

BIH Berlin Institute
of Health
Charité & MDC
Turning Research into Health

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The BIH in Transition
2018 – 2020

BIH Berlin Institute
of Health
Charité
Aus Forschung wird Leben

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What Is Translation?



Professor
Axel R. Pries



Translation is the process of **turning research into health.**



Professor
Geraldine Rauch



For me, translation means thinking **outside of the box.**



Professor
Christof von Kalle



Translation transforms scientific discoveries into **benefits for patients.**



Professor
Fabian Prasser



Translation is a **bidirectional process** that **continuously improves** the health system.



Professor
Georg Duda



Translation is the process of **transferring** basic scientific research into new **preventive, diagnostic or therapeutic procedures** for application in humans.



Professor
Christian Drosten



Translation is developing a diagnostic test for the new coronavirus in such a way that it can **immediately be used by labs all over the world.**



Professor
Christopher Baum



Translation is the **transfer of information into action, of knowledge into practice.** This is nicely illustrated by the genetic use of the term, the **translation of genetic information** in the form of RNA into proteins, which ultimately make cellular functions possible.



Professor
Claudia Langenberg



Translation is **science that matters** for patients and population health.



Berlin Institute of Health (BIH)

The BIH in Transition: 2018 – 2020

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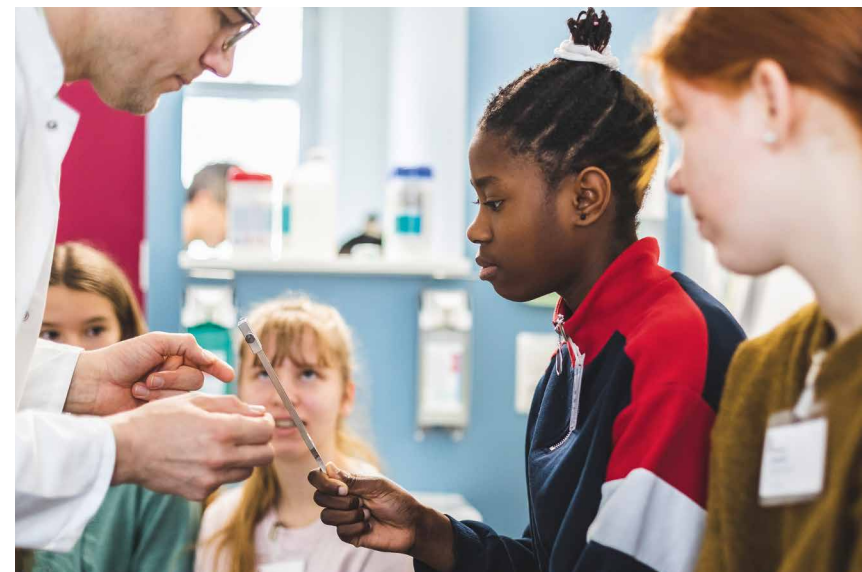
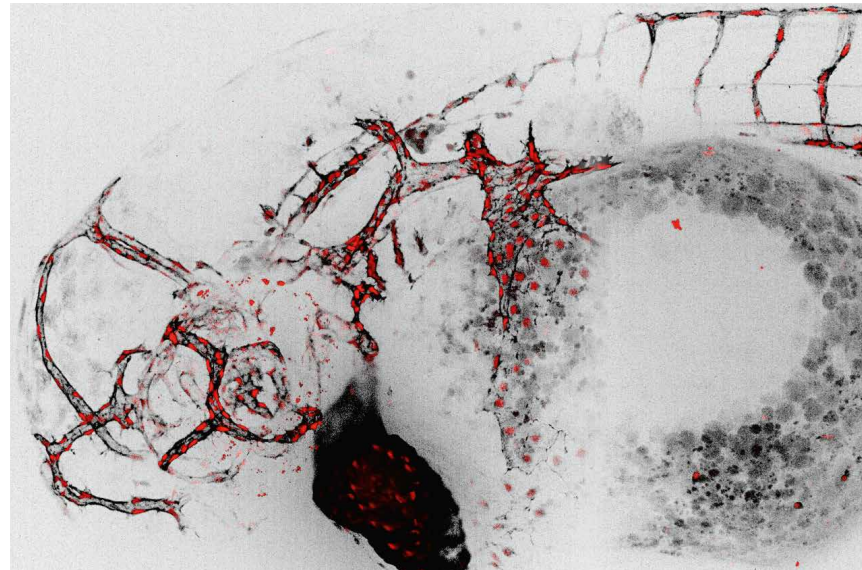
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The BIH: Turning Research into Health.



Professor Christopher Baum
Chair of the BIH Board of Directors and Chief Translational Research Officer of Charité – Universitätsmedizin Berlin



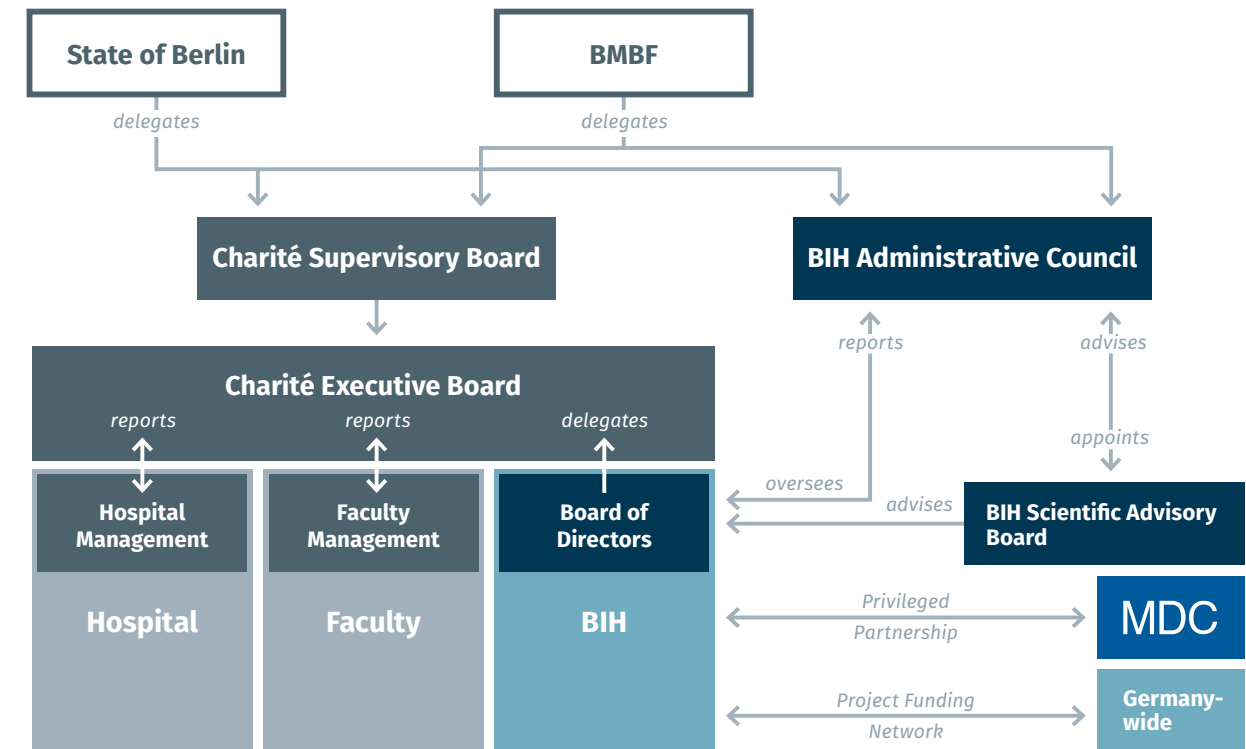
Andrea Runow
Administrative Director of the BIH

Dear Readers,

Since its founding in 2013, the Berlin Institute of Health has not only been constantly evolving but has literally been on the move: Initially housed on the premises of Humboldt-Universität zu Berlin on Luisenstrasse, the BIH's first staff members soon moved to the building of the Federal Ministry of Education and Research on Kapelle-Ufer, and just a few months later rented an entire floor in the Spreepalais near the Berlin Cathedral. The young Institute grew steadily. It wasn't long before the first research groups joined the small administrative staff. In 2014 the Biomedical Innovation Academy with its Clinician Scientist Program opened its doors, followed in 2017 by the BIH QUEST Center. Then BIH Innovations was established as the joint technology transfer office of the BIH and Charité; over time, more and more researchers came on board. Today, the research groups are scattered throughout Berlin at

all Charité sites and locations. It is therefore high time to bring the growing BIH community closer together. Two major BIH construction projects serve this very purpose: On Campus Mitte, the new ATIZ building, where BIH and Charité groups will jointly conduct research, is currently taking shape adjacent to Charité's main patient care facility. On Campus Berlin Buch, the Käthe Beutler Building will be ready for occupancy in spring 2021. Here, BIH and MDC research groups will work together under one roof.

Yet the BIH is also changing in substantive ways. While the Institute was initially founded to speed up the general process of transferring research findings into clinical practice and, vice versa, using clinical observations to develop new research ideas – so-called medical translation – the BIH has since sharpened its

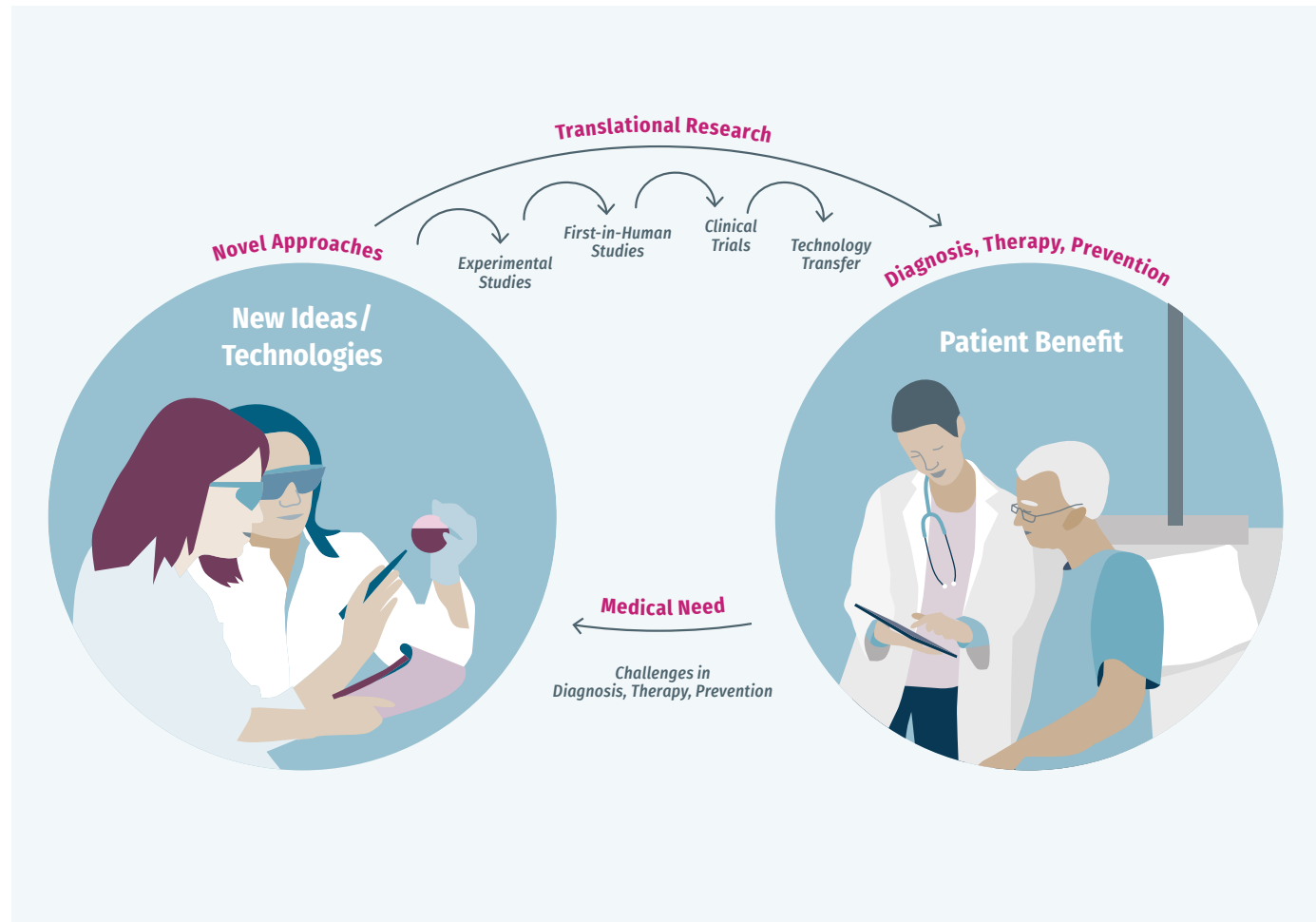


The closer collaboration will be reflected in new administrative structures. As the third pillar alongside the university hospital and the medical faculty, the BIH will be integrated into many processes at Charité. At the same time, the BIH's autonomy will be ensured through its own Board of Directors, its own Supervisory Board (the »Administrative

Council») and a Scientific Advisory Board (SAB). The integration will also mean changes in the already established executive and supervisory bodies of Charité: The federal government will have a seat on Charité's Supervisory Board, and the BIH's Scientific Director a seat on Charité's Executive Board.

