated by plasma cells. Current immuno-suppressive therapies are unselective, make patients vulnerable to severe infections and impair proper vaccine response. Therefore, selective and potent targeting of auto/alloreactive B and plasma cells remains an important medical need. I hypothesize that B cell and plasma cell induction, differentiation and maintenance is distinct between persistent and transient auto/alloimmunity leading to kidney diseases and that different strategies are needed to successfully treat different auto/alloantibody mediated kidney diseases.

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› SLE

STIFTUNG CHARITÉ

Muscle Disease in Systemic Sclerosis

The aim of my project is to understand the nature and mechanisms behind muscle involvement in Systemic Sclerosis (SSc) in order to get a better understanding of the pathophysiology of this poorly understood connective tissue disease. The general concept is that SSc is characterized by the pathophysiological triad of microvascular dysfunction, tissue fibrosis and autoimmune inflammation but detailed understanding and therapeutic options are limited. We have already completed a retrospective analysis of SSc muscle biopsies according to current neuropathological standards and large-scale electron microscopy for ultrastructural analysis. We digitized entire sections and provide open-access pan-and-zoom analysis to our datasets. We identified a morphological pattern that is specific to SSc. This pattern combines severe vasculopathy with minimal inflammation. We termed it »minimal myositis with capillary pathology« (MMCP) and the data was published in Acta Neuropathologica in 2021.

We are currently looking into cellular pathways activated in SSc muscle disease and are planning to clarify the mechanism of action behind obliterative vasculopathy by mapping the fate of different cell types in and around the vasculature using spatial transcriptomics and single nucleus RNA sequencing.

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› Skin immunology
› Autoimmune/inflammatory skin
  diseases
› T cells

Functional Characteristics of T (Follicular) Regulatory Cells in Pemphigus

Pemphigus is a severe blistering disorder of skin and mucosa characterised by autoantibodies against desmosomal proteins of the skin and is a model disease to study autoimmunity in humans. A harmed immunosuppressive capacity of T regulatory cells (Treg) is one of the critical checkpoints leading to autoimmunity, since their deficiency or impairment facilitates the disruption of immune homeostasis. Treg cells constitute ~5 % of circulating CD4+ T cells, and are characterized by the lineage marker forkhead box protein P3 (FoxP3). Treg cells can be defined through detection of FoxP3 and by their expression of CD25 and CD127 (CD4+CD25+CD127low). Accordingly, similarly to several other autoimmune disorders, there is a wide literature demonstrating that the function of Treg cells is impaired in pemphigus. Recent advances depict a more complicated mosaic. For instance, it has been shown that some Treg cells – beside their classical production of the anti-inflammatory interleukin (IL)-10 – may produce IL-17 or Interferon (IFN)-γ, thus indicating that this cell group is more heterogeneous than previously described. Recently, a follicular counterpart of Treg cells has been described, namely T follicular regulatory (Tfreg).

These cells can migrate in to the germinal centers and modulate the immune answer due to the expression of the chemokine receptor CXCR5. The role of this cell population is controversial. While some studies described these cells as anti-inflammatory, there is also evidence that under some circumstances Tfreg can support inflammation and antibody formation in germinal centers. In Pemphigus, several studies tried to analyse the role of Treg cells, whereas any group investigated the role of Tfreg cells. Some studies detected the presence of lower levels of Treg cells in pemphigus patients compared to healthy controls, and the induction of Treg cells has been associated to decreased pathogenicity in a HLA-transgenic mouse model of Pemphigus. In pemphigus, neither the heterogeneity of the Treg/Tfreg cells nor their different capacity to modulate inflammation have been analyzed. This project aims to elucidate the heterogeneity of the Treg/Tfreg subset in pemphigus. The definition of specific subset, which may carry stronger immunosuppressive capacity than others, may help to detect new therapeutic targets and modalities in this strongly debilitating autoimmune disorder.

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› Inflammatory Bowel Disease
› Inflammation
› TGF-beta Superfamily Signalling

Clinical and Molecular Characterization of Pouchitis after Ileal Pouch-Anal Anastomosis in Ulcerative Colitis Patients

Ulcerative colitis (UC) is a chronic autoimmune disease of the colon and rectum affecting approximately 150.000 patients in Germany alone. Despite considerable progress through the initiation of biologicals in the treatment of UC, a significant portion of patients require colectomy in the course of disease, either due to medication-refractory flare or diagnosis of colitis-associated colorectal cancer. After total colectomy, the creation of an Ileal pouch-anal anastomosis (IAAP) is the preferred surgical procedure, as it guarantees the highest possible quality of life by preserving continence and through a reduction of stool frequency. Unfortunately, a significant portion of patients develop at least one episode of inflammation of the pouch, whilst the majority of patients suffering an episode of pouchitis experiencing multiple episodes. The exact pathomechanism of pouchitis is still incompletely understood. An interaction between the gut/pouch microbiome and host factors such as genetic polymorphisems is assumed. In this project, we aim to characterize this underinvestigated disease molecularly and clinically. Through a better understanding of the underlying pathomechanisms, we hope to improve patient care and outcomes.

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› Epithelial regeneration
› Immune microenvironment
› Gastrointestinal infection

Mechanisms of Epithelial Regeneration in Gastrointestinal Infection

Regeneration is a key process gastrointestinal epithelial homeostasis. Various kinds of injury, e.g. chemicals, radiation and infection, induce epithelial damage which is followed by epithelial repair. During this process, stem and epithelial cells have a central role, which, upon damage, show increased differention and de-differentiation, respectively. This results in increased epithelial turnover leading to restoration of the epithelial lining. In this project we aim to investigate the damage induced by Helicobacter pylori. We study immune cell invasion, chemokine secretion and mechanisms of epithelial regeneration using e.g. immunhistochemistry and functional in vitro and in vivo studies.

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Fields of Research
› Translational / preclinical research
› Biomarker discovery in CRC
› Identification of new therapeutical
  options in CRC

Dissecting the Vulnerabilities to Conventional Treatment in CRC Though the Use of Patient Derived Organoids

Focus on my research are: 1. the better understanding of the CRC biology in order to identify new therapeutical options for the treatment of CRC; 2. the identification of biomarkers of resistance/sensitivity to conventional treatment in CRC trough the use of preclinical models. To this end, we use CRC organoid models as well as CRC cell lines and PDX and we try to identify mechanisms of primary resistance/sensitivity to conventional treatment by looking into molecular data generated trough WES, RNAseq, Mass Spectometry as well as protein analysis via WB and protein Arrays. The data generated in the preclinical models are then validated in internal and external clinical datasets of patients treated with same drug treatment for which molecular data are available.

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Fields of Research
› Bone healing
› Immune system

Biomarkers of Impaired Bone Healing in 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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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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› Ischemia-reperfusion injury
› Mitochondria dysfunction
› Myocardial ischemia

Autologous Mitochondria Transplantation to Limit Ischemia-Reperfusion Injury

With complex open-heart surgeries requiring the use of the heart-lung-machine, prolonged aortic cross-clamping becomes necessary. Despite efficient myocardial protection, cross-clamping times > 90 minutes may cause significant ischemia-reperfusion injury. This is most likely caused by dysfunctional mitochondria located in the ischemic heart muscle, which can no longer produce energy in form of ATP. The principle of autologous mitochondria transplantation (MitoTx) is to transplant viable, functional mitochondria, isolated from a non-ischemic muscle of the same subject, to the ischemic area, which is at risk of irreversible damage. The transplanted mitochondria could be visualized to integrate into the cardiomyocyte within 1–2 hours over actin-dependent endocytosis and to overtake ATP production, leading to enhanced contractility. The aim of this study is to establish a large animal model on prolonged aortic cross-clamping as realistic and clinically relevant as possible and to furthermore prevent/limit ischemic damage of the heart muscle by MitoTx. Translating this technique into a clinical setting could potentially help many patients.

Primary endpoints in this project are myocardial function / contractility after prolonged aortic cross-clamping measured invasively through a pressure-volume catheter as well as echocardiographically. Secondary endpoints are loss of cardiomyocytes and mitochondria function visualized by histology and immunohistochemistry.

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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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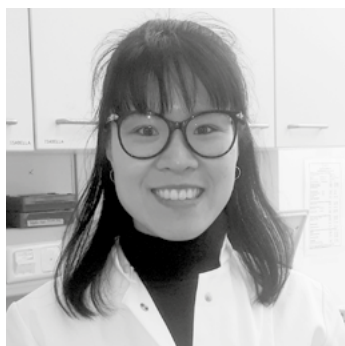
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› Acute-on-chronic liver failure
› Inflammation
› Immunometabolism

Evaluation of Immunometabolism as a Driver of Hepatocyte Immunopathology in Acute-Onchronic Liver Failure

Patients with acute-on-chronic liver failure (ACLF) exhibit a complex immune phenotype ranging from excessive activation of the immune system to immune paralysis. The clinical consequence of this immune dysfunction is increased susceptibility to bacterial infections, which is the most frequent precipitating event of organ failures in patients who develop ACLF. The syndrome is associated with high short-term mortality, and current treatment options are limited to liver transplantation. Whereas cirrhotic patients often present with neutropenia, patients with ACLF characteristically display increased circulating neutrophil and monocyte counts, supporting the view that the innate immune system plays a major contributory role in ACLF pathophysiology. In contrast to their circulating counterparts, information about the immune and metabolic phenotype of tissue-resident immune cells in liver and other organs such as kidney, brain or lungs of patients with ACLF is scarce. Taking into account that patients with advanced liver cirrhosis and ACLF are often situated in the delicate and dynamic balance between exaggerated inflammatory response and

immune exhaustion, it is not surprising that the search for therapeutic targets is cumbersome. Treatment of patients with ACLF thus requires individualized concepts considering the different extent of inflammation and immune dysfunction in each patient. As a prerequisite for devising individualized treatments, this project aims at disentangling the complexity of immune phenotype and metabolic function of circulating and tissue-resident immune cell subpopulations, and to study whether immune cells are able to mediate liver immunopathology. Based on these findings, reprogramming metabolism of immune cells in order to reverse immune cell dysfunction will be investigated as a therapeutic strategy to modify the disease course of ACLF.

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› B-cell mediated Disorders

The Heart as an Endocrine Organ: Chromogranin B and the Inositol-1,4,5-Trisphosphate Receptor in Excitation-Secretion Coupling in 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 car-diomyocytes 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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› Schizophrenia spectrum disorders
› Psychosis
› Negative symptoms

Oxytocin-Augmented Group Psychotherapy for Patients with Schizophrenia

The effectiveness of current treatment options for socio-cognitive deficits and negative symptoms (NS) in schizophrenia spectrum disorders (SSD) remains limited. The cause of NS is thought to be an interference between the mesocorticolimbic dopamine system for social reward expectancy and the network for socioemotional processes. Oxytocin (OXT) may enhance functional connectivity between these neuronal networks. Lower plasma OXT levels correlate negatively with NS severity and deficits in social cognition in SSD. It has been shown that intranasal OXT administration improves social cognition, including empathy, in healthy subjects but in SSD results are inconsistent. According to the social salience hypothesis, the effect of OXT varies depending on the social context and individual factors. Also, OXT-mediated effects on psychopathology, NS, and empathy may depend on genetic variants of OXT receptors (OXTR). In a pilot study, we demonstrated a reduction in NS by OXT administration in a positive social context in SSD. We also demonstrated that NS and other symptoms improved after mindfulness-based group psychotherapy (MBGT). The aim of this study in individuals with SSD is to examine the effect of combining OXT administration with MBGT on NS, empathy, affect, and stress. The main hypothesis to be tested is that the use of OXT compared to placebo prior to MBGT in patients with SSD will result in a greater reduction in NS. The research design is based on an experimental, triple-blind, randomized, placebo-controlled trial. The manualized MBGT sessions are led by two psychotherapists over four weeks. Four sessions take place once a week in a group of six patients. The effects of OXT peak after 30-80 minutes for optimal reinforcement of social behavior. Patients receive 24 I.U. of OXT or placebo intranasally 30 minutes prior to each therapy session. Plasma OXT levels will be determined by radioimmunoassay. To exclude gender bias, both women and men will join mixed-sex groups controlled for hormones. Change in NS as the primary endpoint will be measured with validated interviews (Positive and Negative Syndrome Scale, PANSS) and psychometric questionnaires (Self-Evaluation of Negative Symptoms, SNS). Variables, including plasma OXT levels, will be measured at baseline and post-intervention and the role of genetic variations of the OXTR genes for the NS will be looked at exploratively.