mission. We have examined every single step of translation to determine what hurdles exist and how best to overcome them. From this emerged the BIH mission, which consists of three core components: The Innovation Enablers create the structures and the right mindset for translation, while supporting the BIH faculty in all phases of translation. The Translation Hubs provide state-of-the-art technologies, develop them further and link up the community to ensure these technologies are used for translation. Finally, the Focus Areas implement concrete translational research and development projects under the headings »Single Cell Approaches for Personalized Medicine,« »Translational Vascular Biomedicine« and »Regenerative Therapies.«

In order to be able to realize this mission with even greater effectiveness, the BIH has also changed and developed further structurally: From the start of 2021, the Institute has been integrated into Charité as its third pillar. As the so-called translational research unit, the BIH stands on an equal footing with the other two pillars – the hospital and the medical faculty. This brings the BIH even closer to Charité in substantive terms, without losing its second founding institution, the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC). As a Privileged Partner, the MDC will continue to work closely with BIH scientists, jointly advancing research in common areas and contributing new technologies and approaches. As a unique model in Germany's research landscape, the BIH is playing a pioneering role as a federally funded institution within a university medical center. →



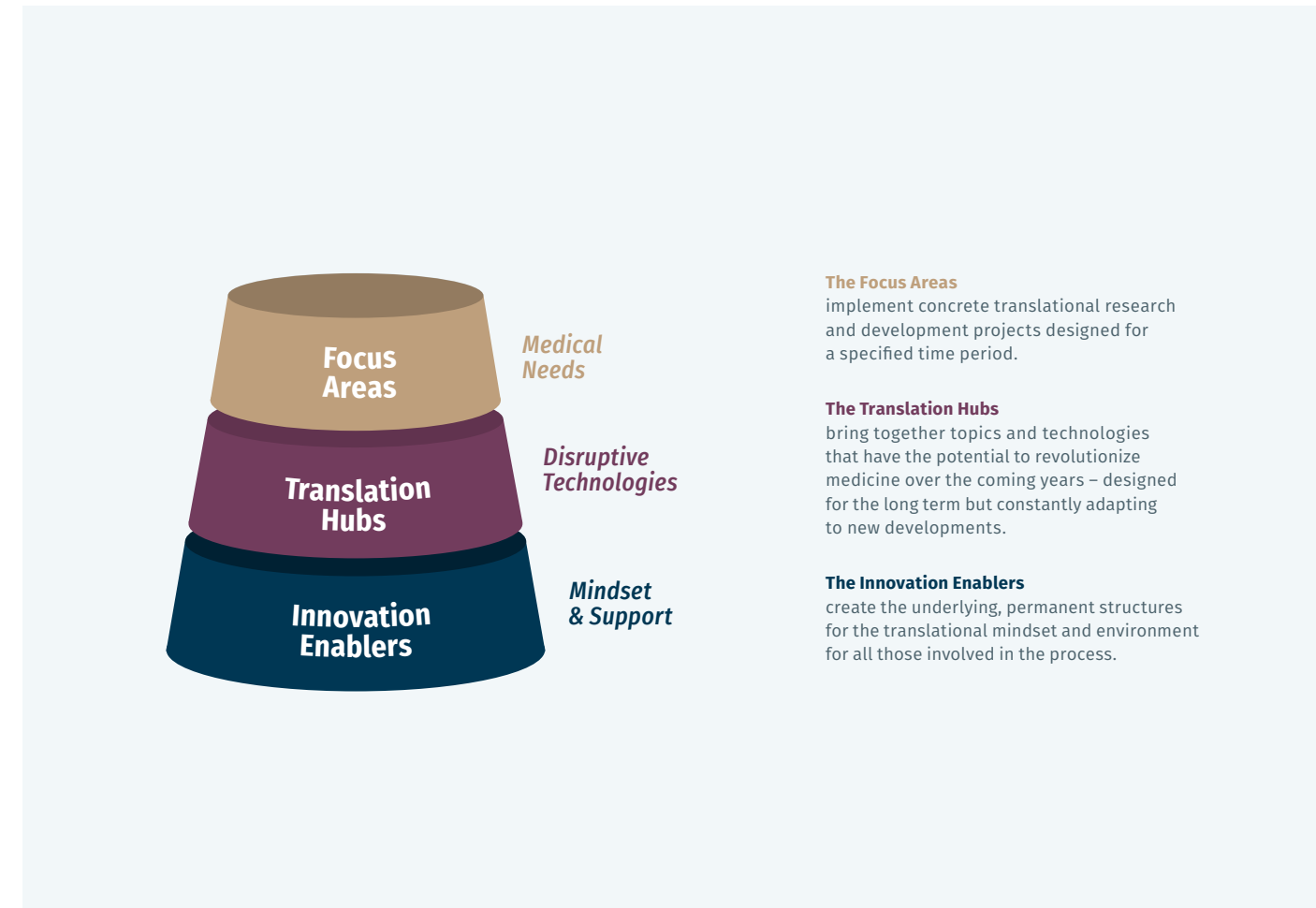
The Translational Value Chain

We are keenly aware of this privileged position and responsibility and will do our utmost to make the greatest possible success out of this opportunity.

Despite facing »turbulent times« on all fronts, which have become even more turbulent due to the coronavirus pandemic, scientists at the BIH have accomplished a great many exciting and important results. They have not only established new technologies, uncovered connections, developed tests and introduced therapies, but have also published study results, programmed health apps and founded their first companies with the BIH's support. We have welcomed numerous new professors to the BIH faculty and launched several new junior research groups. With the BIH Center for Regenerative Therapies (BCRT), we have subsumed an entire institute, and by incorporating the German Stem Cell

Network (GSCN) into the BIH, we have strengthened our ties throughout Germany. As a result, we are well prepared for the next step: The Berlin Institute of Health will in the future also support promising translational projects outside Berlin and thus assume a leading role in medical translation nationwide. To this end, we have established the Excellence Fund as another pillar of our mission.

We would like to take this opportunity to thank the many supporters of the BIH who have been a reliable and enduring source of support, even and especially in times of change. First and foremost, the Federal Ministry of Education and Research and the Berlin Senate Chancellery – Higher Education and Research for their constant financial support and their efforts in integrating the BIH into Charité. Stiftung Charité and



The Components of the BIH

The Focus Areas

implement concrete translational research and development projects designed for a specified time period.

The Translation Hubs

bring together topics and technologies that have the potential to revolutionize medicine over the coming years – designed for the long term but constantly adapting to new developments.

The Innovation Enablers

create the underlying, permanent structures for the translational mindset and environment for all those involved in the process.

the Einstein Foundation Berlin for generating considerable scientific momentum and providing special funding for exceptional projects. The various board members of the BIH, Charité and the MDC for the personal commitment they have made to the BIH Executive Board, in particular Professor Axel Pries, who led the BIH from August 2018 to September 2020 as interim Chief Executive Officer alongside his role as Dean of Charité.

And so, even in times of change, the BIH remains true to its motto: Turning Research into Health. In the following, we have compiled a number of milestones from the eventful past few years. These are, of course, only highlights and are not meant to be exhaustive. We therefore cordially invite you to learn more about the BIH at bihealth.org or to keep up to date on what is

going on at the BIH by subscribing to our newsletter or following us on Twitter at [@berlinnovation](https://twitter.com/berlinnovation). We appreciate your interest in our Institute.

*Best regards,
The BIH Board of Directors*

*Christopher Baum
Andrea Runow*

Key Events of 2018

01.02.

Marcus Mall strengthens translational lung research in Berlin



Professor Marcus Mall takes up the Professorship for Pediatric Pulmonology and Immunology at Charité, a position made possible through the support of the Einstein Foundation Berlin and the collaboration with the BIH.

01.02.

»E-health pioneer,« Professor Sylvia Thun, comes to Berlin



The medical IT specialist, Professor Sylvia Thun, joins the BIH as Director of eHealth and Interoperability.

01.04.

Irina Lehmann becomes BIH Professor for Environmental Epigenetics and Lung Research and sets up the Molecular Epidemiology Lab



01.04.

Roland Eils becomes founding director of the new BIH Digital Health Center



01.06.

Translational bioethics expert Daniel Strech joins the BIH QUEST Center



Daniel Strech assumes the new Professorship for Translational Bioethics at Charité and sets up a lab at the BIH Quest Center.

13.07.

The neuroinformatics platform The Virtual Brain becomes part of the EU's Human Brain Project



Professor Petra Ritter heads The Virtual Brain within the Human Brain Project, an EU-funded FET Flagship initiative.

18.10.

ERC Synergy Grant for Professor Robert Gütig



Robert Gütig teams up with researchers at the BIH, Charité, Humboldt-Universität zu Berlin and the University of Geneva to study how games influence the learning processes of the brain.

18.10.

Cornerstone laid for the Käthe Beutler Building



In 2020 BIH and MDC researchers are slated to move into the Käthe Beutler Building on Campus Berlin Buch, where they will work together on developing new personalized therapies for chronic diseases.

11.12.

Digital Clinician Scientist – Innovative career paths in academic medicine



Charité and the BIH launch the Digital Clinician Scientist Program, an extension of the successful Clinician Scientist Program that is having an impact throughout Germany.

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Key Events of 2019

01.01.

Andrea Runow is the new interim Chief Financial Officer of the BIH



At the start of 2019, Andrea Runow becomes Head of Finance and Controlling and interim Chief Financial Officer and Executive Board member of the BIH.

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01.01.

BIH strengthens translational research: Professor Frank Konietschke sets up a junior statistics group at the BIH and Charité



On January 1, 2019, Frank Konietschke takes up the Professorship for Statistical Methods of Translation and of Early Clinical Studies at the BIH and Charité.

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27.03.

Professor John Ioannidis of Stanford University comes to Berlin as an Einstein BIH Visiting Fellow



John Ioannidis comes to the BIH as an Einstein BIH Visiting Fellow at the BIH QUEST Center – funded by Stiftung Charité and the Einstein Foundation Berlin – to establish METRIC-Berlin, the European branch of his Stanford-based METRICS research center.

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01.02.

Christine Goffinet studies the language of viruses



Since February 2019, Christine Goffinet has been the BIH Professor of Virology at the BIH and Charité's Institute of Virology, where she conducts research on HIV and the chikungunya virus, an »emerging« virus that has spread to Europe as a result of global warming.

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01.06.

Christof von Kalle becomes BIH Chair for Clinical Translational Sciences



On June 1, 2019, the cancer expert Professor Christof von Kalle takes up a tenured Professorship in Clinical Translational Sciences at the BIH and Charité..

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02.07.

New BIH Podcast – Turning Research into Health

In the new BIH Podcast »Turning Research into Health,« scientists at the BIH, Charité and the MDC answer questions about public health and health research.

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19.07.

BIH congratulates the Berlin University Alliance and looks forward to further collaboration

In the Berlin University Alliance's successful application in the German Excellence Strategy competition, the BIH QUEST Center co-writes the section on quality and value of research.

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12.09.

Israeli innovations for Berlin patients – Charité, BIH and Israel collaborate

Charité and the BIH team up with the Israel Innovation Authority to improve patient care through innovative healthcare ideas.



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10.07.

Administrative agreement signed on integrating the BIH into Charité

On Wednesday, July 10, 2019, Federal Research Minister Anja Karliczek and Governing Mayor of Berlin Michael Müller sign an administrative agreement between the federal government and the State of Berlin that lays out the details for the integration of the BIH into Charité.



01.09.

»Data privacy builds trust!«



Fabian Prasser takes up the BIH Professorship for Medical Informatics at the BIH and Charité.

02.12.

Wellcome Trust establishes first translational partnership in Germany – with the BIH and Charité

The BIH and Charité are the first institutions in Germany to receive funding to create a translational partnership with the UK-based Wellcome Trust.



Key Events of 2020



05.02.

Single cells go clinical – BIH, MDC and Charité launch a new research focus

The three Berlin research institutions start to collaborate on single cell analysis.

19.03.

Medical data to speak a common language in the future

All university hospitals across Germany come together under the Medical Informatics Initiative (MII) to establish interoperable digital infrastructures and also agree on a common language: the international terminology standard SNOMED CT.

26.05.

Germany-wide standards for coronavirus data



With the BIH playing a leading role, stakeholders from all parts of the healthcare system join efforts under the Corona Component Standards (cocos) Initiative to establish common data formats and standards for data related to COVID-19 and SARS-CoV-2.

27.02.

Digital collaboration on rare diseases

Twenty university hospitals and other partner institutions join forces across Germany under the CORD-MI (Collaboration on Rare Diseases) project to improve patient care and research in the field of rare diseases.

31.03.

BIH and Charité stand together against the virus: Digital clinician scientist creates coronavirus app



Dr. Alexander Thieme, a fellow at the BIH Biomedical Innovation Academy, develops an app that determines a person's risk of becoming infected with the novel coronavirus SARS-CoV-2 and speeds up the examination process at testing clinics.

20.07.



Research and clinical care under one roof: BIH and Charité hold topping-out ceremony for ATIZ building

The existing building, which formerly housed surgical, intensive care and emergency units, was gutted for reconstruction and will in the future be used jointly by the BIH and Charité.

01.09.

Claudia Langenberg, BIH Professor of Computational Medicine, strengthens data-driven medicine at the BIH



The genetic epidemiology expert and public health specialist examines the molecular mechanisms of metabolic diseases such as type 2 diabetes using

big data from international patient and population studies.



23.09.

National Center for Tumor Diseases is coming to Berlin

Charité's application, which involves close cooperation with the BIH and MDC, is successful: Berlin becomes one of four new NCT locations alongside Heidelberg and Dresden.

01.08.

Michael Potente bolsters vascular research at BIH, Charité and MDC



With the appointment of BIH Professor Michael Potente, the BIH, Charité and the MDC further strengthen their joint Focus Area »Translational Vascular Biomedicine.«

01.10.



Professor Christopher Baum becomes new Chief Executive Officer of the BIH, succeeding Professor Axel R. Pries, who held the position for two years in an interim capacity alongside his role as Dean of Charité

01.11.

Georg Duda becomes BIH Chair for Engineering Regenerative Therapies



The expert in biomechanics and regenerative medicine will further develop and expand the Focus Area »Regenerative Therapies,« with a special emphasis on advanced therapies.

31.12.

All preparations are complete: On January 1, 2021, the BIH is integrated into Charité as its translational research unit

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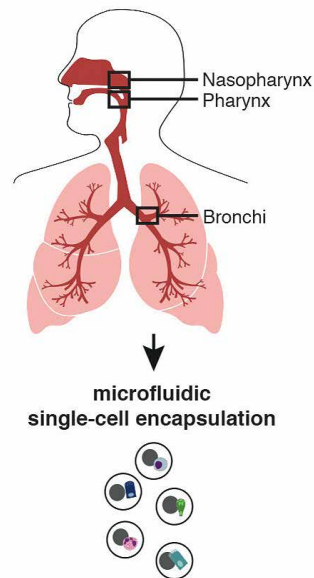
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Coronavirus Research at the BIH

The dangerous dual role of the immune system in COVID-19

Infection with the novel coronavirus SARS-CoV-2 follows a highly variable course: Some of those infected do not even notice it, while others become so seriously ill that their lives hang in the balance. Scientists led by Professor Roland Eils, BIH Chair for Digital Health at the BIH and Charité, and colleagues from Leipzig and Heidelberg have discovered that the immune system has a decisive influence on the progression of the disease. Using single cell analyses, they discovered that epithelial cells affected by the virus issue a »distress call« to the immune system. However, migrating immune cells occasionally overshoot the mark and, due to their excessive reaction, sometimes cause greater damage than the virus itself. The researchers have published their findings in the journal »Nature Biotechnology«.



Germany-wide standards for coronavirus data

Scientists across Germany are studying the novel coronavirus SARS-CoV-2, and the disease it causes, COVID-19. It is now important to bring together the findings and facilitate their collaborative use. Stakeholders from all parts of the healthcare system have therefore joined forces under the Corona Component Standards (cocos) Initiative. Representatives from the BIH – in particular Professor Sylvia Thun, Director of the Core Unit eHealth and Interoperability, and Professor Christof von Kalle, BIH Chair for Clinical Translational Sciences – have been playing a leading role in these efforts. The aim of the initiative is to establish common data formats and standards for data related to COVID-19 and SARS-CoV-2. University hospitals have agreed on a German Corona Consensus (GECCO) Data Set for use in the national network against COVID-19.



BIH Professor Christian Drosten recognized for exceptional communication

During the coronavirus pandemic, BIH Professor Christian Drosten, who is Director of the Institute of Virology at Charité, has been regularly informing the public about every aspect of the pandemic. His Corona Update podcast enjoyed particular popularity. In the podcast, Drosten talked to NDR science journalist Korinna Hennig about the latest developments in the pandemic and new insights into the virus. In April, Drosten received a one-time Special Award for Outstanding Science Communication in the COVID-19 Pandemic from the German Research Foundation (DFG) and the Stifterverband. During 2020 Drosten also received a Grimme Online Award, the Deutscher Radiopreis, the Honorary Award for Outstanding Communication from the Bundesverband der Kommunikatoren – and was even given an Order of Merit of the Federal Republic of Germany by the German president himself.

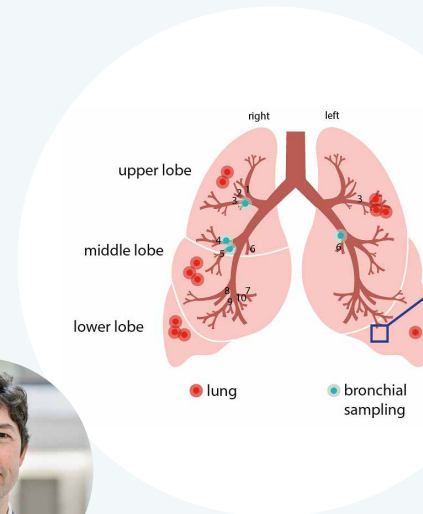


Hot meals for healthcare heroes

Dr. Elise Siegert, spokesperson for the BIH Charité Clinician Scientist Program and junior doctor in Charité's Department of Rheumatology and Clinical Immunology, has started a fundraising campaign that provides COVID frontline workers in Charité's emergency rooms and intensive care units with a free meal each day. In its first month, the campaign raised more than €50,000.

What cells does the coronavirus attack?

Scientists from the BIH, Charité and the Thorax Clinic at Heidelberg University Hospital have examined which cells of the lungs and bronchi are targets for novel coronavirus (SARS-CoV-2) infection. They found that the receptor for this coronavirus is abundantly expressed in certain progenitor cells. Armed with this knowledge, researchers and physicians can develop targeted therapies. The scientists have published their findings in »The EMBO Journal«.



Digital clinician scientist creates coronavirus app

In spring, Charité published an app that allows people to take a questionnaire to determine their personal risk of becoming infected with the novel coronavirus SARS-CoV-2. Those in need of testing can then scan in their answers at the testing clinic to speed up the examination process. The app was developed by Dr. Alexander Thieme, a participant in the Digital Clinician Scientist Program of the BIH Biomedical Innovation Academy.



Focus Areas

The BIH has established three Focus Areas – Single Cell Approaches for Personalized Medicine, Translational Vascular Biomedicine, and Regenerative Therapies – in which concrete translational research and development projects are implemented.

The Focus Areas pursue a systems medicine approach, are fundamentally dynamic and are continuously adapting to scientific, technological and translational developments.



Single Cells Go Clinical

The BIH, the Berlin Institute for Medical Systems Biology (BIMSB) of the MDC, and Charité have launched a joint research initiative. Its aim is to use innovative single cell technologies to answer clinical research questions.

In 2018, the journal *Science* named new technologies that can be used to analyze individual body cells its »Breakthrough of the Year« citing three landmark publications of BIMSB scientists. For the first time it was possible to break down entire organs, tumors, even entire insect larvae into individual cells, measure their gene activity, and – with the help of high-performance computers and artificial intelligence – reassemble these individual cell analyses to form the entire organ or organism.

»It was as if we had invented a super-microscope with which we could suddenly look inside every cell in a tissue, all the cells at once, and see what was going on at the molecular level inside the cell – for example, when and why it gets sick,« Professor Nikolaus Rajewsky explains. He is the Scientific Director of the Berlin Institute for Medical Systems Biology (BIMSB) at the MDC, which has played a major role in the development of single cell technologies through various projects. Rajewsky and Professor Angelika Eggert, Director of the Charité's Department of Pediatric Oncology and Hematology, are the spokespersons for the BIH's Focus Area »Single Cell Approaches for Personalized Medicine.«

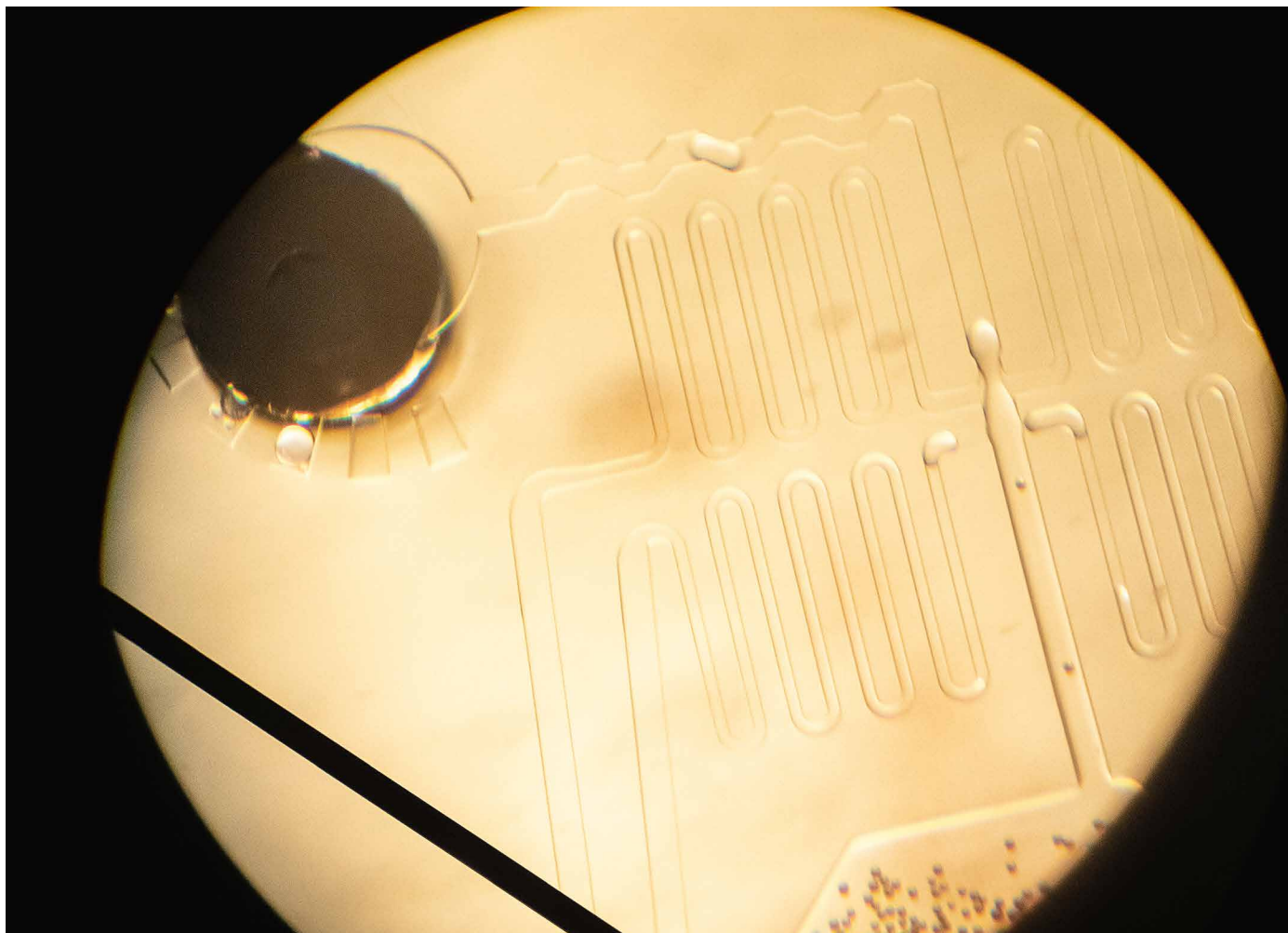
State-of-the-art technologies for clinical use

At the core of the new Focus Area are four new junior research groups, whose leaders were selected in a competitive international recruitment process. Dr. Leif Ludwig, who comes to Berlin from the Broad Institute



This picture shows the four junior group leaders and the heads of the single cell program: from left to right, Ashley Sanders, Angelika Eggert, Stefanie Grosswendt, Nikolaus Rajewsky, Leif Ludwig and Simon Haas.

in Cambridge, Massachusetts, will study with his group how the development and function of stem cells is linked to the DNA of their »cellular power plants,« the mitochondria. Dr. Simon Haas comes from the German Cancer Research Center in Heidelberg and will use cancer stem cell analysis to investigate the origin of leukemia diseases in a targeted way. Dr. Stefanie Grosswendt from the Berlin Max Planck Institute for Molecular Genetics wants to find out which cell types and processes from embryonic development play a →



Enlarged view of a microchip: Individual cells are captured in tiny droplets for further processing.

role in the pathologies of certain cancer types. Dr. Ashley Sanders is Canadian and comes from the European Molecular Biology Laboratory in Heidelberg and will research how new mutations arise in individual cells and drive different characteristics within an organ or tumor.

The junior research groups will be located at BIMSB, and thus in close proximity to Campus Charité Mitte. At BIMSB, they will have access to the latest single cell methods and systems biology expertise. Each junior research group will also work closely with a clinician at Charité, helping to develop single cell technologies for real-world medical issues and clinical application. Ashley Sanders will collaborate with Professor Britta Siegmund, the Director of Charité's Department of Gastroenterology, Infectiology and Rheumatology.

Angelika Eggert will be the clinical partner of Stefanie Grosswendt. Simon Haas and Leif Ludwig will team up with the Directors of Charité's Department of Hematology, Oncology and Tumor Immunology, Professor Lars Bullinger at Campus Virchow-Klinikum (CVK) and Professor Ulrich Keller at Campus Benjamin Franklin (CBF).