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› Computational Medicine
› Next Generation Sequencing

Single-Cell Multi-Omics in Acute Myeloid Leukemia: From Heterogeneity to Precision Medicine

Acute myeloid leukemia (AML) is a hematological malignancy characterized by the aggressive expansion of undifferentiated myeloid precursor cells in the bone marrow. While effective treatment options exist, a large fraction of patients still experience relapse, often with a lethal outcome. Large-scale studies of the AML mutatome have shown that AML is characterized by a heterogeneous cytogenetic and mutational landscape. Based on the genetic alteration profile of the patient, physicians make an informed decision on whether inductive chemotherapy followed by consolidation chemotherapy is likely to lead to long-term remission or whether allogeneic stem cell transplantation should be favored instead. While current molecular classification systems are becoming more refined and incorporate an increasing number of genetic markers, there is still significant intergroup variability in the different prognostic groups defined in those classifications, with some patients achieving long-term remission through the recommended treatment regiments and others experiencing relapse in as little as a few weeks after treatment conclusion. Furthermore, while our understanding of the disease is increasing there is a lack of new effective treatment options, especially immunotherapeutic approaches, which have found their application in other hematological tumor entities. The absence of immunotherapeutic treatment strategies in AML is a reflection of the high molecular heterogeneity of the disease with consecutively high variability of surface expression markers. This leads to immunotherapeutic responses ranging from complete treatment ineffectiveness to unacceptable cytotoxicity. In this project we aim at characterizing the gene and surface marker expression profiles of all major molecular AML subsets by combining single-cell RNA sequencing with single-cell protein profiling and spectral cytometry. Our main hypothesis states that through this approach we can discriminate between healthy and malignant cells in bone marrow biopsies and in a second step identify surface markers that are highly specific for each molecular subset of AML blasts and can be targeted by immunotherapy.

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› Cancer genetics

Molecular Characteristics of Hormonally Active Neuroendocrine Neoplasms

Neuroendocrine tumors (NETs) consist of cells that exhibit endocrine as well as neural cell characteristics and can occur in every organ; however, they occur most frequently in the gastroenteropancreatic system. During the last decades, their incidence has significantly increased. As they exhibit endocrine features, they are able to secrete hormones (e.g., serotonin), and due to over-secretion, some NETs cause a hormone-related disease. These tumors are called functional neuroendocrine tumors (f-NETs). The hormone-related disease, or functional syndrome, affects the quality of life and leads to a decreased overall survival. It is not known what distinguishes a f-NET from a non-functional one on a molecular level, meaning that the molecular characteristics of the functionality are unknown. This knowledge gap leads to a very limited number of specific pharmaceutical treatment options for the functional syndrome.

The purpose of this project is to uncover genes and their products that determine the functionality of NETs. For this, we will perform whole-genome sequencing and RNA sequencing of functional and non-functional NETs of the small intestine using the BIH OneTouch Pipeline to detect upregulated genes in f-NETs. For validation, these genes will be knocked down in models of f-NETs, and their impact will be assessed by determining the level of secreted hormones (e.g., serotonin). If the knockdown of these genes causes decreased hormone levels, it represents a possible novel target for the therapy of the functional syndrome.

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› ICU Acquired Weakness
› Skeletal Muscle

The Role of Circadian Rhythm Disruption in Critical Illness Myopathy

Circadian rhythms adjust behavior and physiological processes to the 24-hour(h)-light-dark cycle according to the Earth's rotation. Circadian rhythms can be disrupted in septic intensive care unit (ICU) patients. In skeletal muscle, clock genes control several downstream processes, involved in the regulation of muscle mass, function, and glucose metabolism. Pathomechanisms in these downstream processes, have been identified by our research group in Critical Illness Myopathy (CIM). CIM remains an unresolved clinical problem that places a high burden on individuals and the health care system. For the first time, my hypothesis-generating project investigates whether circadian disruption contributes to CIM. In a first reverse translational approach, we will investigate circadian patterns, based on high-frequency 24-h vital-sign and glucose data in ICU patients with CIM compared to ICU patients without CIM. From bedside to bench, we will compare circadian rhythms in gene expression and metabolism in the skeletal muscle in the mouse model of sepsis-induced muscle atrophy and in controls.

Circadian disruption may be a key mechanism for the described CIM pathophysiology downstream of the circadian feedback loop. The identification of novel pathways is of great importance for the development of preventive strategies, which are currently unavailable. The future perspective of the project will be the translation by individualized circadian interventions, such as overnight fasting and dynamic light therapy as innovative systems approaches to prevent CIM and improve outcomes. Circadian medicine is an emerging new field with high interdisciplinary relevance because circadian rhythms influence almost all physiological functions, and are essential for health.

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Explainable Machine Learning to Investigate Tuberculosis Transmission

Tuberculosis transmission is ongoing globally and fueling disease rates, yet drivers of transmission are not well understood. M. tuberculosis displays significant genetic diversity that may enhance disease transmission. As seen with SARS-CoV-2, mutations acquired by a pathogen can lead to enhanced transmissibility. The advent of whole genome sequencing (WGS) added considerable insight into Mtb pathogen diversity and high-resolution transmission inference. Several studies support differential TB transmissibility of the 4 major Mtb lineages. But a definitive and well powered study of the combined effect of host factors and Mtb lineage on transmission is currently lacking. We hypothesize that adding Mtb lineage will improve existing models of TB transmission. Using combined clinical host and pathogen sequence data from New York City, Amsterdam, and Hamburg, we will build a tailored artificial neural network of host and pathogen characteristics. This enables us to study all combinations of exposures and their interactions on TB infection, thereby extending existing statistical models of trans-

mission. Disentangling the combined effects of TB pathogen characteristic and host factors can help stratify exposed contacts into lower and high-risk groups, and thus inform the public health and contact tracing response.

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› Patient Reported Outcomes

Patient Reported Outcome Feedback in Hypopituitarism (PROFiH)

Hypopituitarism, which results from a dysfunction of the pituitary gland, can present with a variety of symptoms ranging from acute, life-threatening adrenal insufficiency to less specific symptoms such as fatigue. Although hormone replacement therapy can be successful in improving clinical outcomes, residual effects such as reduced quality of life, fatigue and pain hypersensitivity have been observed. We hypothesise that incorporating patient-reported outcomes (PROMs) into therapeutic decision-making will positively affect quality of life in patients with hypopituitarism.

This study (Patient Reported Outcome Feedback in Hypopituitarism, PROFiH) will introduce PROM feedback into the pituitary consultation hours at our centre using a complete stepped-wedge clustered randomised trial design. The primary endpoint is PROMIS-33 T-scores, with secondary endpoints including physician actionability, blood hormone levels and hospitalisations.

The digital solutions used are based on the TBase infrastructure, which uses a modern database architecture. The integration of PROMIS into a secure, interoperable platform within TBase will enable effective and secure data collection. The implementation of PROM feedback according to the NIH PROMIS guidelines is expected to result in significant immediate benefits for pituitary patients, who will benefit from more personalised care and improved quality of life.

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› Explainable Deep Learning

Towards Informed-Decision Making in Prostate Cancer Diagnosis on MRI Using Interactive Explainable Deep Learning

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer-related death worldwide. Besides clinical and laboratory biomarkers (e.g. prostate-specific antigen), multiparametric MRI (mpMRI) has recently become another pillar and guideline-approved in the setting of primary PCa diagnosis. Thus, the demand for mpMRI is rapidly increasing, calling for strategies to increase diagnostic capacity and throughput. Meanwhile, mpMRI readings and interpretation require extensive practice and expertise, revealing an unmet clinical need not only for workflow efficiency but also high diagnostic accuracy to explore the full potential of prostate MRI. Artificial intelligence (AI) solutions, particularly deep learning systems (DLS), have demonstrated great potential for automated prostate lesion detection. However, clinical adoption of DLS for PCa diagnosis is still hindered by the lack of transparency in their decision-making process. This conflict has been driven further by international legal frameworks that emphasize the right of clinicians and patients to receive an explanation for the results presented by the DLS. Moreover, guideline-compliant prostate MRI may carry an inherent bias towards overdiagnosis and subsequent overtreatment of clinically insignificant PCa given its high sensitivity but only moderate specificity. Thus, feasible and accurate risk stratifiers are urgently needed to identify patients with an increased risk for clinically significant PCa, who would benefit from a biopsy for diagnosis confirmation and treatment. However, as opposed to other common cancers, the etiology of PCa remains largely unknown and established risk factors are often non-modifiable and non-disease specific. Therefore, the aim of this ongoing research project is to utilize quantitative and qualitative methods to develop a holistic approach for the diagnosis of PCa including radiological, clinical, and genetic data from German multi-center patient cohorts with different PCa risk and prevalence. Specifically, algorithms for xAI-assisted prostate MRI readings will be designed and refined to incorporate textual and visual explanations that may facilitate clinical translation and pave the way for an informed decision-making process. Combined with population-specific risk stratifiers, such tools will be of key importance to boost diagnostic accuracy and workflow efficiency in PCa diagnosis and personalize patient management.

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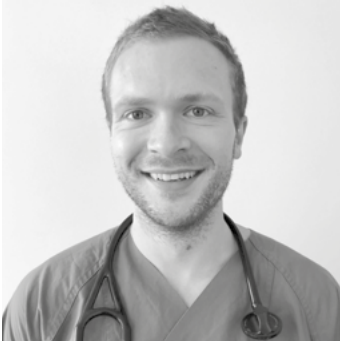
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› Critical Care
› Nephrology
› Data Science

COVID Intensive Care Data Hub (COV ICD)

The introduction of electronic health records (EHRs) in critical care has led to a continuous stream of high-frequency clinical information for all patients admitted to intensive care units (ICUs). This wealth of »big data« offers unprecedented opportunities to gain novel insights into critical illnesses and improve patient care.

However, harnessing the full potential of these datasets presents several challenges. The volume and complexity of the data demand advanced management techniques and a solid foundation in data science. It is essential to develop and implement clinically informed data wrangling approaches to effectively restructure the data.

The objective of the »Charité COVID Intensive Care Data Hub (COV-ICD)« project is to create these strategies while constructing a research database using EHR data from critically ill COVID-19 patients.

The database's structure will be tailored to address specific research questions submitted by a consortium of critical care researchers at Chartié.

The data processing techniques developed within this project will not only be adaptable, but also applicable to future projects that involve EHR data. Furthermore, the database will be made available to clinical research groups throughout Charité, promoting extensive collaboration in clinical research.

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› Neurocritical Care

Quantification of Regional Brain Tissue Water Uptake from Head-CTs after Cardiac Arrest

The aim of this project is to identify and potentially validate a novel, easily accessible diagnostic and prognostic parameter for the reversibility of brain damage after cardiac arrest (CA) that could be used for outcome prediction and therapeutic interventions.

We will investigate comatose patients that had an initially successful resuscitation after CA in this multidiciplinary project in cooperation with the Department of Medical Intensive Care, the Department of Neuroradiology and the Department of Clinical Sciences at Lund University (Sweden).

Selective water uptake of neurons and brain tissue edema are key pathophysiological phenomena of hypoxic-ischemic encephalopathy (HIE) after CA. Although brain computed tomography (CT) is the most used tool to assess the severity of HIE, current guidelines only recommend measuring abnormalities within a single scan without considering changes over time. Recent studies quantifying net water uptake (NWU) in CT imaging of stroke patients have discovered thresholds for the reversibility of brain damage in focal lesions. The evolution of radiodensity in serial CT imaging could be used to quantify regional brain water uptake as a prognostic marker after CA. We aim to do this using an extended version of an algorithm for automated CT analysis from our previous work. We will investigate NWU for a variety of brain regions, and correlate it with neurological outcome and other biomarkers for HIE such as electroencephalography (EEG) and blood markers. For the validation of our results, we will be able to use data from a large international randomized multicenter trial on hypothermia after cardiac arrest (TTM2).

A successful project could facilitate future neuroprognostication through deriving relevant information from an already well-established diagnostic tool.

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› Virtual Reality
› Psychophysiological measurement
› Addictive disorders

Craving Assessment in Patients with Alcohol Use Disorder Using Virtual Reality Exposure

Virtual Reality (VR)- based therapies as a major component of digital mental health applications have received increasing scientific attention for diagnosis and treatment of alcohol use disorders (AUD). AUD cause a substantial burden of disease with worldwide 3 million deaths per year and high relapse rates. Alcohol craving is a major predictor for relapse and a main diagnostic criterion. Craving is associated with psychological and physiological responses and can be induced by presenting alcohol cues (»cue-exposure«). Cue-exposure therapy (CET) is an effective strategy in Cognitive Behavioral Therapy (CBT) to reduce craving, but due to high organizational, timely and financial efforts it has not yet been established in clinical routine. Our research group aims to develop an innovative Virtual Reality-based cue exposure therapy for AUD. This study will examine if the therapy software induces a transient change in craving levels and if this is measurable via subjective and physiological parameters. Data on severity of AUD and craving, comorbidities, demographics, side effects and the feeling of presence in VR will be additionally collected. Patients will use a 3D VR headset to immerse themselves into three different situations (neutral vs. target situations) while heart rate, heart rate variability, pupillometry and electrodermal activity will be measured continuously. This project contributes to the development and careful adjustment of the software and is the first step to clinically validate an innovative VR tool that we plan to use for an effective VR treatment for AUD.

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› Equity effects of digital interventions

Implications of Electronic Patient-Reported Outcome Measures in Psychiatric Care on Recovery Aspects

Psychiatric illnesses can lead to high costs and negatively impact patients' quality of life. Poor continuity of care can exacerbate these issues, leading to decreased adherence to treatment, worsening of symptoms, avoidable re-hospitalizations, and increased costs. In an effort to address these concerns, the use of electronic Patient-Reported Outcome Measures (ePROMs) have become increasingly popular in mental health care. However, many digital health technologies are not integrated into existing care pathways, are stand-alone solutions mainly operated by patients, and focus on light mental disorders. The purpose of this project is to implement an app that supports the outpatient treatment of patients with severe mental disorders. Specifically, a pilot study is conducted to investigate the impact of an app-based symptom monitoring and electronic PROM recording on various aspects of recovery. The study is non-randomized and case-controlled, with 20 patients in each case and control group. The study is conducted over three months at two psychiatric outpatient clinics: Campus Charité Mitte and Theodor Wenzel Werk Berlin.

The outcomes that will be assessed in relation to recovery include quality of life, patient empowerment, daily activities, severity of illness, and hospital readmission. Additionally, the study aims to explore the feasibility of using statistical models such as Bayesian structural time series models to evaluate time series data. The hope is that this app-based intervention will improve outcomes for patients with severe mental disorders, reduce costs associated with avoidable hospitalizations, and provide clinicians with valuable data to better support their patients.

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Utility- and Privacy-Preserving Anonymization of Health Care Data: Developing an Evaluation Framework Focused on Use Case Specific Utility

Access to and sharing of health data provides a huge potential for translational medicine in terms of secondary purpose research, innovation, reproducibility and transparency. It requires technical prerequisites as well as awareness and responsible handling of sensitive data according to European General Data Protection Regulation (GDPR). However, the on-going growth of data availability and linkage with accompanying examples of disclosure attacks in real-world have lead to substantial privacy concerns. This, in turn, makes individuals reluctant to seek care as well as adopt other privacy protective behaviours. Also, privacy concerns by patients and regulators have acted as a barrier to sharing of health data. Against this background, privacy considerations and privacy-enhancing technologies (PETs) are becoming more important.

Modern PETs include anonymization (or de-identification) where data is manipulated in a way that it cannot be related to a person anymore. Manipulation (e.g. via suppression, generalization or randomization) in turn compromises data quality which is typically referred to as privacy-utility trade-off. Anonymization procedures have been optimized in recent years, and open-source software solutions were developed ensuring compliance to statistical privacy models while balancing off against general-purpose data utility. However, it's rather unclear if these metrics translate into actual utility and if there is an application-specific superiority of individual anonymization procedures. These ambiguities make integration into standard data management much more difficult.

Thus, we aim to establish a comprehensive evaluation framework including various dimensions of utility with general purpose but also use case specific metrics. The latter will be based on the German Chronic Kidney Disease (GCKD) study which represents a typical medical dataset with its diversity and complexity. Using the developed framework, we want to evaluate and benchmark differently anonymized datasets. This project will contribute to the growing evidence of successfully deployed anonymization and provide targeted recommendations. This, in turn, will facilitate the integration of anonymization procedures into data providing pipelines.

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Fields of Research
› Computational pathology
› Artificial intelligence

AI-Based Anomaly Detection in Histopathology

Histopathology, the microscopic examination of tissue, has been the diagnostic standard for a wide variety of diseases since its introduction by Rudolf Virchow in the 19th century. Nowadays high-resolution digitalization of tissue-slides enables computer based processing of image data using various methods of computer vision and machine-learning.

So far, research in the field of image analysis in digital pathology has largely been focusing on classification or mutation prediction of the most frequent diagnostic findings. With rare changes, however, the commonly used methods of supervised learning are severely limited because often no sufficient training data is available and the training process of a high number of different rare changes is time-consuming and impractical.

Lately in computer science so-called anomaly detection methods, that allow the identification of data points which deviate from the majority of the data, have been gaining popularity. These methods usually work in an unsupervised or semi-supervised learning manner, eliminating the need for extensive annotations, and can importantly even detect anomalies not present in the training data.

Within the Junior Digital Clinician Scientist Program, I aim to implement a robust method for anomaly detection in histopathological images of gastrointestinal specimen. A functioning anomaly detection system could in the future act as a warning label, informing pathologists of the increased possibility of an atypical finding during sign-out of cases in an understandable way. I think that my proposed approach can substantially decrease the number of missed diagnoses of rare entities and lead to a reduced turnaround time of cases, therefore also increasing the pathologists' efficiency.

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Fields of Research
› Adaptive
› Radiotherapy
› Oncology
› Adaptive radiotherapy

Automatized High Precision Response-Adaptive Radiotherapy with Integrated Patient-Feedback for Lung Cancer

Lung cancer represented the second most common diagnosis of cancer and the leading cause of cancer death in 2020. Primary radiotherapy (RT) with concurrent chemotherapy and consecutive immunotherapy has been established as a major cornerstone in treatment for stage III non-small cell lung cancer (NSCLC). The median 5-year survival rate is 43 % and progression-free survival is only 33 %. However, RT dose escalation to the tumor is limited by the radiation dose to thoracic organs-at-risk (OAR) such as heart, lung and esophagus and treatment-related morbidity. State-of-the-art treatment is performed using image-guided intensity-modulated RT in standard fractionation schemes of 60-66 Gy in 30-33 daily fractions over a treatment course of 6-6.5 weeks. Note that current RT is based on a single computer tomography (CT) image taken prior to therapy planning. Consequently, standard therapy does not take intrathoracic structural and spatial anatomical changes during treatment into account. To overcome this problem, adaptive radiotherapy (ART) has been developed to allow for alteration and individualization of radiation plans according to these changes based on regular imaging and corresponding RT re-planning during the course of treatment to spare sensitive OAR while achieving high tumor control. Currently, imaging data and RT re-planning are not yet integrated in the clinical treatment workflow and only manual, non-systematic and time-consuming adaptations are possible. First proof-of-concept developments suggest that a combination of AI-based image segmentation and autonomous RT treatment planning may overcome this technological challenge. Therefore, the aim of this study is to develop a novel digital workflow by combining new technological advancements for automated repetitive image-guided ART. In addition, physician and electronic patient reported feedback on individual radiation associated current toxicity will be systematically integrated into the process of ART prioritizing and re-planning with the aim of taking a step forward towards personalized cancer treatment. As a first evaluation of the feasibility of the proposed ART workflow a prospective simulation analysis based on CT image data of patients treated for stage III NSCLC with standard RT with curative intention is designed.

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Fields of Research
› Postoperative Delirium
› Multivariate Prediction

Clinical Neuroimaging Data and Electronic Health Care Records for the Prediction of Postoperative Delirium

By using machine learning techniques complex and multidimensional routine healthcare data can be utilized for the individual prediction of postoperative delirium (POD). Delirium incidence after surgery ranges from 5-54 % for different patient cohorts and is associated with high complication rates, prolonged hospitalization and increased mortality. In the literature a variety of serological, molecular and neuroimaging factors have been described to be relevant for the pathogenesis of POD. On the neurobiological level functional connectivity as well as volumetric measures have been associated with POD. However, as the neurocognitive mechanisms behind POD have not been fully uncovered prediction of POD on an individual level remains insufficient. In my project I will use multivariate analyses and include data from electronic healthcare records as well as magnetic resonance brain images from the clinical routine to establish a machine learning algorithm to predict POD. A similar outcome prediction has already been successful in past, where a multivoxel classification algorithm was successful to predict relapse in alcohol dependent patients and future drinking in an independent cohort of young adults (Sekutowicz et al., 2019).

In addition to neurocognitive symptoms, affective and psychotic symptoms occur frequently in POD patients including forms of perceptional disturbances, hallucinations and delusional thinking. Therefore, subclinical to clinical symptoms along a continuum between normal and delusional thinking may account as predisposing factors for the development of POD. To evaluate this hypothesis patients with POD will be analyzed according to their psychiatric comorbidities in routine healthcare data as well as according to their psychosis proneness using validated questionnaires. Taken together, this project aims at a multivariate prediction of POD to pave the way for a clinically applicable practice and get further insight into predisposing factors for POD.

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› Cardiology
› Intensive care medicine
› Emergency medicine

Development and Validation of a Machine Learning Model to Aid Discharge Processes for Intensive Care Patients in the Cardiac Arrest Center – An International, Multi-Center Study

The need for cardiac intensive care unit (ICU) beds remains high in order to monitor and treat emergency patients with severe cardiovascular diseases. Therefore, timely discharge policies from the ICU to normal wards, as well as efficient patient management strategies between intensivists, nurses and care managers have become crucial to meet the continuously increasing demand for ICU beds. Importantly, ICU transfer to the normal ward is considered a high-risk event due to constraints in critical care expertise and equipment on the normal ward which may results in worsening of the patient's clinical condition with readmission to the ICU. The vast amount of daily clinical, physiologic, laboratory and monitoring data in the ICU may overwhelm critical care providers in order to make well informed decisions on patient discharge readiness in situations of constrained capacity. Machine learning (ML) algorithms may provide a timely, systematic and accurate discharge decision support system for intensivists based on comprehensive, multi-dimensional ICU data. We aim to develop and validate a ML-based algorithm which would indicate as to whether a cardiac ICU patient is discharge-ready to the normal ward. On a long-term perspective, we seek to implement the algorithm at the patient bedside to ensure patient safety and enhance efficient ICU discharge policies leading to a net gain of intensive care capacity.

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› Dynamic Computed Tomography
› Radiomics

Evaluation of Wrist Patho-Biomechanics in Inflammatory Joint Diseases with 3D Radiomics Using 4D-CT as Reference Standard

The ever-advancing technical development in the field of computed tomography (CT) is constantly opening up new possibilities for generating additional information. The most modern CT detectors enable the acquisition of images under motion. This allows excellent assessment of both static and dynamic phenomena of three-dimensional objects within a complex anatomy. The carpus is of particular interest for four-dimensional CT (4D-CT or CT cinematography) because certain motion patterns cannot be accurately visualized with conventional cinematographic techniques. Damage to the carpal ligaments has been described for a number of diseases, including inflammatory joint diseases. This structural damage can lead to permanent loss of function and secondary osteoarthritis, which can perpetuate symptoms despite sufficient anti-inflammatory therapy. For this reason, 4D-CT has been developed for the assessment of dynamic, biomechanically relevant stages of carpal ligament lesions and evaluated to the point that it can be used as a noninvasive alternative in this research project. Furthermore, radiomics is of increasing importance in modern medicine, providing imaging-derived biomarkers by extraction of quantitative features beyond human

recognition. Segmentation processes can then be used to generate multidimensional features indicating destruction of the microscopic architecture. In this way, radiomics can contribute to a better understanding of remodeling processes and differentiate ruptures and biomechanical instabilities using 4D-CT as standard of reference. This research aims to further understand the patho-biomechanics of the wrist in patients with inflammatory joint disease using radiomics analysis and to compare these findings with healthy controls.