»I believe that cancer research in particular will benefit from the new single cell technologies,« Eggert says. »That's because tumors are not made up by one type of cells, but are often a very heterogeneous mixture of distinctly differentiated cancer cells, connective tissue cells, blood vessel cells and immune cells. The more precisely you know the cellular composition of a tumor, the more specifically you can target your strategies to combat it.«



Nikolaus Rajewsky

»It was as if we had invented a super-microscope with which we could suddenly look inside every cell in a tissue, all the cells at once, and see what was going on at the molecular level inside the cell – for example, when and why it gets sick.«

»The more precisely you know the cellular composition of a tumor, the more specifically you can target your strategies to combat it.«



Angelika Eggert

The beginning of a »Cell Hospital«

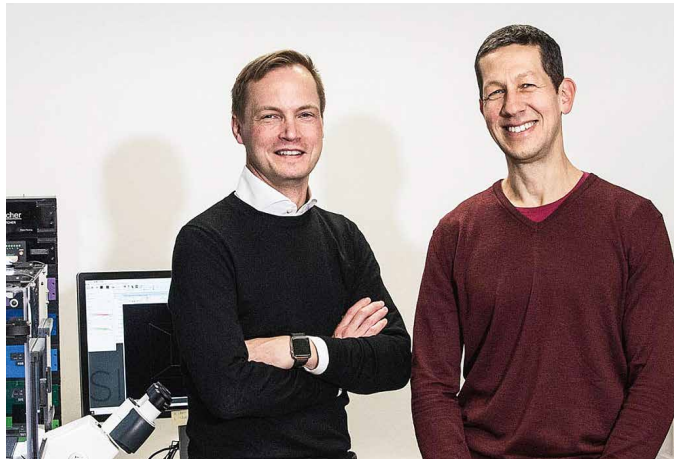
»I am very pleased and also a little proud that we were able to bring these amazing young people to Berlin,« Rajewsky says. At the same time, they could hardly miss up such a unique opportunity. While the researchers can gain an in-depth understanding of the molecular details, the partnering physicians assess the clinical relevance of the findings and provide the researchers with insights into pathologies that single cell technologies could potentially elucidate.

»I therefore consider this initiative to be the beginning of a »Cell Hospital« in which the basic research of the MDC/BIMSB, the clinical research of Charité and the translational research of the BIH are brought together,«

Rajewsky explains. »The idea is not only to understand the mechanisms that cause cells to become diseased, but also to discover these cells early enough to restore them to health before a disease takes such a hold that it can only be treated with great difficulty – or invasively and expensively. I am sure that we will make significant progress for at least some diseases.« •

Understanding Blood Vessels

Cardiovascular diseases are still one of the most frequent causes of death worldwide. Scientists in the Focus Area »Translational Vascular Biomedicine« are investigating the role blood vessels play in these diseases.



Michael Potente (left) and Holger Gerhardt are investigating the role blood vessels play in the onset of cardiovascular diseases.

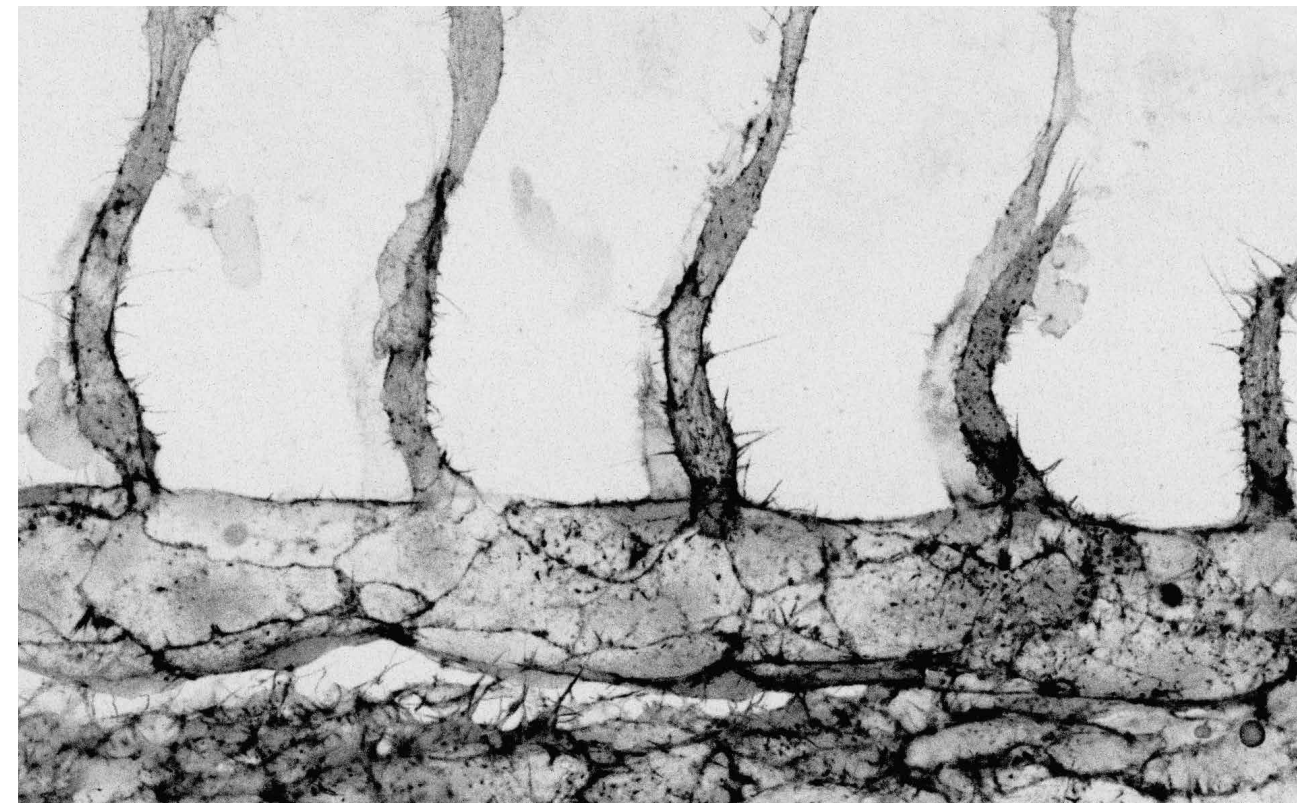
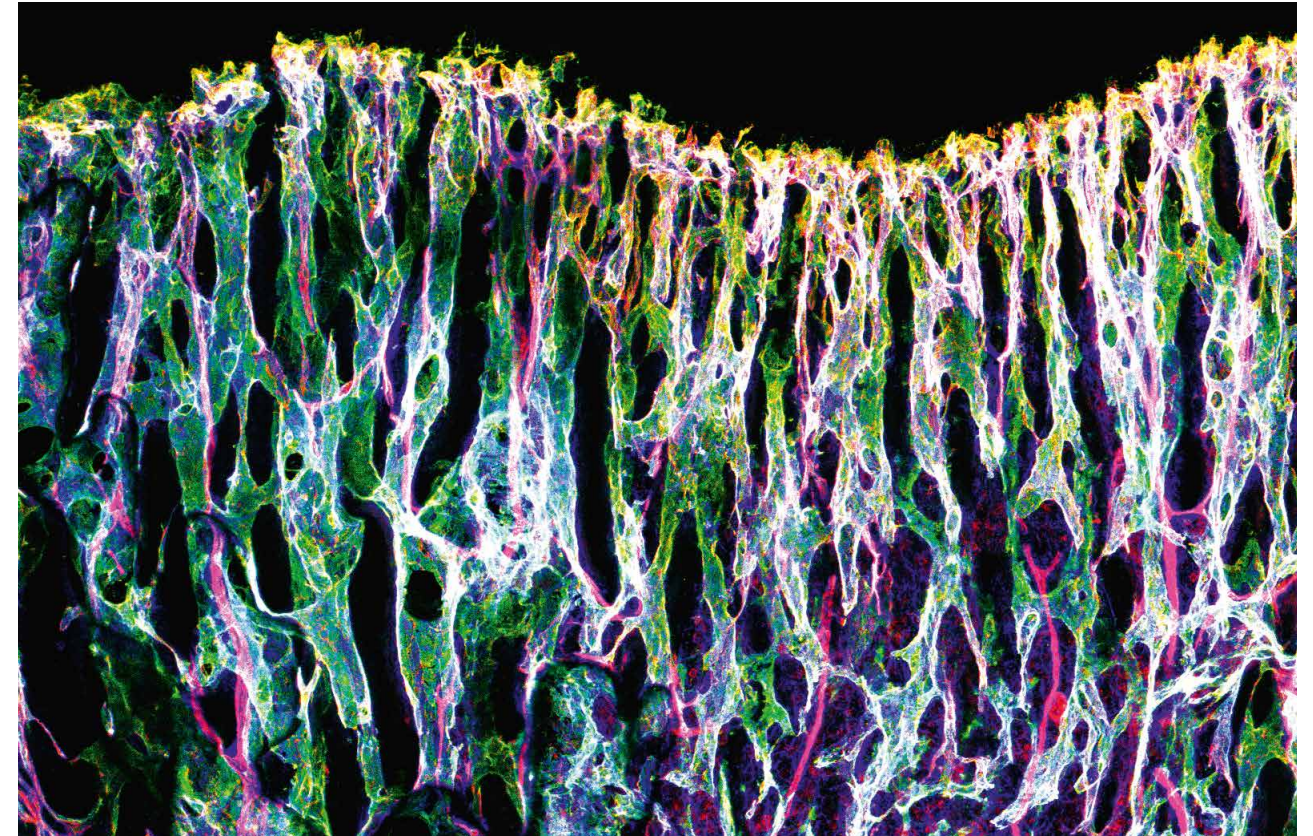
»Since changes in vascular function underlie many diseases, the BIH decided some time ago to establish the Focus Area »Translational Vascular Biomedicine« to achieve significant progress and translational success in this field,« says BIH Professor Holger Gerhardt, who heads the Integrative Vascular Biology Lab at the MDC. Two years ago, the BIH initiated the ten-year BeLOVE study, in which a total of 10,000 patients with various cardiovascular diseases – from strokes to heart attacks to acute kidney injuries – will be observed over a long period of time. »We know that heart attack patients have a higher risk of suffering a stroke and vice versa,« Gerhardt says. »Vascular disease in one organ therefore increases the risk of disease in others. What they all have in common are problems in the small blood

vessels. We want to find out not only the reasons for this, but also how we can prevent the second event from occurring.« BeLOVE has just enrolled its 2,000th patient.

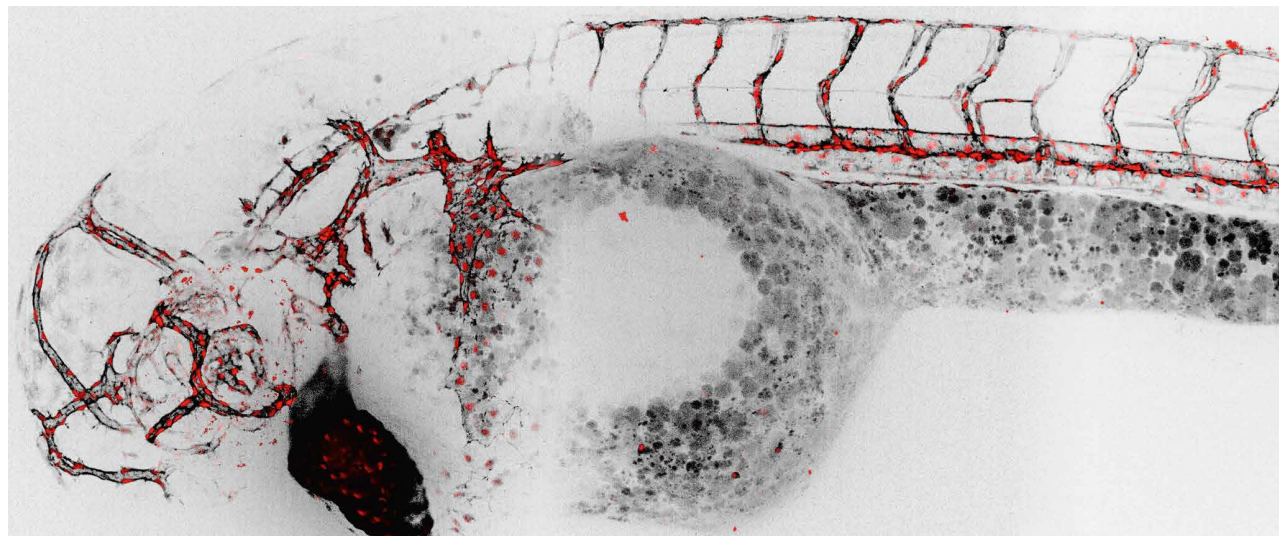
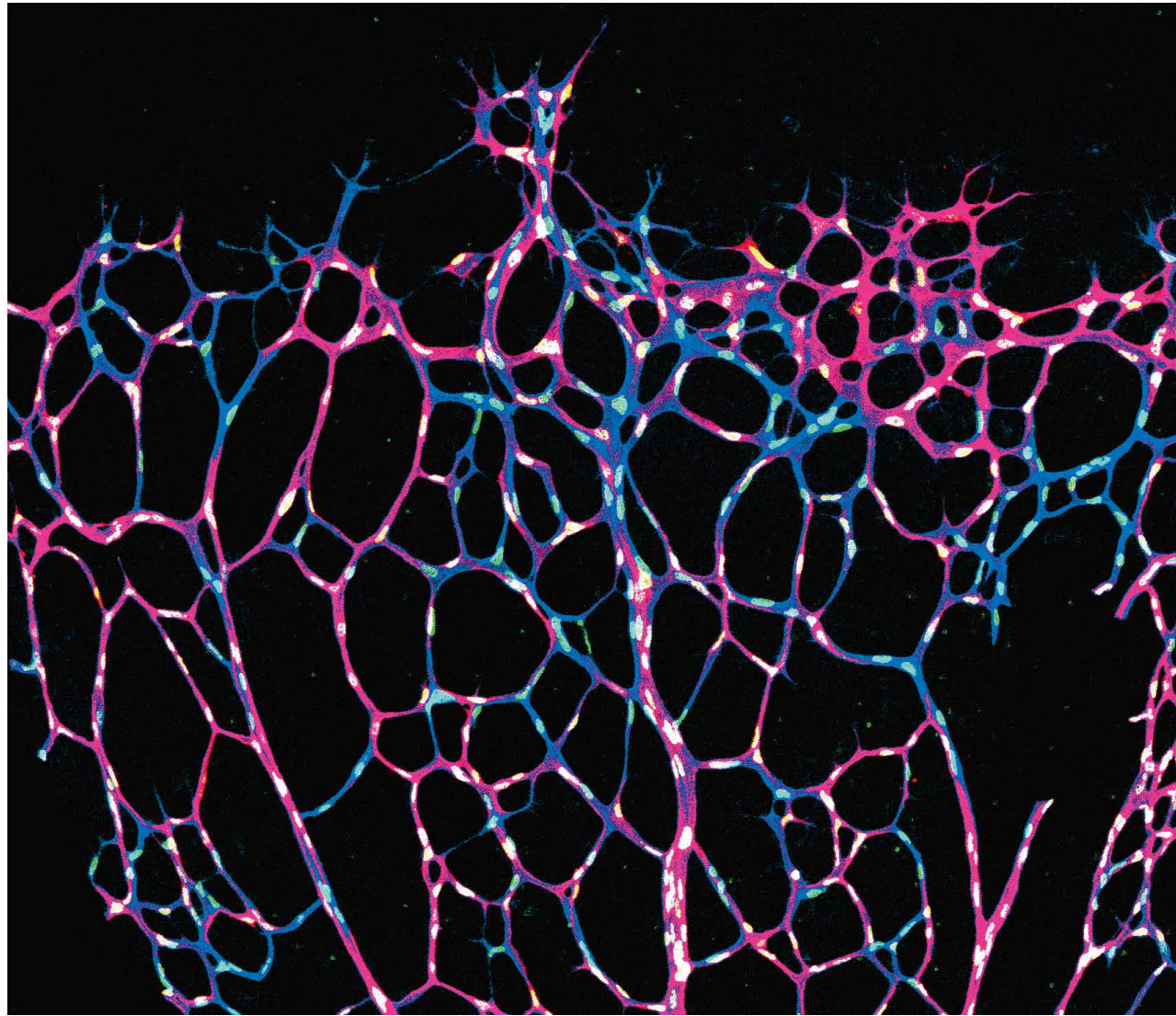
Understanding the growth and function of blood vessels