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Fields of Research
› Drug targeting epigenetic regulators
› Early onset and neuromuscular
  scoliosis
› 5q-spinal muscular atrophy
› Applied Machine Learning in rare
  Diseases

ML-Based Prediction of Scoliosis in SMA in Response to Novel Therapies

5q-spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by the biallelic loss of the SMN1 gene. The absence of SMN1 transcripts leads to an SMN protein deficiency that causes progressive degeneration of anterior motor neurons and muscular atrophy. Patients with severe forms of disease manifestation often lack sufficient copy numbers of the gene paralog SMN2, which also encodes for the full-length SMN protein, but is truncated and rendered functionless through an alternative splicing mechanism.

Groundbreaking research throughout the past three decades has provided us with insights into the molecular genetic basis of SMA. These insights have fueled drug development to treat the underlying cause of this devastating disease: In 2017, the first FDA-approved anti-sense-oligonucleotide, splice-modification therapy nusinersen Spinraza® became available, which promotes the full-length transcription of SMN from available SMN2 genes. In 2019 the first gene replacement therapy arrived, onasemnogen Zolgensma®, which utilizes the AAV9 platform for delivery of SMN1 cDNA. In 2020, the first oral splice modification therapy, risdiplam Evrysdi®, followed.

SMA therapies have shown promising outcomes in increasing survival and improving motor functions in SMA patients. Thus, in December 2020, the Gemeinsamer Bundesausschuss (G-BA) approved the implementation of SMA in extended newborn screening programs, which will take a Germany-wide effect in October 2021.

Researchers, as well as medical practitioners, expect the efficacy of these novel therapies to change the natural history of the patient phenotype. As a result, many disciplines will require updated treatment standards and strategies for SMA-associated sequelae, of which the SMA-associated scoliosis is an essential one.

The objective of this project is to use a Machine Learning approach to predict SMA-associated scoliosis development in response to novel SMA therapies. Our ultimate goal is to provide a helper tool that will help physicians and surgeons in their decision-making during treatment optimization for SMA patients.

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› Machine Learning
› Artificial Intelligence

Artificial Intelligence in Functional Imaging for Individualized Treatment of HNSCC Patients

Head and neck squamous cell carcinoma (HNSCC) represent the sixth most common cancer worldwide. The two curative treatment modalities for patients with HNSCC – primary chemoradiation (CRT) or primary surgery (often combined with postoperative (C)RT) – are both associated with serious side effects. Therefore, further stratification, optimization and personalization of treatment is urgently needed. As novel quantitative image analyses are a promising tool for further risk stratification, we´re training a three-dimensional Convolutional Neural Network on 18F-Fluorodesoxyglucose (FDG) positron emission tomography (PET) imaging and clinical / histopathological data of a multicentric, retrospective cohort of 1200 patients treated with primary CRT and 800 patients treated with primary surgery at Charité and cooperation institutes in order to predict individual treatment-specific outcomes and identify patients with excellent outcome after primary CRT or primary surgery or unfavorable outcome by both. The trained algorithm of the artificial intelligence will be validated in a prospective trial to see if predicted loco-regional control and recommended treatment strategies are reliable. In total 250 curative HNSCC patients, treated with CRT or primary surgery, will be enrolled on this prospective validation trial with observational character, while biomarker, clinical and FDG-PET data are collected from these patients and follow-up visits concluded.

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› Healthcare-associated infections
› Applied infection control

Automated Surveillance of Hospital-Onset Bacteremia

Bloodstream infections (BSI) are among the most frequently occurring healthcare-associated infections (HAI) in German hospitals and complicate the treatment of hospitalized patients. The German Protection against Infection Act (»Infektionsschutzgesetz«) requires all hospitals in Germany to routinely conduct surveillance of HAIs. Conventional surveillance of HAI, or more specifically BSI, requires manual review of patient charts and represents a time-consuming and resource-intensive process. As a result, surveillance of HAI is often limited to only a few areas of a hospital. Automation of certain steps of the surveillance process may represent a viable solution to overcome this limitation.

Our project aims to establish an automated method for the surveillance of hospital-onset bacteremia (HOB) episodes, in which an algorithm evaluates and identifies patients with HOB, based on microbiological and movement data. Due to the presumed high correlation between bacteremia and clinically relevant infection (e.g. sepsis),

and the potential to fully automate the identification process, HOB could serve as a prime example for promoting automated surveillance in Germany.

Given that HOB is different from conventional surveillance metrics, our project not only aims to develop a suitable algorithm for HOB detection, but also to evaluate the clinical relevance of HOB as well as its concordance with conventional surveillance indicators.

The HOB algorithm is intended for application at Charité-Universitätsmedizin Berlin. Once a functioning algorithm and method will have been created and validated, it is aspired to disseminate the method among other suitable hospitals in Germany. The existing surveillance network »KISS« with over 1,000 participating hospitals in Germany, may serve as a basis for a broader dissemination of HOB surveillance.

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Fields of Research
› Automated insulin delivery
› Closed-loop systems
› Dosing algorithms
› Patient-led Innovation

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

Traditionally, patients have been considered passive recipients of therapies provided to them. However, under the mantra »Nothing About Us Without Us«, there is increasing demand for the patient voice to be included in the development of services, products, policies, and educational resources alike. A primary example of this is the #WeAreNotWaiting movement, where a community of people with diabetes created »do-it-yourself« systems for automated insulin delivery. Taking matters into their own hands, this unique community demonstrates how peer support, intelligent computing, and open sharing of information and data combine to push innovation while privacy and safety are not compromised. What initially began as a »hack« has been collaboratively developed by volunteers into open-source systems with predictive algorithms, wide device interoperability and personalized features. As these innovations sit outside traditional commercial and regulatory processes, they understandably create ethicolegal dilemmas, but also opportunities. Anecdotal reports from users suggested various health benefits, but until recently, the rich vein of expertise of #WeAreNotWaiting remained largely untapped by research. To address this gap, an interdisciplinary group of patient innovators founded the EU-,

BIH- and Wellcome Trust-funded OPEN project. Recognizing the need to engage on eye level, OPEN has been instrumental in translating this experienced-based evidence to academia and industry, and vice versa. Over the course of four years, OPEN extensively studied physical health impact, user characteristics and motivations, lived experiences and psychosocial outcomes, but also explored disparities in access to diabetes technology, barriers to uptake and possible solutions. Based on these insights, an international consensus statement was created to provide guidance to healthcare providers and published in The Lancet '100 Years of Insulin' special issue.

While the search for a biological cure continues, technology remains at the forefront of diabetes therapies. As #WeAreNotWaiting is unlikely to be the last bottom-up patient initiative, it is important to determine the lessons learned by all stakeholders involved in development and regulation of medical devices and involve users at all levels and as early as possible. Mutual efforts will help us to finally »close the loop«.

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Fields of Research
› Deep Learning
› 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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› Hematology & Oncology
› Multi-Omics
› Lymphoma Biology
› Machine Learning
› Novel Study Design

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

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma disease worldwide. The standard therapy R-CHOP has a high cure rate in the first-line setting, but relapsed cases have poor survival despite extensive treatment options. To date, there are no clinically relevant risk group biomarkers that can predict therapy efficacy or determine improving therapy additions. Previous studies used static data to try to make predictions and do not take into account changes in tumor tissue that are triggered under therapeutic pressure.

My research is dedicated to the dynamic change of lymphoma disease under therapy in order to enable a better, individualized therapy selection and control in the future. My interdisciplinary project in close cooperation with Prof. Dr. Roland Eils at the BIH Center for Digital Health aims to develop new prediction parameters through a unique and innovative multimodal evaluation approach of combining clinical data, basic tumor biology research and current bioinformatics analysis methods.

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› Kidney transplantation
› Surveillance of immunosuppressed
  patients
› Opportunistic infections

Intersectoral EHealth Concept of Care in Patients with an OPAT

TPatients with certain infections require long-term intravenous (IV) antibiotic therapy, and, as IV therapy is usually only possible at hospital, patients need to stay there although they feel well after a short period. Outpatient parenteral antibiotic therapy (OPAT) is an innovative approach, which enables patients with long-term IV antibiotic therapy, to go home and applicate antibiotics on their own or with help of specialized nurses. However, data silos as well as no or little communication between patients, OPAT-nurses, and doctors lead to complications and misunderstandings. Patients feel alone and some even scared. Doctors are insecure. Thus, only a small group receives access to this modern concept. The current project builds on an existing digital infrastructure with a patient app, electronic health record (EHR) called TBase, and telemedicine team. Aims of this current project are (1) to design a patient journal to support the connection between patients with OPAT and the doctors as well as nurses via an app, (2) to integrate a sufficient »eRezept« compatible to Gematik, (3) to visualize micro-biological test results in the mentioned EHR via logical observation identifiers names and codes (LOINC), (4) to design an app in order to seek questionnaires for patient reported outcome measures (PROMS) via health level 7 (HL7) and fast healthcare interoperability resources (FHIR) and visualization in the EHR via LOINC, and finally (5) to initiate the implementation of SNOMED CT. The patient journey shall, in a first step, be developed in the frame of an explorative and observational study, and, in a second step, be evaluated for usefulness by a multicenter randomized controlled trial.

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› Atopic dermatitis
› Food allergy
› Food provocation

Genome Wide Association Study to Identify Patients at Risk of Severe Anaphylaxis Using Single Nucleotide Polymorphisms

Anaphylaxis is a potentially life-threatening type I hypersensitivity reaction, with an acute onset, that requires immediate therapy with adrenaline. In order to identify patients with a higher risk of severe anaphylaxis (and therefore provide personalized treatment recommendations), reliable biomarkers are sought for. Genome-wide association studies (GWAS) are increasingly used to identify associations between single nucleotide polymorphisms (SNPs) and clinical phenotypes. With the costs of full genome sequencing decreasing and abundance of databases containing whole-genome sequencing data, the technical tools for GWAS are becoming increasingly more accessible. There is an unmet need to identify patients at higher risk of developing severe anaphylaxis in order to provide personalized care recommendations and reduce unnecessary healthcare costs. Based on our recent publication, identifying differences in miRNA profiles of patients prone to anaphylaxis, it is likely that GWAS will reveal differences in SNPs associated with risk of severe reactions.

The project will contribute to our understanding of anaphylaxis processes and may help reveal underlying biological processes that could contribute to anaphylaxis pathomechanisms. Ultimately, if the resulting models could explain who might be predisposed to severe anaphylaxis, this project has a real potential for changing current clinical guidelines on the management of anaphylaxis, and therefore has deep consequences in optimizing personalized medicine approach and reducing healthcare costs.

The project will be developed according to open science and reproducible science principles. The analysis writing process will be version-controlled, and the data will be shared publicly according to Open Data principles and DFG Guidelines on the Handling of Research Data.

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› Photoplethysmographic visualization
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› 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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Enhancing Guideline Adherence in Cardiovascular Disease Treatment Through Automation

Cardiovascular diseases remain a significant health burden, with evidence-based guideline recommendations often failing to translate into real-world practice. This discrepancy results from factors such as adherence to treatment recommendations, dosages, and sociocultural disparities. Our project aims to develop an automated system that identifies and addresses gaps in guideline adherence for patients with coronary artery disease (CAD), heart failure (HF), and valvular disease, focusing on closing the gap between prescribed and guideline-recommended medication. By optimizing treatment regimens and adhering to evidence-based guidelines, our approach can improve patient prognosis, leading to fewer hospitalizations and better survival rates. The main product of this project is an alert system that detects discrepancies in guideline adherence and provides evidence-based recommendations, enabling healthcare providers to make informed decisions and standardize care. Automation in healthcare offers benefits such as reducing human error, saving time, and allowing providers to focus on other aspects of patient care. Through a series of work packages, we will extract relevant guidelines, catalog disease diagnoses, review and adjust alerts for diagnosis and indication, integrate recommendations, and validate the application.