As spokesperson for the Focus Area »Translational Vascular Biomedicine,« Gerhardt has overseen its establishment and is delighted about the appointment of his colleague Michael Potente, who has been strengthening the Focus Area since August 2020. The newly appointed BIH professor is mainly interested in the influence of metabolism on blood vessels. »We want to understand how metabolic processes control the growth, remodeling and function of blood vessels,« says Potente, who previously led a lab at the Max Planck Institute for Heart and Lung Research in Bad Nauheim. For example, a lack of oxygen and nutrients can lead to the formation of new blood vessels in tumors. Similar processes also play a central role in eye diseases like wet macular degeneration, which leads to blindness if left untreated. »In this case, therapeutic interventions are already possible thanks to the use of inhibitors that suppress the abnormal growth of the blood vessels,« Potente reports.

In other disorders, such as chronic ischemic heart disease or peripheral artery disease of the legs, blocked vessels also cause a shortage of oxygen and nutrients in the tissue; however, unlike in tumors, this often does not lead to the sufficient formation of new blood vessels. »We would hope for new, functional →



This bone is very well supplied with blood (top). Small branches sprout from the larger blood vessels (bottom).



The branching structures of the finest blood vessels can be studied particularly well in the retina of the eye (top) and in transparent fish embryos (bottom).

» If it were possible to specifically promote the growth of new blood vessels, this would have great therapeutic value. «

Michael Potente

vessels to grow that would restore the supply – but here, the underlying disease prevents that from happening,« Potente explains. »If it were possible to specifically promote the growth of new blood vessels, this would have great therapeutic value.« Unfortunately, previous attempts to do so have not achieved long-term success.

Differing endothelia in different organs

Potente and his colleagues therefore intend to study how blood vessels differ across organs – in particular how the organ-specific environment affects the function of blood vessels. Their main focus here will be on the endothelium. Endothelial cells not only line the inside of all blood vessels, but are also responsible for stimulating their growth. »Interestingly, endothelial cells look very different in different organs,« Potente reports. »In the brain, for example, they are particularly tightly interconnected and form the blood-brain barrier; in the liver, the endothelium is permeable, enabling the organ's filter function.« These organ-specific functions are disrupted in many diseases. In diabetics whose blood glucose levels are consistently above normal, endothelial cells change over time and can lose specific properties, contributing to the common vascular problems associated with this widespread condition.

In order to discover the molecular and cellular mechanisms behind these differences, Potente was awarded a €2 million ERC Consolidator Grant from the European Research Council in 2017. It was also at this time that he came to Berlin regularly as a BIH Visiting Professor. Stiftung Charité supported this collaboration, which has been fundamental for the appointment, through its Private Excellence Initiative Johanna Quandt. He was invited by BIH Professor Holger Gerhardt. »I know very few scientists like Michael Potente who carry out innovative research at the highest level with such enthusiasm, curiosity and a keen sense of the most important

issues,« Gerhardt says. »His work is constantly uncovering new connections and has a lasting impact on our understanding of the fascinating biology of blood vessels. I am hugely looking forward to working with him to further advance the translation of these findings into clinical practice.« From March 2021, the two scientists will team up with other colleagues to study »endothelial dysfunction,« as the improper functioning of the small blood vessels is known in medical jargon. The research will take place at the new Käthe Beutler Building on Campus Berlin Buch, which is scheduled to be completed by then. »Our vision is a university-based vascular outpatient clinic,« Gerhardt says, looking ahead to the future.

The aesthetics of blood vessels

As a cardiology specialist, Potente hopes to contribute his experience working at the interface between basic research and patient care – and thus strengthen the Focus Area »Translational Vascular Biomedicine.« »I am fascinated by the aesthetics of blood vessels and the principles behind their formation and, of course, by the possibility of one day making basic research applicable in the diagnosis and treatment of disease,« he says. This is a sentiment fully in line with the BIH's mission of turning research into health. •

Deubiquitinase USP10 regulates Notch signaling in the endothelium.

Science. 2019 Apr

Lim R, Sugino T, Nolte H, Andrade J, Zimmermann B, Shi C, Doddaballapur A, Ong YT, Wilhelm K, Fasse JWD, Ernst A, Kaulich M, Husnjak K, Boettger T, Guenther S, Braun T, Krüger M, Benedito R, Dikic I, Potente M. 364(6436):188-193. doi: 10.1126/science.aat0778

Helping the Immune System and Transplants Make Peace

Professor Petra Reinke of the BIH Center for Regenerative Therapies (BCRT) has developed a procedure that could partially revolutionize the biggest problem in transplant surgery – the body rejecting the new organ. Journalist Christian Heinrich met Reinke and her patient at the Charité Campus Virchow-Klinikum.



One of the first patients treated with the new method was K. Stokowska.

K. Stokowska can still clearly remember her last thoughts before the anesthetic kicked in: »I was worried about how my mom would cope with her operation,« she recalls. Her mother had also been put under anesthetic and wheeled into the operating theater just a few minutes earlier, so that doctors could remove a kidney from her, the donor, and give it to her daughter, the recipient.

When Stokowska woke up a few hours later to find that the transplant had been a success and that her mother was also doing well, the quality of the new life she began was to be significantly higher than is usual for organ transplant recipients.

Today, five and a half years after the operation, K. Stokowska is back in the clinic. The blond, bright-eyed and gregarious 41-year-old is sitting in the office of Professor Petra Reinke, nephrologist, transplantation specialist, and head of the immunology research field at the BIH Center for Regenerative Therapies (BCRT). The doctor, who has been taking care of Stokowska for more than 15 years, hoped that things would go this well – but it was by no means certain. After all, Stokowska's treatment was a sort of experiment.

The novel therapy that Stokowska underwent had been developed by Reinke and only used on one other person at that time. It was designed to finally solve the main problem with all transplant procedures: controlling the immune system's response to the donor organ. If the immune reaction to the transplant is too strong, the new organ will be rejected and destroyed. To prevent this, all transplant patients receive a cocktail of drugs that sufficiently suppresses their immune system. However, this suppression is so effective that it leaves them more susceptible to infectious diseases caused by viruses, bacteria and fungi – and even metabolic disorders and cancers. Patients must therefore live an extremely cautious life, which is a dilemma for every transplant recipient.



For 20 years, Petra Reinke had been treating K. Stokowska for chronic kidney disease.

How aggressively the immune system responds to a transplanted organ is influenced by two different types of immune cells, both of which originate from T-cell lines: The destructive effector T cells are responsible for organ rejection, while their »adversaries« – the so-called regulatory T cells – inhibit the effector T cells and serve to keep a strong or excessive response in check.

In the case of transplant rejection, the destructive effector T cells far outnumber their adversaries – spurred on, in a way, by the foreign tissue. Reinke wanted to use modern molecular biology methods →

» Today, we are able to isolate regulatory T cells from the patient's blood and apply special techniques to enrich and multiply them. «

Petra Reinke

to counteract this harmful imbalance: »Today, we are able to isolate regulatory T cells from the patient's blood and apply special techniques to enrich and multiply them,« Reinke explains. And this is achieved on a considerable scale: In about two weeks, two million cells can become two billion – i.e., 1,000 times as many. Seven days after transplantation, the vast quantities of regulatory T cells are injected back into the patient.

Extensive laboratory and animal studies have shown that the regulatory T cells migrate into the transplanted organ and permanently prevent the effector T cells from rejecting the new organ. And it would seem the same occurs in humans. This means that, instead of having to take three different immune-suppressing drugs, the patient only requires one drug a day. This not only keeps the immune system comparatively robust, it also largely prevents the potential side effects of immunosuppressants – which include hypertension, osteoporosis, visual disturbances and skin changes. But does the immune system remain in this peaceful state over the long term? And does such cell therapy carry risks?

When Stokowska's transplant was scheduled in 2015, the outcome was far from certain. She was receiving the treatment as part of a phase I clinical trial, where the main thing under scrutiny is the safety of the new therapy.

Regardless, Stokowska only needed a few seconds to think it over.

»I immediately said, »Yes, I'll do it!« Stokowska recalls. »And I was amazed,« responds Reinke, who has been caring for Stokowska since the onset of her kidney disease more than 20 years ago. »Up until then, she had taken quite a long time to come to decisions – and that's putting it mildly.« When she was first diagnosed with chronic kidney disease at age 19, Stokowska initially tried to manage without dialysis. But after eight years and a lot of coaxing from Reinke, she finally decided to undergo the treatment. This meant spending three nights a week at a dialysis clinic so a machine could clean her blood as she slept. Another nine years later and Stokowska, then 36 years old, finally decided to undergo transplant surgery – and experimental therapy with her own regulatory T cells. »By that time, I had known Professor Reinke for a long time and knew that I could trust her 100 percent,« Stokowska says.

Fast forward to today, and Reinke has now used the novel treatment method on a total of eleven patients. The results have been astounding, almost across the board: Despite patients taking significantly fewer immunosuppressants, no organ rejection occurs. Reinke is convinced that this treatment could revolutionize medical transplants, and has already taken the first steps to ensure that the method can be applied more



»I had known Ms. Reinke for a long time and knew that I could trust her 100 percent,« K. Stokowska recalls.

broadly. At present, it is still very costly to multiply the cells individually for each patient in the laboratory. That is why she is in talks with biotech companies about the possibility of growing »neutral« variants of these cells in the lab that can be given to all patients. And, of course, it is also conceivable that regulatory T cells could be used in the transplantation of other organs. Here, Reinke is in conversation with colleagues in other fields, such as hepatology, who want to apply the method to liver transplants.

Although the study's observation period officially ends in the fifth year, Reinke will continue to monitor Stokowska's progress beyond this cut-off point. Currently, all signs point to her patient remaining fit and healthy. Stokowska's mother, who was the kidney donor, is also still doing well – and has even become a grandmother. Three years ago, two years after the surgery, Stokowska gave birth to a healthy baby girl after experiencing a completely normal pregnancy – a joyous event that may in part be due to Reinke's novel regulatory T-cell therapy. •

Instead of having to take three different immune-suppressing drugs, the patient only requires one drug a day.

Regulatory T cells for minimising immune suppression in kidney transplantation: phase I/IIa clinical trial.
BMJ. 2020 Oct 21

Roemhild A, Otto NM, Moll G, Abou-El-Enein M, Kaiser D, Bold G, Schachtner T, Choi M, Oellinger R, Landwehr-Kenzel S, Juerchott K, Sawitzki B, Giesler C, Seifrin A, Beier C, Wagner DL, Schlickeiser S, Streitz M, Schmueck-Henneresse M, Amini L, Stervbo U, Babel N, Volk HD, Reinke P. 371:m3734. doi: 10.1136/bmj.m3734.

Translation Hubs

The BIH Translation Hubs represent topics and technologies that will revolutionize medicine across disciplines in the years to come: Digital Medicine, Multi-Omics, Organoids and Cell Engineering, and Clinical Translation.

The Hubs allow experts to connect and build a research community, develop innovative technologies and provide excellent scientific services in the Core Facilities.



Digital Collaboration on Rare Diseases

Twenty university hospitals and other partner institutions have joined forces across Germany under the *CORD-MI (Collaboration on Rare Diseases)* project to improve patient care and research in the field of rare diseases. *CORD-MI* is being funded by the German Federal Ministry of Education and Research (BMBF) to the tune of almost six million euros over two years. Its aim is to facilitate the privacy-compliant sharing of information on rare diseases that arises from diagnosis, treatment and research nationwide.



cord_mi

Rare diseases are not necessarily that rare: They affect some four million people in Germany alone. But of the estimated 8,000 different diseases that fall into this category, there are usually only a few recorded

cases of each one. As a result, it can take years for those affected to receive the correct diagnosis, and in most cases there is a lack of effective treatment options and barely any research.

On the basis of the German National Plan of Action for People with Rare Diseases (NAMSE), many university hospitals have in recent years established centers for rare diseases that provide help for these patients. But some rare diseases are so rare that even centers such as these have only ever experienced a few cases. It is therefore all the more important that efficient use is made of the limited data that are available on such diseases. This is exactly where *CORD-MI* comes in. »We make sure that the BMBF's Medical Informatics Initiative also benefits the centers for rare diseases at university hospitals,« says Dr. Josef Schepers, Deputy Director of the BIH Core Unit eHealth and Interoperability and coordinator of *CORD-MI*. »Digital networking

can be extremely helpful,« Schepers explains. »Especially for medical diagnoses that occur perhaps just 100 times throughout Germany.«

Shining a light on orphan diseases

»You can only improve what you can measure, and it is here that research into these so-called orphan diseases already gets stuck, because they cannot be counted accurately using the usual ICD diagnosis codes,« Schepers explains. »We urgently need rare diseases to be documented and classified using Orphan numbers in regular clinical care, so that the patient data can be used across various locations and in accordance with data protection regulations,« he continues. »The appropriate documentation and digital networking of the existing centers for rare diseases should improve the visibility of these orphan diseases and thus help to accelerate the diagnosis of those affected, develop adequate treatments and promote research on rare diseases.«

The study portion of *CORD-MI* focuses on a selection of rare diseases, including cystic fibrosis. »Cystic fibrosis is one of the more common rare diseases, with a correspondingly large database that has been growing over a long period of time,« explains Professor Helge



Dr. Josef Schepers



Professor Marcus Mall

Hebestreit, a participating clinician from the University Hospital of Würzburg. »It therefore provides a perfect basis for demonstrating the added value of innovative data analyses across different locations.« Professor Reinhard Berner from Dresden's Carl Gustav Carus University Hospital adds: »We want to demonstrate the added value that medical informatics also represents for people with particularly rare diseases. This means that we are also focusing on diseases that potentially affect only ten people in Germany.«

Uniform documentation required

»Under the Medical Informatics Initiative, almost all German university hospitals are setting up data integration centers tasked with jointly developing concepts for documenting and sharing data in compliance with strict data protection rules. This opportunity should also be used for people with rare diseases,« says Professor Sylvia Thun, Director of the BIH Core Unit eHealth and Interoperability, outlining the task ahead. To achieve this, the parties involved will introduce the FAIR principles, which state that scientific data should be findable, accessible, interoperable and reusable. In this way, *CORD-MI* is also contributing to the Medical Informatics Initiative's goal of developing innovative and privacy-compliant approaches to linking and analyzing data.

From a fatal to a treatable disease

An international team led by BIH and Einstein Professor Marcus Mall, Director of the Department of Pediatrics, Division of Pneumology, Immunology, and Critical Care Medicine at Charité, has conducted a clinical trial involving 403 cystic fibrosis patients at more than 100 study sites in North America, Europe and Australia.

The three-drug combination they tested proved to be highly effective. The new therapy led to a noticeable improvement in the lung function and quality of life of many test subjects. The drugs do not target the symptoms of cystic fibrosis, but the basic defect of the disease. They could possibly even prevent the onset of the genetic disease if started early in childhood.

European-wide collaboration, too

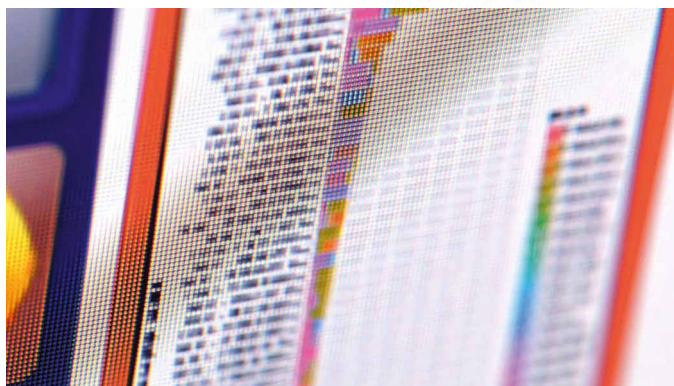
Germany is not the only place where data on rare diseases are poorly managed. Rare diseases are a perfect example of an area of research that would greatly benefit from the networking of patients, researchers and physicians at the European and international level. The European Commission is therefore supporting the establishment of European Reference Networks (ERNs) for complex and rare diseases as part of the EU's Horizon 2020 research and innovation program. »We are naturally making efforts through *CORD-MI* to also achieve the interoperability of patient data across Europe. In the case of many rare diseases, we can only understand what factors contribute to the disease and how it progresses by collaborating across borders,« Schepers says, adding with conviction: »Many people working together can produce results that a few people working alone never could.« •

✂ **Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele.**
N Engl J Med. 2019 Nov

Middleton PG, Mall MA, Dřevínek LC, et al.
381:1809–19. doi: 10.1056/NEJMoa1908639

VarFish Detects Disease-Causing Mutations in DNA

A serious illness is often the result of a single genetic defect. But given that two healthy people already have around three million differences in their three billion DNA building blocks, it is no easy task to pick out the one disease-causing deviation from the many harmless genetic variants. Scientists at the Bioinformatics Core Unit have joined forces with colleagues from Charité and MDC to develop a software called VarFish that helps locate this genetic »needle in a haystack.«



The human genome is comprised of three billion building blocks.

Rare diseases often have a genetic cause: In many cases, they begin as a result of a single letter being different or a small change to a section of DNA. Because the diseases occur so rarely, it can take years for those affected to receive the correct diagnosis – and yet this is a prerequisite for effective therapy. »The parents of affected children often end up sitting across from us after a long and arduous journey,« says Dr. Nadja Ehmke, a specialist at the Charité's Institute of Medical Genetics and Human Genetics and an alumna of the BIH Charité Clinician Scientist Program. »They

have a sick child who is not developing properly, either mentally or physically, and they want to know why. If we can use a genetic analysis to explain to them where the defect lies, this is often a huge relief for the parents – even if it does not necessarily mean anything can be done for their child in terms of treatment.« Such knowledge enables parents to exchange information with others in the same situation, to visit or set up self-help groups, and to better assess whether another child could also fall ill.

Powerful VarFish software detects differences

To determine where the defect lies, scientists isolate the genetic material from patients' blood cells, read the sequence – i.e., the order of letters – and compare it with the genetic material of parents, siblings or existing genetic analyses in large databases. »This is where humans reach their natural limits, and it's no wonder given that each person's genome contain three billion building blocks,« reports Dr. Dieter Beule, Head of the BIH Core Unit Bioinformatics. »Even if we only analyze the protein-coding regions of the genetic material, there are millions of building blocks to compare. In the genetic material of two healthy individuals, there are around 30,000 positions in these coding regions alone

that differ. We require powerful software that not only detects the differences, but also identifies which of the variants are benign and which are responsible for the disease.«

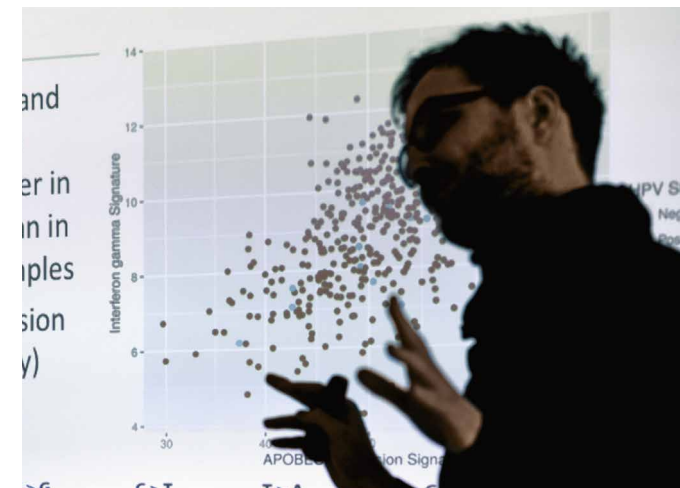
This was what motivated Beule and his team to develop VarFish. VarFish compares the patient's sequence with sequences from worldwide databases. The Core Unit Bioinformatics scientists made use of many open and free data resources, including the U.S. databases of the National Center for Biotechnology Information (NCBI) at the University of Washington in Seattle, and the European Bioinformatics Institute (EBI) in Cambridge, UK, as well as Charité's and the BIH's own databases and algorithms.

Comparison within seconds

»In a matter of seconds, VarFish can eliminate 29,950 of the 30,000 differences as harmless variants,« Beule explains. »This is because the software finds many of the same deviations, for example, in the sequences from population samples, where it apparently does not lead to noticeable problems and is therefore in all probability not responsible for the rare disease.« The scientists can then compare the remaining 50 genetic variants with known hereditary diseases, thus narrowing down the group of possible culprits to about ten genetic mutations.

Accurate diagnosis

Dr. Manuel Holtgrewe, a bioinformatician in the Core Unit Bioinformatics and developer of VarFish, is delighted that the new software is finding so many users: »In just the first few weeks, VarFish has been used hundredfold by scientists and doctors around the world. In our own laboratory we analyzed thousands of data sets with the help of VarFish.« International cooperation is particularly important in the research and treatment of rare diseases, as each individual mutation usually occurs only a few times in each country. Professor Stefan Mundlos, Director of the Institute for Medical Genetics and Human Genetics at Charité and the Development and Disease Group at the Max Planck Institute for Molec-



The VarFish software can identify which variants in the genome are disease-causing and which are benign.

ular Genetics in Berlin, reports: »VarFish has been very helpful in enabling us to quickly and accurately diagnose participants for our clinical trials.«

Holtgrewe and Beule are now planning to expand VarFish so as to enable the genome-wide analysis of so-called structural variants, in which not only individual letters but also entire sections of the DNA are altered or even deleted. In addition, further functions will be added for the effective and safe cross-locational collaboration of human geneticists. »VarFish supports users in the analysis of their molecular genetic data in both basic research and clinical application,« Beule says. »The core mission of the BIH is translation – which involves transferring results from research to the clinic and, vice versa, bringing clinical observations back to the lab. With our software VarFish, we are supporting this very goal.« •

VarFish: comprehensive DNA variant analysis for diagnostics and research
Nucleic Acids Research, 2020 July

Manuel Holtgrewe et al.
doi.org/10.1093/nar/gkaa241

Growing New Muscle from Stem Cells

Professor Simone Spuler researches genetic muscle diseases at the Experimental and Clinical Research Center (ECRC) of Charité and the Max Delbrück Center in Berlin-Buch. In this interview, the spokesperson for the BIH Translation Hub »Organoids and Cell Engineering« talks about how she is able to isolate stem cells from the muscles of diseased patients and genetically modify them to rebuild missing muscle fibers.



Professor Simone Spuler

Professor Spuler, what are the muscle diseases that you are interested in?

SPULER There are about 45 to 50 different muscle diseases that we call »muscular dystrophy.« They are all progressive, which means they get gradually worse over time and eventually lead to the patient losing the ability to walk. Many other movements, like bringing a glass of water to the mouth, also end up impossible. And all these diseases are currently incurable.

When do these diseases become apparent?

SPULER These 45 to 50 diseases are caused by 45 to 50 different genes, each of which is responsible for protein production at a different site in the muscle

fiber. The onset and course of the disease and the muscles that are most affected all depend on which gene is at the root of the disease. As a result, some muscle diseases are already apparent when a child is born, while others may develop during the early school years. Then there are certain genetic muscle diseases where a child can have a very active, even athletic youth right up to adulthood, and only then do their muscles start to get progressively weaker, eventually preventing them from being able to do these activities.

And as of yet, there is no treatment for this whole group of diseases?

SPULER We have witnessed an increase in life expectancy over the last two decades, thanks to improved treatment regarding lung function, breathing techniques, the prevention of secondary complications like tendon shortening, or support for the heart muscle. But no cure currently exists for any of these diseases.

And you want to change this by developing a therapy that gets to the root of these diseases?

SPULER I would like to make my own modest contribution to our highly ambitious goals. We are focusing on the muscle stem cell – a very interesting cell that is capable of regenerating muscle fibers in both sick and healthy individuals well into old age. These muscle stem cells are located in a special niche in the muscle belly, or venter, and are quite few and far between. It takes a lot of effort to isolate these cells and expand them without losing their beneficial properties. But



From left to right: Dr. Verena Schöwel, Janine Kieshauer, Prof. Simone Spuler, Dr. Andreas Marg.

with the arrival of the CRISPR-Cas9 gene-editing tool, we now have a far, far better method of gene manipulation that we can use to conduct our »repairs« on the muscle stem cells.