The alert system's adaptability and scalability make it versatile for accommodating updates in guidelines or extending to other disease areas, enhancing evidence-based care in various clinical settings. The successful implementation of this project has the potential to significantly improve cardiovascular disease treatment by ensuring patients receive equitable and evidence-based care. By aligning real-world practice with guideline recommendations, we can reduce health disparities and enhance patient outcomes. In turn, this will contribute to a reduction in disease burden, hospitalizations, and mortality, ultimately improving the quality of life for affected individuals. By leveraging automation and integrating evidence-based guidelines into routine clinical practice, our project aims to make a substantial impact on the management of cardiovascular diseases. The alert system's implementation promises to bring about a meaningful shift in patient care, fostering a more equitable, standardized, and effective approach to managing these prevalent and life-threatening conditions.

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› Postoperative Neurocognitive
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› Multiomics Analysis
› Geriatric Anesthesiology

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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› Hepatology
› Inflammation
› Immunology
› Single-cell genomics

Mapping Single-Cell Dynamics in the Regression and Recurrence of Liver Fibrosis in Non-Alcoholic Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) is characterised by the excess accumulation of liver fat in the absence of other causes of liver steatosis and often progresses to steatohepatitis (NASH) and fibrosis, the latter being the main determinant of patient outcomes, including liver cirrhosis, liver failure and hepatocellular carcinoma. It is now well known that liver fibrosis can regress upon cessation of the causative hepatotoxic injury, but the mechanisms of fibrosis regression in NAFLD and NASH are poorly understood.

We aim to close this gap in our current understanding by applying single-cell Multiome sequencing and spatial transcriptomics to mouse models of liver fibrosis regression and NASH recurrence as well as patient biopsies. This will enable us to provide an in-depth characterisation of the cellular landscape and the mechanisms underlying the regression and recurrence of NASH fibrosis and to describe the specific functional states of involved cell populations. A better characterisation of these mecha-

nisms will help to identify novel therapeutic targets for treating liver fibrosis, and biomarkers for predicting and monitoring treatment responses.

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› Hyperinflammatory syndromes in
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› Immune dysfunction in critically ill
  patients
› Immune stimulation during
  immunosuppression

Telemedicine for Quality Improvement in Diagnosis and Therapy of Hemophagocytic Lymphohistiocytosis

Hemophagocytic Lymphohistiocytosis (HLH) is a rare though life-threatening hyperinflammatory syndrome in which uncontrolled immune activation leads to excessive cytokine release – the so-called cytokine storm. Due to its clinical overlap with sepsis, HLH remains frequently undetected. Mortality rates are high, particularly among critically ill patients (58 %). In a previous systematic review, we could demonstrate that a multitude of therapeutic strategies are applied in HLH patients while current recommendations remain inadequately implemented. Here, telemedicine offers a unique opportunity for research while at the same time improving diagnosis and therapy of HLH. Within this project, we will establish a reference center for national and international consultation requests. In that we concentrate digitally all HLH cases in one center, we will generate a sufficient number of cases to perform robust data analysis. Diagnosis and therapy recommendations are based on current guidelines. For therapy evaluation, daily telemedical visits are carried out from the day of the first consultation. Serious and refractory cases are assessed interdisciplinary by a Charité expert panel.

Moreover, there is an unmet need of targeted therapies. One reason lies in the poorly investigated pathophysiology of HLH. Therefore, we will establish and expand a biobank of cytokine profiles to enable safe diagnosis and causal treatment. Collecting data of a rare disease prospectively will allow us to create a machine learning algorithm which will ultimately support deep disease characterization. The database will be used to develop an app for physicians as a diagnostic and treatment tool. Simultaneously, data will be transmitted via the app for scientific evaluation. Our aim is to reduce in hospital mortality through rigorous adherence to current guidelines. Moreover, we will assess treatment efficacy and develop an HLH severity score to improve classification of HLH patients. This project is the first international study in HLH patients using telemedicine.

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› Hepatology
› Immunology
› Bioinformatics
› Next Generation Sequencing

Deciphering the Inflammatory Microenvironment in Fatty Liver Disease on a Single Cell Level by Single Nuclei RNAseq Analysis

Non-alcoholic fatty liver disease (NAFLD) is a chronic inflammatory liver disease that represents the leading cause of chronic liver diseases worldwide. Without intervention, NAFL may progress to its inflammatory form, non-alcoholic steatohepatitis (NASH), with an increased risk of cirrhosis and hepatocellular carcinoma development. While numerous novel pharmacotherapeuticals have been tested in clinical trials, most have failed to deliver the desired outcomes of steatohepatitis resolution or reversal of fibrosis. The early identification of patients at risk for disease progression is an unmet need while disease-specific mechanisms that drive chronic inflammation in NASH are still enigmatic. Single cell RNA-seq techniques are indispensable for an unbiased approach for the study of gene expression but are challenging in the liver due to its complex cell composition. In our collaborative project we will apply the innovative method of single nuclei RNA-sequencing to decipher the inflammatory microenvironment on a single cell level in routinely performed liver biopsies of patients developing NASH, to identify possible new treatment targets.

By identification of novel non-invasive biomarkers and implementation of machine learning techniques we strive to develop diagnostic and prognostic tools to identify patients at risk for disease progression.

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› Neurology
› Rare diseases
› Digital health
› Remote patient monitoring
› Digital biomarkers

Digital Monitoring for Predicting the Course of Rare Diseases

Patients with rare diseases require highly individualised therapy by specialists, which is often only available to a limited extent. Myasthenia gravis, a chronic autoimmune disease leading to exercise-induced muscle weakness, is in many ways a model disease for rare diseases:

Fluctuations in the course of the disease can lead to severe crisis-like deteriorations if timely intervention is not provided, including adjustment of immunosuppressive therapy.

Through the development of MyaLink, the digital platform for monitoring vital signs and PROMs (patient reported outcome measures) of patients with myasthenia, real-world data can be collected, enabling new insights into disease progression and therapy response. The platform enables communication between doctor and patient and the sharing of data, which can concretely improve care. These effects are to be measured in studies within the framework of the digital clinician scientist programme. In addition, machine learning algorithms will be developed that can detect potential deteriorations. The implementation of such digital biomarkers in MyaLink can then bring direct benefits to patient care by supporting doctors in decision-making and automatically identifying patients at risk of crisis.

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Fields of Research
› Neuro-oncology
› Tumor evolution
› Single cell genomics

Longitudinal Dissection of Glioblastoma Evolution at the Single Cell Level

Glioblastoma is the most common malignant CNS-intrinsic tumor and presents a leading cause of cancer-related death. To date, primary untreated tumors have been well molecularly characterized at the bulk and single cell level, yet glioblastomas inevitably recur despite standard therapy consisting of resection, irradiation, and alkylating chemotherapy, and the cellular and molecular processes underlying their evolution and therapy resistance remain incompletely understood. Previous studies have pointed towards a potential role of non-genetic mechanisms in driving glioblastoma evolution, which encompass adaptive changes in tumor cell states as well as non-malignant microenvironmental factors, that together cooperate to promote tumor recurrence, but cannot be adequately resolved at the bulk level.

In this collaborative project between multiple departments at the Charité, the BIH, and the MDC-BIMSB, we propose to systematically analyze the evolutionary landscape of tumor and microenvironmental cell states in paired clinical samples of human glioblastoma, profiled by single nucleus RNA-sequencing (snRNA-seq) at diagnosis and recurrence following standard therapy. We expect that this work will enable an improved pathophysiological understanding by uncovering the non-genetic dynamics and heterogeneity that underlie glioblastoma evolution, and, via multimodal integration with clinical, molecular, and histological data, guide the improvement of diagnostic and therapeutic avenues.

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› Machine Learning & Neuronal Networks
› Remote Monitoring
› Clinical Decision Support Systems

Intelligent Antimicrobial Therapy Reviewing and Optimizing System (IATROS) – Development and Validation of an Intelligent Antibiotic Cockpit for Nosocomial Infections in Visceral Surgery

Nosocomial pneumonia and urinary tract infections are among the most common hospital-acquired infections in visceral surgery patients with incidence rates reaching up to 20 % and 4 %, respectively. Inaccurate use of antimicrobial therapy increases patient morbidity and contributes to local and cumulative global antibiotic resistance which is already considered a leading medical challenge of the 21st century by the World Health Organization. The goal of the Intelligent Antimicrobial Therapy Reviewing and Optimizing System (IATROS) is to develop and validate an automatic, intelligent solution for guideline-based real-time review and monitoring (S3 and S2k guidelines) of antibiotic therapies after surgical major resections using nosocomial pneumonia and urinary tract infections as proof of concept. This will include real-time support for diagnostic and therapeutic follow-up steps, active and intelligent integration of local resistance patterns, automatic consideration of patient-specific factors in drug selection, and the ability to network simultaneously given antibiotics on the same ward. The hypothesis whether an intelligent antibiotic support system enables a significant quantitative and qualitative improvement in the implementation of antibiotic therapies in accordance with S3 and S2k guidelines will be tested. The primary endpoint is defined as the selection of the administered antibiotic in accordance with the respective guideline recommendation. Secondary endpoints include indication- and patient-specific dosing, timely de-escalation, total duration/guideline-compliant discontinuation of antibiotic therapy, and implementation of additional diagnostic measures as recommended by the guidelines. The technical project implementation includes the generation of a digital patient profile incorporating the real-time treatment course in terms of a digital deep patient representation. In parallel, the decision tree will be digitally implemented in accordance with the S3 and S2k guidelines for pulmonary and urogenital infections. Finally, a prospective, non-interventional, diagnostic accuracy study will be conducted for validation.

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› Computer Vision
› Next Generation Phenotyping
› High Throughput Sequencing

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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› Clinical decision support systems (CDSS)
› Viral Pathogenesis
› Respiratory medicine

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 around, imaging techniques, such as immunohistochemistry, give 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 solving 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 algorithm's decisions would help to gain profound 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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› Machine learning
› Prediction models

Machine Learning Based Imaging of Acute 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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› Schizophrenia
› Bipolar disorder

Natural Language Processing of Digital Communication: the Linguistic Markers of Schizo-Bipolar Disorders

Despite the progress of modern medicine, there is a lack of objectifiable (bio)markers for the diagnosis and individualized therapy of diseases from the schizo-bipolar specrtum. At the same time, patients show periodic changes in language production and comprehension, which are related to the dynamics and acuity of the disorder. Natural language processing (NLP), a rapidly developing branch of artificial intelligence, now offers methods to study natural language production in an automated way. A large proportion of all current daily communication takes place via short text messages in the context of messenger services. Such digital data is particularly interesting because it is naturalistic, ecologically authentic, unplanned, and instantaneous in large quantities. In the current study, I examine the natural language of patient:s from digital text messages obtained through data donation. These data will be used to create a speech corpus (highly structured and annotated database), which will then be used to identify the computational linguistic markers of disorders on the schizo-bipolar spectrum and to extract specific markers that may predict an episode of illness. The findings of this study will contribute to the development of a prototypical tool that allows patients to self-monitor their own speech production and thus enables them to recognize an exacerbation risk in time and thus counteract this risk.

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› Digital Phenotyping
› Precision Pain Medicine

Real-Time De-Catastrophizing: Developing a Just-in-Time Adaptive Intervention for Chronic Pain

Chronic pain is a global health epidemic. Among the psychological aspects that exacerbate pain and contribute to the transition from acute to chronic pain is pain catastrophizing (PC). PC is defined as persistent negative cognitive and emotional response to actual or anticipated pain. There is growing evidence that PC is a promising treatment target in patients with chronic pain. Recent evidence even suggests that focused treatment of PC may replace conventional treatments. However, pain and pain catastrophizing are dynamic processes. This means that these symptoms are constantly changing over time depending on many factors including how the patient feels and whom he is with at that moment. Previous treatment approaches do usually not account for these dynamic changes or interactions. Fortunately, modern digital solutions are making it easier to capture dynamic processes and intervene in specific situations. Just-in-time adaptive interventions (JITAIs) based on high-resolution assessments (Ecological Momentary Assessments, EMA) can provide the best intervention for a person at the best time. Therefore, the aim of the proposed project is to develop a JITAI that can reduce PC in patients with chronic pain (Part 1) and to evaluate the effectiveness of the JITAI in reducing PC in patients with chronic low back pain (Part 2).