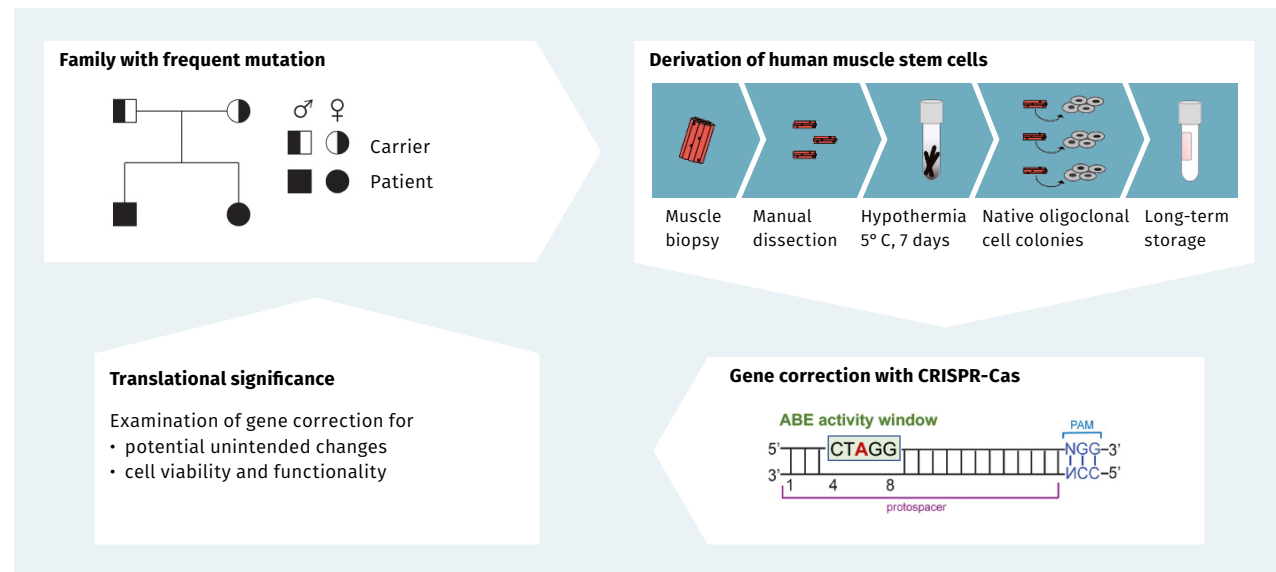
This involves taking muscle stem cells from the patient, transferring them to the petri dish, and then using the CRISPR-Cas9 tool to carry out a very targeted manipulation that »repairs« the malfunctioning gene in the stem cells. What happens then?

SPULER Yes, the next step is to return these cells to the patient – and this is the crucial part. The reagents used in the laboratory are not intended for human use, which means we have to convert each reagent so that they meet the requirements of good manufacturing practice (GMP). We have already achieved this for the cultivation of muscle stem cells – a process that took two years. But we still need to achieve GMP-grade gene manipulation, which is uncharted territory worldwide. This is what we are currently working on.

Is the idea that you multiply the repaired stem cells until you have enough to give back to the patients so they can build new, healthy muscle fibers again?

SPULER Yes. And it not only leads to the formation of new muscle fibers, but also the creation of new stem cells. It is interesting that a cell that forms a fiber can also form another cell that returns to its niche and reassumes stem cell properties. In this respect, there is in fact regenerative potential in the newly formed muscle, and the injected muscle cell can also fuse with existing muscle fibers. That's a special property of muscle – as soon as these cells touch, they connect. But it also means that, for our method to work, some muscle fibers still have to be present. If a disease is at an advanced stage where muscle fibers have already been converted into connective tissue, it becomes difficult.

We are talking about genetic muscle diseases, which are quite rare. How many patients can hope to benefit from your therapy? →



SPULER One in 2,000 people is affected by muscle disorders. Of these 45 or 50 different diseases, we have selected three – which could become four in the future – that are relatively common. However, we are also working on mutations that not only affect individual patients. Once these therapies are developed, a few thousand people will benefit.

You are also a doctor, so you meet the patients face to face. Is the feeling of sitting across from these people and knowing that there's not really anything you can do for them part of what motivates you to develop something new?

SPULER Absolutely! Many of our patients also ask if we have time to explain what we do in a little more detail – and some have even asked to visit the lab. This has been a new experience for the scientific researchers here, that there are patients who actually want to know: »Could this help me?«. At first, it caused some uneasiness, but now the whole group finds it extremely motivating, because it reminds us why we are actually doing this work.

Dare you predict when the first gene therapy for muscular dystrophy will be available?

SPULER Gene therapy is a big term. There are already clinical studies that are using shuttle vectors, mostly viruses, to deliver an additional copy of a gene into the cell. The gene repair work that we do – precisely correct-

ing muscle cell mutations in tissue cultures – is also already possible for a few selected mutations thanks to the various, highly targeted CRISPR gene-editing tools. Fortunately, we have just received funding to begin GMP-compliant production, so we hope to be able to start the first clinical trials soon.

We wish you all the best going forward.

SPULER Thank you! •

Base editing repairs an SGCA mutation in human primary muscle stem cells.

J Clin Invest Ins. In press (online on April 13, 2021)

Escobar H, Krause A, Keiper S, Kieshauer J, Müthel S, Garcia de Paredes M, Metzler E, Kühn R, Heyd F, Spuler S.

The Heart of Translation

Since June 2019, BIH Chair for Clinical Translational Sciences Professor Christof von Kalle has headed the BIH-Charité Clinical Study Center as founding director. This is where all studies of both institutions converge. Christof von Kalle talks about his tasks and goals in our interview.

Professor von Kalle, what is the goal of the Clinical Study Center?

VON KALLE Charité is a very strong research organization with a historically rooted network of different study facilities that support physicians and researchers in conducting clinical trials. BIH and Charité are now bundling these activities into a single Clinical Study Center. On the one hand, the aim is to support the studies in meeting increasing regulatory requirements, and, on the other hand, to further develop the study landscape at Charité. For this field will undergo major changes and upheavals in the coming years.

What challenges will the centers face?

VON KALLE Simply put, clinical centers are currently not in a position to know everything essential about each of their patients. In the future, an organization will not have a limited number of study protocols, as it does now, and think about which patients are eligible for these particular study protocols, but will instead ask the question: Which study protocol does each patient need?



Professor Christof von Kalle

So every patient who arrives at Charité will be enrolled in a clinical trial?

VON KALLE Every patient receives information about which clinical studies exist for his or her illness. This question is increasingly being asked by the patients themselves. Patients are usually highly motivated to participate in studies. After all, they come to Charité because it is such a high-quality institution for medical care and research, and most patients know that this very high quality can, of course, only be maintained if research, including clinical research, takes place. For example, with the help of blood or tissue samples that are no longer needed, a patient can provide his or her data for research or be contacted for follow-up →

» Every patient receives information about which clinical studies exist for his or her illness. «

Professor Christof von Kalle

questions. And all these processes, including communication with the patient, require an infrastructure. In the 21st century, much of this is naturally digital and provided via online services, apps, etc., which also need to be further developed.

However, this also means that all clinical studies running at Charité must be known by the attending physician in the outpatient clinic or ward. Furthermore, it must be possible to make these studies available to patients so they can obtain comprehensive information.

VON KALLE For this purpose, we have set up a study register in which centrally compiles this information. There are currently more than 600 active study protocols at Charité, and counting those in various follow-up phases, there are more than 1,000 studies.

You've also been working on developing a data box, in which patients can keep all their health data and share them with the doctor or scientist of their choice. How far along is this project?

VON KALLE We have defined a patient-centric data room and are now moving into a major trial phase for patients with lung cancer, in which this will be tested with a larger number of patients. This involves a considerably expanded version of the electronic patient file, which in our version also includes communication options for studies, imaging and various other data formats, enabling patients to systematically organize their treatments and maintain an overview.

What would such a data box look like? Would the patient carry around a CD collection, would it be in the form of a USB stick or is the data in the cloud?

VON KALLE The data are in a virtual space, and, of course, medical data are subject to special security requirements in terms of the servers on which they are stored and how they are encrypted.

Why is it important for the patient to have access to and control over his or her data?

VON KALLE Patient autonomy means the patients understand processes, can inform themselves and have the option of making these data available wherever they wish. This might be to the next attending physician, it could be a connection between the attending physician at home and a large medical center, it could include commercial healthcare services in the future, which might evaluate the genome data once again, and it could also be the idea of making one's data available for study enrollment or general research.

How busy has the Clinical Study Center been as a result of the coronavirus pandemic? Did this throw the whole operation into disarray, or could something be learned from it for future study operations?

VON KALLE Both (laughs). Of course, research has been adapted to the pandemic. Conversely, we are still available for everything that is urgent and important. We



have devoted resources that have been freed up in this way entirely to the coronavirus. Together with our colleagues from infectious diseases and intensive care, we have created an overarching study protocol in which every COVID-19 patient who agrees is included, so that Charité can systematically evaluate data related to the treatment of all COVID-19 patients. These data are also included in developing the national network of university clinics, a process which is supported by the Federal Ministry of Education and Research and coordinated by Charité throughout Germany. At this point, I would like to express my sincere thanks to all the people who work in the Study Center and the specialist departments. It was truly incredible how everyone pitched in so selflessly, even in their free time. We have made so much progress that would not have been possible before.

You've achieved a lot with the Study Center in one and a half years. What is your next goal?

VON KALLE Our next goals are helping to overcome the coronavirus pandemic, making study services accessible to every patient, and achieving better and

greater integration of the various digital platforms. Data processing in patient care is already very digitalized, but at the moment we still have a lot of work to do to ensure such data can be analyzed in research and, conversely, to make research results available for treatments. With its digital platform, BIH has done outstanding preparatory work in this area and can provide key technologies so that we can also achieve this in healthcare.

Thank you very much for your time. •

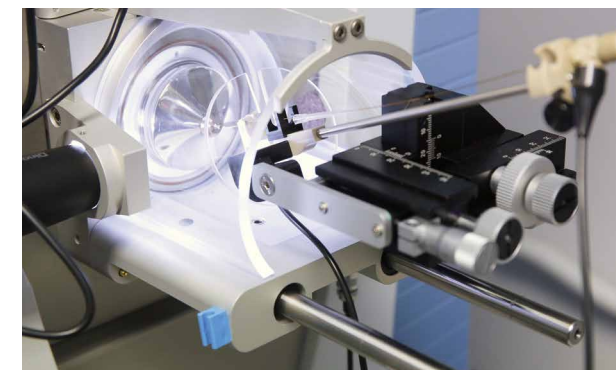
→ **BIH/Charité Clinical Study Center**
www.bihealth.org/en/research/clinical-study-center

Jennifer Kirwan Heads the BIH Core Facility Metabolomics

Dr. Jennifer Kirwan is interested in metabolites. These are substances that are naturally produced in the body during metabolism. Metabolomics is concerned with recording the totality of all metabolites in the body and their respective concentrations. It becomes particularly interesting when the concentration of metabolites changes, e.g., in the event of an illness, under certain environmental conditions or even during normal development.



»What fascinates me is the diversity – when we look at 100 people, each has their own metabolome,« Jennifer Kirwan says.



Each person has his or her own individual metabolome

In her Core Facility Metabolomics, Dr. Jennifer Kirwan has a staff of 12 people and also impressive instrumentation: »We use a variety of mass spectrometers. They are basically sophisticated weighing scales that can determine the weight of individual metabolites. With their help, we can discover in which quantities individual metabolites occur in various cells and organs. This gives us information about how the metabolites of healthy and sick people differ, for example. What fascinates me is the diversity – when we look at 100 people, each has their own metabolome.«

»Our Core Facility collaborates with different groups, and helps answer many different and interesting research questions,« says the veterinarian. »For example, we just found out that energy production changes in cells are central to many diseases, including Alzheimer's and certain heart diseases. Or that some metabolites of the amino acid tryptophan are related to inflammatory markers in kidney disease in children.«

The most accurate measure of a person's condition

Metabolomics, i.e., the ability to measure and assess a person's metabolism in its entirety, is particularly important for precision medicine. This is because the metabolite composition depends on both genetic predisposition and lifestyle. The concentration of the various metabolites in the body, including fats, proteins, nucleic acids or carbohydrates, rapidly adjusts, making it probably the most accurate measure of a person's current condition.

How do the heart, gut and brain work together?

»We focus primarily on the health of the heart, gut and brain and how these three organs are connected,« Kirwan says. »We also devote a lot of time to quality control in metabolomics research, because only reliable results can be easily translated into clinical applications.«

Alternative path to a biological understanding of illnesses

Research in precision medicine follows two main strategies. Traditionally, samples from one group are compared with those from another, e.g., healthy and sick individuals, to determine the differences. Increasingly, however, scientists are conducting longitudinal studies, i.e., taking samples from the same person at multiple points in time. These provide information on how the acute physiological state changes in response to external influences. In addition, measuring a person's metabolome regularly over a longer time can help assess why a person develops an illness. In this way, metabolomics offers an alternative means of understanding illnesses biologically. •

Core Facilities

The Core Facilities, which the BIH jointly operates with Charité or the MDC in some cases, provides a state-of-the-art research infrastructure to scientists at the BIH, Charité and the MDC. The range of technologies and services available are specifically designed to meet the requirements of translational and systems medicine research.