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› Tumor immunology
› Germline genetics
› Single cell technologies

Germline Genetics in Anti-Tumor Immunity

Immunotherapy has transformed the treatment of cancer, offering curative potential even in some patients with metastatic disease. However, currently approved immunotherapies, such as the antibody-mediated inhibition of the immune checkpoints PD1/PD-L1 and CTLA4, are not effective in the majority of cancer patients. Thus, a better understanding of the factors that govern treatment response as well as the identification of novel treatment targets constitute urgent public health needs.

Recent studies have uncovered several factors that modulate the response to cancer immunotherapy. These factors include the tumoral mutational burden and host factors, such as the host microbiome. Not surprisingly, the degree of pre-existing anti-tumor immunity also predicts for response to immunotherapy. However, the predictive value of established markers for immunotherapy outcome, such as pre-existing immunity, is not universal: For example, in melanoma patients receiving PD1-inhibition after failing anti-CTLA4 therapy, the degree of T cell infiltration does not associate with therapy outcome. Similarly, tumor mutational burden and the expression of PD-L1 do not predict for treatment response in all cancer types. These findings highlight that our understanding of the factors that determine immunotherapy outcome is limited.

Here we propose to assess the contribution of germline genetics to shaping anti-tumor immunity. We recently found that germline variants of the APOE gene causally modulate anti-tumor immunity in melanoma, suggesting that germline genetics may be an underappreciated factor modulating anti-tumor immunity. We will combine the analysis of large-scale human clinical data with functional genomics screens to identify germline variants that shape anti-tumor immunity. We will validate our findings using in-vitro co-culture and in-vivo systems to ultimately identify novel pathways and biomarkers for cancer immunotherapy.

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› Patientmonitoring and Alarm
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› Implementation Science in Digital Health
› Data-driven Medicine

Intelligent Alarm Optimization for Patient Monitoring – a Machine Learning Approach

The digitization of the healthcare system has progressed rapidly in recent years. However, to digitally transform clinical care processes in the next step, a link is needed between the characterization of individual risks through high-resolution health data and the sustainable user- and patient-centered implementation of digital technologies and systems.

Due to demographic change and the shortage of specialized staff (both in the clinical and IT sectors) the importance of a modern healthcare system and thus, not least, of digital medicine and medical informatics is becoming increasingly evident. In this context, the Hospital Future Act (KHZG), the electronic patient record (ePA) and the Medical Informatics Initiative (MII) can be classified as milestones for the digitalization of care in Germany. Today, however, high-resolution (sensor-based) health data are neither regularly captured nor linked with other medical data, or even used in real time for personalized and predictive medicine in the sense of a

smart hospital. In addition, existing digital technologies in clinical routine cannot develop their full potential due to an often-missing evidence-based implementation and orientation towards the users as well as a lack of digital training of the staff.

In the working group led by Dr. Akira Poncette, these challenges are being addressed to establish highly effective and efficient implementation processes in the context of digital transformation based on existing technologies and ambitions (e.g., modernization of the hospital information system, telemonitoring) in order to create real added value for patients and to enhance staff competencies with digital tools.

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› 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 inflamma-tion in chronic liver and intestinal diseases using quan-titative 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 chol-angitis), 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-indep-en-dent database and provides the basis to train neural networks. This enables identification of the best param-eters 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 dif-ferent 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 bio-markers could be established for stratification of clinical trials and development of new therapies.

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Fields of Research
› Quantitative image parameters
› Non-small cell lung cancer
› 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 individual-ized 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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› Navigated transcranial magnetic
  stimuation
› Brain tumor surgery

Towards an Automated Risk Assessment in Brain Tumor Surgery Using AI-Based Methods: a Pilot Study

Recently, regression tree analysis using data from navigated transcranial magnetic stimulation (nTMS) and diffusion tensor imaging (DTI) has been established to predict postoperative motor outcome in brain tumor surgery. However, clinical application requires human resources, technical requirements and expertise. The aim of this project was to establish an automated pipeline using advanced methods as well as deep learning-based models, providing automated risk assessment for the motor outcome. The automated pipeline is structured as follows: 1) preprocessing of MRI data (skull stripping, co-registration) using Freesurfer, nibabel, ANTs and FSL, 2) automated tumor segmentation using deep learning-based models (Vnet), 3) automated motor cortex segmentation using FastSurfer, 4) preprocessing of DTI data including denoising, gibbs-ringing removal and bias correction using MRtrix3, 5) automated tractography of the CST using TractSeg and MRtrix3 and 6.) automated measuring of the tumor-tract-distance (TTD) and estimating motor cortex infiltration. Automated risk strati-

fication in brain tumor surgery is a use case for standardizing clinical patient care, improving treatment quality, and economizing medical resources. Through the pipeline, more patients will benefit from differentiated preoperative planning that has been shown to lead to better functional and oncologic outcomes, not least by assigning patients to the right treatment pathway (based on their individual risk profile).

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› Remote Patient Monitoring
› Congenital Heart Disease

Digital Care Hub for In-Home Surveillance of Infants with Single Ventricle Heart Disease

One percent of all children are born with a congenital heart defect. Most severe are single-ventricle heart defects (SVHD) such as hypoplastic left heart syndrome (HLHS). Children born with SVHD have been experiencing substantial improvements from compassionate care to long-term survival due to the development of an innovative three-stage surgical palliation. After the first surgery there are physiological challenges that put children particularly at risk for life-threatening events. High mortality rates during this period have led to the implementation of in-home surveillance strategies for early detection of changes that may lead to hemodynamic decompensation. This project aims to conduct a clinical trial with application-based remote patient monitoring of infants with SVHD. Our aim is to avoid life threatening events during in-home surveillance, to improve somatic growth and to optimize heart failure therapy. We will furthermore investigate the adoption of technology and the impact on adherence by the caregivers. Additionally, we aim to investigate a potential reduction of the psychological burden for caregivers and the long-term health-related quality of life of the children reported as patient-reported outcome measures (PROMs).

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Fields of Research
› Digital Medicine
› Image Based Modeling
› Artificial Intelligence/ Machine Learning
› Cardiology

Precision Therapy Planning – Clinical Application of Image Based in Silico Modeling

Valvular heart diseases are one of the most common causes of heart failure that can affect both children and adults. Accurate treatment planning is crucial but can be very challenging especially in complex valve defects such as combined aortic stenosis (AS) and mitral valve regurgitation (MR). To date, clinical guidelines are based on rather indirect parameters such as valve orifice area, heart size or pressure gradients to determine if, and when, an intervention is recommended. However, they do not provide any support as to which procedure will have the best functional effect in each patient. Decision support systems that help the physician not only with the optimal timing but also with deciding which type of intervention provides the best results are therefore of high clinical relevance. The aim of the project is to develop a decision support system that combines AI- and mechanistic models, allowing physicians to interactively simulate treatment strategies and their hemodynamic outcomes for heart valve diseases, including complex cases such as combined AS/MR.

In order to train the AI-based algorithms we will use data from real as well as synthetic patient cohorts. While synthetic data allows to accelerate clinical AI development and application, they also have the potential to include pathophysiological conditions that are rare and therefore often underrepresented in real patient cohorts. With the use of synthetic data, we aim to increase the prediction accuracy of the AI-based algorithms and to facilitate the clinical translation of image-based in silico modeling for a better precision therapy in cardiovascular medicine.

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› Chronic Kidney Disease

Metabolomics-Based Prediction of Chronic Kidney Disease Progression and Frailty

Chronic kidney disease is a major public health problem with a prevalence of over 10 % in the general population worldwide. Patients with kidney disease are at risk of progressive loss of kidney function and premature death. Moreover, patients are often affected by physical and cognitive degeneration which, summarized under the term »frailty«, is a major cause of reduced quality of life, loss of independence, and greater caregiver burden. Consequently, the prediction of kidney disease progression and frailty as well as early detection of high-risk patients is vital for healthcare providers to make decisions about prevention, monitoring, and treatment. This research project aims to use novel scientific methods, such as metabolomic profiling, which is the quantification and characterization of small metabolites found in biological samples. These metabolomic profiles can serve as indicators for the onset or worsening of medical conditions. Kidney function directly impacts circulating metabolite levels and analyzing metabolites could provide insight into subclinical kidney disease and trend of disease progression beyond the diagnostic means currently available. Innovation potential of this research project lies in identifying metabolomics patterns, which have not yet been implicated in kidney disease progression and frailty status. This also provides opportunities for the discovery of novel metabolites, which could extend our understanding of underlying disease mechanisms and could be used in clinical practice as diagnostic biomarkers. Additionally, this project has the potential of building new machine learning-based models to predict kidney disease progression and frailty based on serum metabolites and clinical parameters.

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› Applied Deep Learning/Machine
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Early Prediction of Clinical Deterioration Using Ambient Intelligence in the Pediatric Cardiac Intensive Care Unit

The postoperative intensive care management of patients with congenital heart defects is complex and newborns and infants are particularly vulnerable to postoperative complications. Early detection of clinical deterioration is crucial for reducing morbidity and mortality by timely initiation of treatment. Development of a model for real-time prediction of critical events before they occur could help clinicians to evaluate information and augment decision-making processes. Ultimately, this could lead to a reduction in complications and greater patient safety. The objective of the study is a real-time analysis of movement and perfusion patterns using a high-resolution multispectral camera (visual and infrared spectrum). In addition, routinely recorded parameters and the high-frequency curve data of the vital sign monitor are analyzed with the help of machine learning pattern recognition.

The aim is to use the prospectively collected data to develop a model for the early detection of clinical deterioration after cardiac surgery in newborns and infants, which enables a real-time prediction of the individual patient's risk for cardiorespiratory failure and neurological complications. We plan the research, development, validation and exploratory and predictive modeling on a prospectively collected data set.

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› 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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› Medical informatic

Semi-Automatic Study Infrastructure (SASI) for Intervention Trials in Critical Care

Critical care medicine is focused on providing the treatment for life-threatening medical conditions. Most or the used treatments and interventions however, are not backed by evidence from clinical trials. Most large randomized controlled trials (RCTs) in critical care produced negative results and there is a tremendous unmet need for further studies. Significant challenges for such trails have been recruitment problems with low overall inclusion rates and the labor and cost-intensivness of clinical research. With the increasing digitilization of patient data, digital methods offer unique opportunities to simplify the planning and conduction of clinical trials. The goal of this research project is the development and clinical application of a semi-automated study infrastructure for the conduction of clinical intervention trials in intensive care medicine. The first step is the development of a »Patient-Finder« for real-time identification of eligible study patients by use of the Health Data Platform (HDP). Besides patient identification for prospective trials the Patient-Finder can help in the process of study planning, e.g. to assess the feasibility of a study. Another part of the study-infrastructure is the development of a data pipeline for the automated export of endpoint-relevant data from the HDP into a study database. After implementation of the study infrastructure it will be translated into clinical application by conducting a »simulated trial« and an RCT. We are planning to extend the study infrastructure beyond intensive care medicine to other clinical areas in the future.

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› Precision medicine
› Machine Learning

Predicting the Response to Antipsychotics with Individual Patient Data from Clinical Studies and Machine Learning

The average efficacy of antipsychotics for the treatment of acute psychotic symptoms has been demonstrated by numerous randomized placebo-controlled trials (RCTs) but there appears to be a large heterogeneity in the treatment effects. To date, however, there are no clinically relevant predictors for estimating the individual response to antipsychotics prior to initialization. Based on that, my project aims to develop models for individual prediction of expected treatment response by examining large data sets of clinical trials with modern multivariate data science methods. The Yale University Open Data Access Project (YODA) allows the use of clinical trial datasets for secondary questions, such as the predictors of efficacy of specific therapies and granted me access to the original data of a total of 67 RCTs on antipsychotics with more than 23000 included patients*. Based on these data, I plan to use the wealth of demographic, clinical and laboratory parameters in combination with machine learning to predict the individual response of patients to antipsychotics. If it were possible to predict treatment response with clinically useful accuracy, this would represent, to my knowledge, the prognostic prediction model for psychotic disorders with the most robust data base to date. Significant interaction terms with the type of treatment (antipsychotic or placebo) would inform clinicians in which patients to expect a strong effect of antipsychotics, but also in which patients to expect no improvement with antipsychotic administration. The results could thus have a substantial influence on the prescribing practice.

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Fields of Research
› Electronic patient reported outcomes
› Artificial intelligence
› Mobile health apps

Personalized Recommend Systems to Improve Patient Outcomes

While electronic Patient-Reported Outcomes (ePROs) promote patient-centered care, artificial intelligence (AI) has demonstrated successful applications in detecting unfavorable medical conditions. At the heart of this digital health project, an open-source personalized recommendation system (PRS) was developed that integrated ePROs and AI to improve patient outcomes. This PRS has found implementation in three distinct cases: cancer relapse detection, SARS-CoV-2 risk assessment, and early detection of Mpox (formerly known as Monkeypox) infections. In the first use case, the »OncApp« aids in detecting cancer relapse, crucial for head and neck squamous cell carcinoma (HNSCC) patients, who face a 15-50 % relapse rate. HNSCCs are known for rapid proliferation, and any delay in treatment can lead to stage progression. Machine learning techniques are utilized to detect patterns with the aim of relapse detection at lower recurrent stages resulting in a significant improvement of overall survival in this patient population. For the second use case, the application was launched as »CovApp.« It demonstrated rapid deployment capabilities during the onset of the SARS-CoV-2 pandemic and provided guidance for millions of users. CovApp delivered individualized recommendations based on patient answers regarding COVID-19 testing, severe COVID-19, and vaccination. CovApp increased hospital efficiency by patient preselection and reducing anamnesis time, as patient answers could be scanned directly from the patient's smartphone via QR code. CovApp became part of a larger effort to develop an Data- and AI driven early warning system awarded 12.5 Million Euro by the German Federal Ministry for Economic Affairs and Climate Action. The third use case, the »PoxApp,« was developed in response to the Mpox outbreak in 2022. The app integrated a deep convolutional neural network (CNN), capable of identifying the characteristic skin lesions caused by the Mpox virus. The CNN was trained on 139,000 skin lesion images and could detect Mpox skin lesions at various disease stages with an accuracy of approx. 90 %. The aim of PoxApp was to allow a fast and anonymous way for first assessment of a stigmatizing disease to mitigate the outbreak. These innovative applications underline the potential of the developed PRS in paving the way for personalized, patient-centered care to improve outcomes in multiple fields of medicine.

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Fields of Research
› Stroke
› Computational Medicine
› Multiomics

Identification of Stroke Biomarkers Based on -Omics Datasets of the BeLOVE Study

The Berlin Long-Term Observation of Vascular Events (BeLOVE) is a large prospective longitudinal observational cohort study that is rooted inside the BIH Infrastructure. BeLOVE is aiming to improve prediction and disease-overarching mechanistic understanding of cardiovascular disease progression and outcomes by comprehensively investigating a high-risk patient population with different organ manifestations. It combines the full spectrum of deep molecular phenotyping and deep clinical phenotyping to monitor patients with acute cardiovascular events (including stroke). These cardiovascular events are the leading cause of death and disability worldwide. Patients with a history of a cardiovascular events or multiple risk factors are at very high risk for future major cardiovascular events (MACEs) or death, but substantial uncertainties remain in risk estimation and in our understanding of disease progression. This is particularly true for stroke, a highly heterogeneous disease with different etiologies ranging from cardioembolism and large artery atherosclerosis to small vessel disease.

This diversity translates into a highly variable individual disease progression with wide-ranging risk of poor functional outcomes and of secondary MACEs. The integration of proteomics and metabolomics data together with clinical data will help to identify a stroke population at high risk of poor functional outcome and secondary cardiovascular events. I propose the implementation of a generalizable computational workflow to investigate the O-link proteomics dataset and the metabolomics dataset from the BeLOVE study to identify novel biomarkers that predict long term outcomes of stroke patients. The ultimate goal is to establish a well-documented »gold standard« workflow that integrates pre-processed Olink Proteomics data and Metabolomics data with clinical outcomes. This will not only facilitate biomarker studies for other subpopulations of the BeLOVE study, but also future -omics based biomarker studies at BIH.

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Fields of Research
› Acute respiratory infection
› Common cold
› Picornavirus

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 patient specific 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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Fields of Research
› Breast cancer
› Systems Biology
› RNAseq

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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Reprogramming; Disease Modeling; Regeneration; CAKUT

Forced expression of transcription factors can change the fate of somatic cells, directing them to alternate cell fates in a process called direct reprogramming or transdifferentiation. This technique represents an easy and fast approach for the generation of desired cell types in vitro and in vivo. One practical use of direct reprogramming is in vitro disease modeling. Here, a cellular model, which reflects basic properties of the disease, allows for investigation of the disease-specific phenotype, pathogenesis and potential therapeutic interventions. The derivation of cell sources for reprogramming from affected patients allows for investigation of the disease on a patient-specific genetic background.

Further, overexpression of transcription factors in vivo enables regeneration of tissue lost through injury or disease. This strategy has been proven to be successful in mouse models of myocardial infarction, diabetes and liver fibrosis. In my previous work, we succeeded in generating renal tubular epithelial cells (iRECs) from human and mouse fibroblasts through the overexpression of 4 transcription factors. The resulting cells resembled their native counterparts in morphology, transcriptome, metabolome and function. The main goal of the proposed research is to improve renal reprogramming in order to generate nephron segment-specific renal cell types and to use renal reprogramming for disease modelling and in vivo regeneration. The results will contribute to a better understanding of the transcriptional control of renal cell identity and help deciphering the molecular causes of some forms of genetic kidney disease. Further, renal in vivo reprogramming will explore new avenues for regenerative medicine applications. To reach this overall goal, we will apply novel synthetic biology tools, which we have developed at MIT. This includes genetic reporters of renal cell fate, enabling high throughput screening of candidate reprogramming factors, as well as synthetic genetic feedback circuits to precisely steer the expression level of reprogramming factors. Building on our previous work on congenital anomalies of the kidney and urinary tract (CAKUT), we will employ direct reprogramming to derive renal cells from skin cells of affected patients and investigate CAKUT pathogenesis in a patientspecific manner. Finally, we will use mouse models of fibrosis and ischemia reperfusion injury to test the potential of direct reprogramming to regenerate tissue function in vivo. With this project, we aim to contribute to our understanding of the molecular mechanisms of kidney diseases and establish a novel regenerative approach that may be translated into future clinical practice.

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Fields of Research
› Pediatric liver diseases
› Gene therapy
› In vivo reprogramming, organoids

Healing from Within – Establishing a Code to Create Therapeutic Human Hepatocytes in Situ

The development of regenerative therapies for chronic liver injuries is hindered by limited understanding of genetic and microenvironmental factors driving human hepatocyte function, regeneration and injury-specific resilience. I will address this unmet need and test the hypothesis that such factors can be defined in faithful settings. Therefore, I will identify transcription factors and zonal signals that confer mature hepatocyte function via an in vivo competitive gene selection screen. This will be followed by establishing genes that encode for injury-specific resilience and proliferation without transformation. Human organoid models of liver injury supplement the genetic screen for regenerative factors. Ultimately, I will apply these information on maturity and injury-specific fitness to in vivo reprogramming of hepatocytes in a humanized model of liver injury to establish a regenerative liver therapy strategy in situ.

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Fields of Research
› Image-Guided Ablative Tumor Therapy

The Immune Modulation Effect of Locoregional Therapies and Its Potential Synergy with Immunotherapy

Recent successes in the field of immuno-oncology have generated considerable interest in the investigation of approaches that combine standard of care treatments with immunotherapies. Locoregional therapies (LT) represent attractive candidates for this approach given the potential for immune system stimulation through the large-scale release of tumor-associated antigens (TAA) following LT-induced cell death. In fact, LT-induced necrosis of tumor cells leads to massive release of tumoral neoantigens, facilitating recruitment and activation of dendritic cells into the microenvironment. This effect can be leveraged to transform an immunosuppressive microenvironment that is not conducive to checkpoint inhibitor therapy into an immunosupportive setting, in which systemic therapies might be more effective.

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Fields of Research
› Pediatric Precision Oncology
› Liquid Biopsies
› Diagnostics development

Liquid Biopsy-Based Diagnostics for Pediatric Solid Tumors

The Deubzer laboratory research program addresses the three central monitoring areas essential for optimal personalized treatment of children with high-risk neuroblastoma: (1) therapy response assessment, (2) minimal residual disease monitoring and (3) actionable target identification. The primary aim is to accelerate transfer of liquid biopsy-based approaches to the clinic within these monitoring areas to make clinical phenotypes of residual, refractory and/or relapsed disease predictable. Implementing our molecular techniques to characterize cell-free nucleic acids, proteins, metabolites and exosomes in biofluids is expected to improve patient monitoring, secondary treatment selection and, ultimately, overall patient survival. Liquid biopsies are likely to better reflect spatial intratumor heterogeneity, tumor evolution and drug sensitivities, thereby, greatly contributing to personalized medicine. Our analyses are focused on validating recently identified candidate biomarkers in large patient cohorts and on expanding the existing biomarker portfolio. A newer focus is translating predictive biomarkers/signatures identified in multi-omics data from liquid biopsies into diagnostic kits for clinical application.

We assess test sensitivity in multicenter round robin tests, and measure complementarity in predictive power within the framework of clinical trials. Maintaining, expanding and updating the biobanking infrastructure, technology platforms and data analysis tools supporting the paradigm shift towards personalized care of patients with high-risk neuroblastoma is an underlying essential part of work in the Deubzer laboratory, which we have plans to extend to pediatric patients with other serious and debilitating solid cancers.

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Fields of Research
› Cardiovascular disease
› Cardiometabolic disease
› Atherosclerosis

Identification of Gut Microbiota Related Pathways in Cardiometabolic and Cardiovascular Disease

A growing body of evidence suggests a crucial role of gut microbiota in regulatory processes of host metabolism and cardiometabolic disease development. Recent insights in metagenomic and metabolomic research have led to discoveries of new pathways linking intestinal microbial metabolism of dietary nutrients to metabolic profiles and cardiovascular disease risk. Many of these pathways involve gut microbiota-related bioactive metabolites which impact host lipid and glucose metabolism or directly affect vascular or myocardial physiology, and thereby shape the cardiovascular disease risk. The focus of my research group is the identification of novel gut microbiota-related metabolites which are associated with the cardiovascular disease risk in clinical studies. These metabolites are then further investigated in experimental disease models to decipher their potential causal role in the development of cardiovascular disease. In clinical studies, alteration of their circulatory levels e.g by dietary interventions is tested to explore their potential for modulating disease phenotype. One of the lead candidates is imidazole propionate (ImP), a microbially generated amino acid-derived metabolite which contributes to the pathogenesis of type 2 diabetes. In our current studies, we investigate the effect of ImP on endothelial cell physiology and its role in atherosclerotic coronary artery disease. Moreover, its role in modulating the susceptibility to develop heart failure upon ß-adrenergic stress is currently investigated. My long-term goal is to develop novel concepts based on targeting gut microbial pathways as a potential strategy to prevent or treat cardiovascular disease.

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Fields of Research
› Neuroimmunology
› Cell death
› Neuroprotection

Neurology & Oncology - Neurological Sequelae of Tumor (Therapy)

Neurological sequelae are among the most common side effects of many tumor therapies. They can affect the peripheral nervous system resulting in a mono- or poly-neuropathy (e.g. chemotherapy-induced polyneuropathy, radiation-induced neuropathy) or lead to diffuse changes in cognitive functions (e.g. post-chemotherapy cognitive impairment, radiation-induced leukenchalopathy). In addition, immune-related adverse events (irAE) are becoming more common due to the increased use of tumor immunotherapies such as immune checkpoint inhibitors or cell-based therapies like CAR-T cell therapy. In general, the underlying pathomechanisms of neuro-logical sequelae after tumor therapy are poorly under-stood and often no or insufficient treatment options exist. At the same time, they further reduce patients' quality of life, lead to potentially long-term disability and frequently cause treatment limitations, which directly affect patients' chance of survival. Our research group investigates the molecular mechanisms by which tumor therapies damage the peripheral and central ner-vous system. We use (personalized) induced pluripotent stem cell (iPSC)-based cell and organoid models as well as animal models. Preclinical findings are validated in clinical cohorts, in which we also investigate predictive and disease biomarkers. After identification of target candidates, we conduct interventional trials with a focus on prevention of tumor therapy-associated neurological sequelae (e.g. PREPARE study). Lastly, our group is involved in the design and evaluation of novel infra-structures and interdisciplinary approaches to enhance patient care of cancer patients and cancer survivors.

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Fields of Research
› Surgical oncology
› Hepatobiliary surgery
› Liver cancer

Improving Outcomes in Hepatobiliary Surgery

Felix Krenzien is principle investigator and highly qual-
ified surgical oncologist, currently working full time at
Charité. He is actively engaged in both basic and clinical
research, being funded by the Else-Kröner Fresenius
Foundation and the Innovation Fund of the Federal Joint
Committee. His primary focus is on liver cancer, specif-
ically on the development of early detection methods
and the identification of key factors for progression to
fibrosis and cirrhosis, which are significant risk factors.
In recognition of his exceptional accomplishments in
this field, he was honored with the prestigious Ferdinand
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Fields of Research
› Pediatric stem cell transplantation
› Cellular immunotherapies

Development, Production and Application of CAR-T Cell Therapy for Children with Solid Tumors

My main clinical interest is in pediatric hematopoietic stem cell transplantation (HSCT), where I am an attending physician. This form of immunotherapy was started with the idea that a »new« allogeneic immune system would help fight cancer. An innovative, very promising form of immunotherapy is chimeric antigen receptor (CAR)-T cell therapy, in which patients' immune cells are genetically modified to be able to specifically recognize and destroy tumor cells. I am responsible for the selection, treatment and follow-up of these patients as the principal investigator of all CAR-T cell studies at our center. While great success has already been achieved with CAR-T cell therapy in leukemias and lymphomas, success in the treatment of solid tumors is still lacking.

My scientific focus is therefore on the development and optimization of CAR-T cell therapy for solid tumors. In this regard, my research group focuses on (i) the discovery of novel tumor-specific targets for CAR-T cells, (ii) the enhancement of tumor infiltration ability and improved function/persistence of CAR-T cells in tumors, and (iii) smart therapy combinations that combat resistance mechanisms. As a Clinician Scientist, my top priority is to bring CAR-T cell therapies to patients. Therefore, an important cornerstone in linking my research concept to my clinical focus is to establish a GMP-compliant manufacturing platform for CAR-T cells on site and to build an infrastructure that ensures the safe delivery of these novel cell therapies to patients.

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  Oncology
› Explainable AI
› Research Networks

Quantitative Imaging / Prostate Imaging, Abdominal / Urogenital Radiology

The scientific focus of my laboratory (Quantitative Imaging Lab, www.qilab.org) is on the development, validation and implementation of quantitative imaging biomarkers, validation of structured reporting tools and explanatory machine learning based applications for oncology imaging. In these areas, external funding has been successfully obtained and the results obtained have been published in high-impact publications. Understanding the value of image-based diagnostic tools such as structured diagnostic criteria or automated quantitative analyses including Al-based biomarkers is a complex and challenging task. Not only the technology used, but also high-quality data sets – accurately representing the population under study – are critical and seminal components for exploring the diagnostic and prognostic value of radiologic imaging. Because data quality management is of central importance, a key element of this work is the development of highly specific tools for organizing and annotating the data used. We have incorporated two principles into our Kl-driven biomarker development: (a) rigorous end-to-end validation of findings against radiologist performance and (b) application of explainable artificial intelligence to identify and correct biased models for decision making. Projects planned for the next few years specifically address the implementation of the results obtained to date: (a) work on PI-RADS classification (analysis of PI-RADS classifications, evaluation of new PIRADS versions), which will be incorporated into the classification via broad evaluation (participation in multicenter studies, contribution to ESUR/ACR Prostate Working Group) (b) prototypical implementation and paraclinical validation of the Explainable AI model we developed for prostate MRI diagnostics, focus on end-to-end validation with analysis of the clinical value of the method by translating the models for image-based biomarkers. Further development, expansion and participation in national and international network projects in the field of imaging research is another stated goal. In doing so, we will build on our previous experience, especially in setting up the Germany-wide RACOON network for COVID-19 research, but also the oncological imaging initiatives at national (National Center for Tumor Diseases, NCT, German Network for Personalized Medicine, DNPM) and international level (CHAIMELEON, EUCAIM).

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Fields of Research
› Liver transplantation
› Organ reconditioing
› Colorectal liver metastases

Regenerative Concepts in Transplantation

The success of liver transplantation is limited by the number of available liver grafts, and a relevant number of liver grafts is declined due to quality concerns. The aim of our work is to increase the number of liver grafts for transplantation by applying of concepts from regenerative medicine. We are using ex vivo liver machine perfusion to assess the quality of marginal liver grafts, which are compromised e.g. by steatosis hepatis or by elevated age of the donor, and we are developing strategies for reconditioning of these grafts. We have developed a rodent model of normothermic liver machine perfusion which we are using for dose-response studies, and we are using a rat liver transplant model to assess liver grafts after reconditioning. Moreover, we are developing clinical protocols for quality assessment of marginal or declined liver grafts by machine perfusion to expand the donor pool for transplantation.

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Fields of Research
› Post-stroke cardiovascular
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› Brain-heart interaction
› Cardiac imaging after stroke

Brain-Heart Interaction

Jan F. Scheitz is consultant stroke neurologist and Professor of Clinical Stroke Research at the Department of Neurology Charité in Berlin, Germany and at the Center for Stroke Research Berlin (CSB). Dr. Scheitz is head of the research group »Integrative Cardio-Neurology«. Together with his group, his major research interests include all aspects of Heart & Brain interaction, post-stroke (cardiac) complications, mechanisms and prognostic impact of cardiac troponin elevation after stroke, and use of cardiovascular MRI in acute stroke. His major motivation is to improve clinical awareness of post-stroke cardiac complications, and to promote interactive collaborations between stroke neurologists and cardiologists. He is Fellow of the European Stroke Organisation (FESO) and founding member of the »Heart&Brain Task Force« of the World Stroke Organisation (WSO).

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Fields of Research
› Chronic lung disease
› Diagnostics in Cystic Fibrosis and
  Innovative Therapies

Characterization of Early Cystic Fibrosis Lung Disease and Innovative IITs

Cystic fibrosis (CF) lung disease starts early in the first months of life with structural changes, lung function impairment and neutrophilic inflammation. We established TRACK-CF as a longitudinal cohort (clinicaltrials.gov NCT02270476) to investigate the onset and progression of CF lung disease in infants and children with CF. Clinical data of the deeply phenotyped TRACK-CF cohort will be used in conjunction with blood and throat swab samples of study participants to identify influencing factors (risk or protective ones) of early CF lung disease. To achieve this goal, several approaches are planned: (i) Investigation of the longitudinal relationship between the multiple-breath washout (MBW)-derived lung clearance index (LCI) and findings in magnetic resonance imaging (MRI), graded by a scoring system, to better understand the relationship between functional and structural pathologies in the established TRACK-CF cohort; (ii) relate findings in the course of LCI and MRI scores with microbiological results and clinical findings in the deeply phenotyped TRACK-CF participants; and (iii) investigation of proteomic and metabolomic signatures in blood samples of distinct patient groups with

CF: a) Based on previous results, we will compare frequent exacerbators vs. stable patients, b) patients with extreme phenotypes, and c) children diagnosed following newborn screening (NBS) vs. children diagnosed due to clinical signs of CF. Characterization of potentially avoidable or influencable risk factors for disease progression can help to further reduce disease progression and improve long-term outcomes of patients with CF. Identification of non-invasive biomarkers that have the potential to indicate e.g. a deterioration early will be useful for clinical management. In addition, such biomarkers could be used as endpoints in future studies on preventive therapies. Based on results from a preclinical study in a mouse model with CF-like lung disease, we have already developed an innovative IIT on efficacy and safety of anakinra in people with CF, which we are currently conducting within the German Center for Lung Research, using MBW and MRI as endpoints.

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01.2023–01.2025

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Department of Pediatric Respiratory
Medicine, Immunology and Critical Care
Medicine

Director
Prof. Dr. med. Marcus A. Mall

Fields of Research
› Chronic lung disease
› Infection and diagnostic in lung disease
› Telemedicine

Optimizing Care for Patients with Chronic Lung Disease

In my current role as consultant in the Clinic for Pediatrics m.S. Pneumology, Immunology and Intensive Care Medicine, my clinical focus lies on the outpatient and inpatient care of patients with acute and chronic lung diseases. In this context, our Christiane Herzog Cystic Fibrosis Center with about 400 patients and our outpatient clinic for Primary Ciliary Dyskinesia (PCD) with 100 patients as well as the immunological-infectious outpatient clinic are among the largest centers in Germany. My clinical work allows me a close connection with my scientific focus, which is on pulmonary infections in patients with and without chronic lung disease. In recent years, I have not only contributed to an improved, evidence-based therapy of tuberculosis in children through extensive work on the pharmacokinetics and toxicity of antituberculotics, but also characterized the current management of children with different forms of tuberculosis in low-incidence countries through international collaborations. This highlighted the particular challenge of pathogen diagnosis in patients who cannot produce sputum. In collaboration with the Research Center Borstel (National Reference Center Mycobacteria) we have initiated a study to evaluate the application of an innovative diagnostic method, the so-called »face-mask-sampling«. Based on this, I plan to evaluate this non-invasive diagnostic procedure in other lung diseases such as CF or PCD. In a cooperation with the Max Delbrück Center for Molecular Medicine (MDC) it is further planned to investigate the lung and gut microbiome of patients with chronic lung diseases and to associate it with clinical data. Building on our cohorts, expansion to international cohorts is planned with the addition of registry data. In addition to diagnostics, the adherence of patients with chronic lung diseases to therapy plays a decisive role in the course of the disease and the development of resistance. As part of the multicenter »conneCT CF study«, I am currently evaluating an innovative form of care using coaching and telemonitoring in patients with cystic fibrosis with the aim of improving adherence and thus reducing progressive pulmonary deterioration. The structures and knowledge gained from the conneCT study will be used to evaluate similar forms of care for other chronic lung diseases.

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Index

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Page 40, 46, 48, 63, 85, 87, 111, 134, 173,
179, 196, 197, 201, 203, 216, 217

4, 55, 58, 152	Simone Baar
25, 74	Christoph Weber
91, 109, 110	Birgit Formann
126	Sarah Paff
140	Rene Krempin

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5	STAGEVIEW.DE (Pedro Becerra / Frederic Schweizer)
94	David Ausserhofer
224, 225	Thomas Raflzyk

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84, 146	
176	Michael Gotthardt

Other

20	Götz Schleser
27	Sophie Lehnerer
28	Jespah Holthof
29	Renata Ch. Feldmann
32, 98	Simon Moosburner
34	Goetz Schleser
39, 170	Studioline Photography
41, 112	Studio Monbijou
43	Steffen Fuchs
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53	L. Eigel
56, 80, 83, 135	Foto Kirsch
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90	Steffen E. Künzel
96	Simon Hellwig
104	Thomas Gardner
113	Lea Dietschmann
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116	Fotoladen Mitte (Iris Fischer)
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119	Christian Maier
123	UKE Unternehmenskommunikation Hamburg
125	Katharina Hellwig
128	Dirk Scharf
136	Jenny Graumann
139	Tina Ober
156	Elias Ben Engelhardt
158, 214	Fotostudio Farbtonwerk
161	Jessy Chen
175	apropos_foto
181	iKlicK Fotostudio
183	Cornelia Knaak
186	Michael Goderre
188	Manuel Tennert
193	Marie Burns
199	Hoffotografen
202	Anette Koroll Fotos
208	Andreas Thiel
219	Peter Kierzkowski

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