Core Facility Biobank

Prof. Michael Hummel
Prof. Tobias Pischon

- Storage of a wide range of samples generated by BIH research projects and clinical trials under controlled and quality-assured conditions
- Consultancy and support to BIH projects involving biosamples with regard to the design, planning and implementation of studies (e.g., SOPs), data protection and ethical issues
- Tissue sections, histology and DNA extraction

Core Unit IT Services

Michael Mallach
Dr. Peter Brunecker

- Essential IT services, including basic IT setup for BIH staff and researchers
- User support, network support, central storage services, email and groupware services, central server and computing power services
- High-performance computing (HPC) infrastructure for computing- and data-intensive research areas
- Training in the use of the HPC infrastructure and scientific programming

Cytometry Core

Dr. Désirée Kunkel

- Expert service and state-of-the-art equipment for multiparameter cell analysis and high-speed cell sorting
- Close cooperation with research groups to establish new methods, which can then be made available to all users of the Core Facility
- Regular maintenance of all instruments and implementation of quality management procedures

Core Facility Stem Cells

Dr. Harald Stachelscheid
Dr. Sebastian Diecke

- Derivation, differentiation and distribution of human iPS cell lines
- Isolation of primary cells from patient samples, characterization and quality control of hPSC reference lines and banking, establishment of differentiation protocols and provision of cells differentiated from hiPSC, organoid services
- Provision of infrastructure and equipment
- Project consultancy and training opportunities

Cell Harvesting

Prof. Karsten Perka

- Provision of fully characterized human tissue, which has been harvested in a standardized manner
 - Primary tissue: blood, bone marrow, bone, cartilage, hematoma, fat, etc.
 - Clinical information: age, sex, medication, risk factors, comorbidities, prognosis for cure, etc.

Core Facility Genomics

Dr. Tomasz Zemojtel

- Translation of genomics-based applications into clinical care
- Liquid biopsy service for monitoring the effectiveness of cancer therapies
- Various automated next-generation sequencing work flows
- Strong bioinformatics and biology know-how
- Use of state-of-the-art equipment for genomics services

Core Facility Proteomics

Dr. Philipp Mertins

- Precise quantification of proteins in complex samples using label-free techniques and various isotopic labeling techniques
- Profiling of different biological states in cells, tissues and body fluids
- Measurement of protein interactions
- Determination of the spatial information of proteins

Core Unit Bioinformatics

Dr. Dieter Beule

- Provision of expertise and tools and consulting services for bioinformatics and data analysis
- Current focus: cancer bioinformatics, regulatory genomics, rare-disease genetics
- Data processing methods and tools

Core-Unit E-Health and Interoperability

Prof. Sylvia Thun
Dr. Josef Schepers

- Strategies and concepts for the fast, secure and reliable usage of medical data across different systems
- Creation of interoperability solutions using international IT standards and terminologies from the ISO environment, in cooperation with hospitals, trade associations, research institutions, industry and government
- Specification of research data infrastructure
- Goal: a unified digital ecosystem that facilitates innovative medicine, characterized by more accurate predictive tools, highly personalized therapies, increased patient participation and greater patient safety

BIH Core Facility Metabolomics

Dr. Jennifer Kirwan

→ Pages 44–45

→ Core Facilities

www.bihealth.org/en/research/scientific-infrastructure/core-facilities

A close-up photograph of a hand wearing a blue nitrile glove. The hand is holding a clear plastic pipette, which is dispensing a small amount of blue liquid into one of the wells of a white microplate. The background is a soft-focus laboratory setting. The image is split vertically by a thin white line, with the text on the right side.

Innovation Enablers

The BIH's Translational Ecosystem is founded on ensuring that all those involved in the process have a translation-oriented mindset, while providing support to scientists and physicians in all phases of translation.

The Innovation Enablers fulfill the following functions: The BIH Biomedical Innovation Academy guides the careers of translationally minded physicians and scientists, the BIH QUEST Center ensures the quality and sustainability of research, and BIH Innovations helps to translate innovative ideas into products and clinical solutions.

An App for Fighting the Virus

The BIH Biomedical Innovation Academy has since 2019 been offering the Digital Clinician Scientist Program, which is funded by the German Research Foundation (DFG). As a result, the BIH is enabling young doctors doing their residency at Charité – Universitätsmedizin Berlin to combine specialist clinical training with scientific research, just as its renowned and proven Clinician Scientist Program has been doing for many years. The Digital Clinician Scientist Program focuses on preparing tomorrow's physicians for the digitalization of healthcare. The program's spokesperson, Alexander Thieme, has created an app that lets users assess whether they might be infected with the novel coronavirus.

Dr. Alexander Thieme, a radiation oncologist, treats cancer patients and conducts research into targeted therapies at Charité's Department of Radiation Oncology and Radiotherapy. Since radiation often destroys not only the tumor but also the nearby healthy tissue, the physician and computer scientist had already developed an app that allows patients to record cancer treatment side effects while at home. »While the success of a cancer therapy is tangible – for example, a longer survival time – the situation with side effects is considerably more complicated,« Thieme explains. »Side effects can arise years after the treatment is completed, manifesting themselves in various different symptoms and with varying severity – and can significantly reduce quality of life.«

Electronic reporting of side effects

A procedure in which patients themselves document the effects of a therapy is known as patient-reported outcomes, or PROs for short. In order to make the app more user-friendly for patients, Thieme employed QR code technology in his solution. The technology is already widely used in the industrial sector. A key

innovation in the app was the incorporation of this technology into the electronic reporting of PROs. Last year Thieme received an award for this idea from the German Society for Radiation Oncology (DEGRO).

In just three days, the first version was up and running

Dr. Valerie Kirchberger heads up the PRO project at Charité. »As the number of people infected by SARS-CoV-2 continued to rise, I had the idea to ask Dr. Thieme if the solution he developed for cancer patients could also be used in the coronavirus crisis,« explains the physician, who is also an adviser to Charité's Chief Medical Officer, Professor Ulrich Frei. »Many citizens were worried that they had been infected, and the testing sites at Charité had already become overburdened.« Professor Frei liked the idea and freed up Thieme to work on the app. After the first meeting of the Coronavirus Working Group, which, along with Kirchberger and Thieme, included physicians in the outpatient clinic and representatives from Data4Life, and once the specifications had been defined, it took only three days for Thieme to program the first fully functional version of the CovApp.



The app uses a questionnaire to determine the likelihood of infection.



Dr. Alexander Thieme

Based on users' answers to questions about symptoms like fever, coughing and fatigue, about whom they have come into contact with and their recent travel to high-risk areas, and about their underlying health conditions, smoking status and age, the CovApp makes a recommendation. If there is a certain combination of risk factors, the CovApp recommends the user to visit an examination center where he or she will be tested if necessary. It also creates a QR code that can be taken to the clinic and scanned there to save valuable time during the patient interview, thus allowing more patients to be examined.

»We need to direct the flow of patients into the right channels in order to optimally utilize the capacity of our healthcare system and to help as many people as possible,« Kirchberger explains. »And the CovApp helps us to do just that.« According to initial estimates, millions of people across Germany have already used the CovApp to complete the questionnaire. »We are updating the CovApp almost daily,« Thieme reports. »The Robert Koch Institute, for example, has several times expanded its list of high-risk areas, and on multiple occasions we have had to revise the questions about symptoms as well as the decision logic for determining the risk profile.«

Shaping the digital transformation of healthcare

Professor Duska Dragun, the charismatic Director of the BIH Biomedical Innovation Academy, sadly passed away prematurely in late 2020. She was rightly proud of what she had achieved, of the entire Clinician Scientist Program, with its more than 100 fellows and now

more than 100 alumni, but also of individual participants such as Alexander Thieme. The Digital Clinician Scientist Program is supporting young medical doctors in shaping the digital transformation by enabling them to pursue innovative research projects during their residency training. Dragun was very pleased that after only a year into its existence, the program was able to support a project of such crucial importance to all of Germany.

Further optimization and translation into other languages

The current version of CovApp was conceived and designed in collaboration with the nonprofit organization Data4Life, and the app is being developed further. »We plan to publish the algorithms online so that anyone interested in the app can view and further optimize them,« Thieme explains. Several hospitals in Germany and even some overseas, like the renowned Mount Sinai Hospital in New York City, have expressed interest in the CovApp, which is why translations into other languages are planned. »Throughout human history, there have unfortunately always been pandemics, but this is the first time that we can use modern information technology to help people in such a situation,« Thieme says. •

→ Learn more about the Digital Clinician Scientist Program and other BIH Biomedical Innovation Academy programs, such as the recently launched Advanced Clinician Scientist Program, at: www.bihealth.org/en/translation/innovation-enabler/academy

QUEST Takes Study Results Down from the Shelf

The BIH QUEST Center aims to increase the value and benefit of biomedical research at BIH and beyond. This naturally includes publishing research results. But until now, this has not occurred enough for clinical studies, of all things. The staff at the BIH QUEST Center have now initiated a positive change in the research culture and – with the help of the Clinical Study Center – have been able to significantly increase the rate of published study results, and not only in Berlin!

Clinical trials are the »heart of translation.« This is where new therapeutic agents and treatments are tested on humans for the first time. Their safety is initially tested on a very small number of healthy volunteers. Subsequently, the efficacy of the new treatment or therapeutic agent must also be confirmed with a few hundred subjects, and finally it is tested on thousands of patients to see whether the new drug works better than existing medicine.

The results of clinical trials are therefore highly relevant. If a new substance or procedure proves to be better than the conventional approach, approval and market entry usually follow. However, recent studies show that about one-third of the clinical trials results from German universities are not published – instead, they are merely shelved. What's more, despite legal regulations, the results are not published in the EU Clinical Trials Register (EU-CTR). As a result, other scientists and physicians cannot know whether a substance has already been tested, whether comparative trials have been conducted with two existing drugs, or whether a second evaluation of the study results might have shown an advantage for a smaller subgroup of patients.

Daniel Strech, BIH Professor of Translational Bioethics and Deputy Director of the BIH QUEST Center, found this situation unsatisfactory. »Patients have agreed to

participate in studies with the hope of advancing science and medicine. We have an obligation to them to publish study results,« he argues. »Moreover, from an ethical perspective, it is at least questionable not to disclose the results of trials that have been funded by taxpayer money.« Therefore, in line with the BIH QUEST Center's mission, he decided to improve the quality, ethics and openness of biomedical research in Berlin and beyond.

The challenge

It was found that universities and hospitals often did not publish the results of clinical trials because they simply lacked the expertise to do so. Some institutions did not have a sufficient overview of their central studies or lacked systems to support them in timely reporting. In addition, the user interface of the EU Clinical Trials Register caused numerous difficulties.

The workshop

BIH QUEST Center staff organized a one-day workshop in Berlin, in which experts from four British institutions explained how they had managed to successfully overcome hurdles in clinical trial reporting. The audience traveled from Germany and neighboring countries; half of all academic clinical trial units from Germany sent representatives to the workshop, as did staff from major



Clinical trial results provide important new insights.



Professor Daniel Strech is Deputy Director of the BIH QUEST Center.

institutions in Denmark, France and Italy. Participants learned how to use management systems to keep track of their own studies and how to enter their results into the Clinical Trials Register.

The manual

In addition, colleagues from the BIH QUEST Center created a practical manual. Based on interviews with experts from 15 leading institutions across Europe, the manual guides study leaders through the process of publishing study results step-by-step. The QUEST staff then analyzed Charité's study portfolio and outlined the steps needed to quickly and efficiently transfer results to the EU Clinical Trials Register.

Initial success

The BIH QUEST Center initiative has significantly improved study reporting – and not only at Charité, but also at numerous German university medical centers, as well as at universities and hospitals throughout Europe. In exchange with The Charité Clinical Trial Office, the BIH QUEST Center started entering missing trial results into the register after the workshop. As a result, Charité now leads the list of German university hospitals and is among the ten European institutions that publish study results most quickly. In the year following the QUEST workshop, German university hospitals were able to enter the results of 154 clinical trials into the register, a notable increase over just 32 results reported within the previous five years. Many of these university hospitals participated in the workshop organized by the BIH QUEST Center.

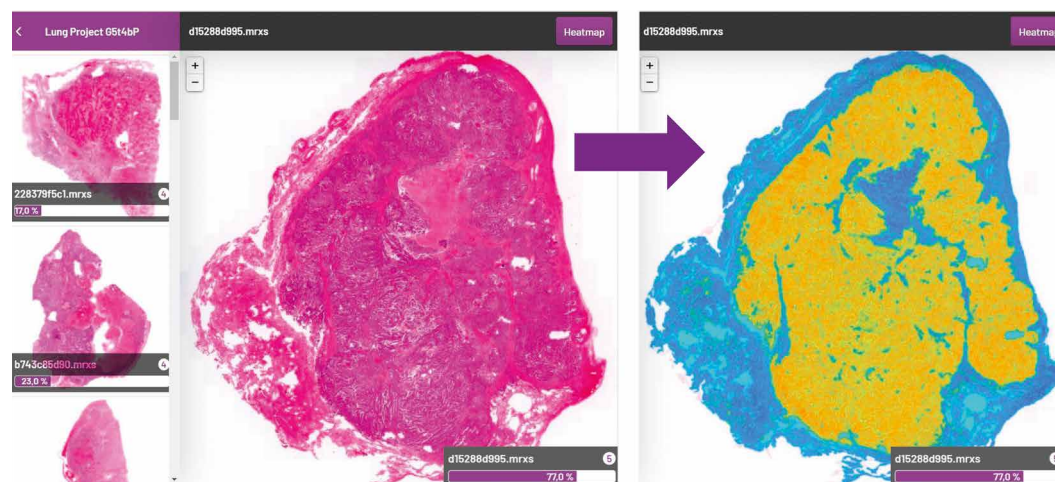
Positive impact on Europe

Of the top ten European institutions now entering the most study results, five participated in the QUEST workshop. At a meeting of the European University Hospital Alliance, QUEST employees reported on their measures and promoted exchange between the Charité Clinical Trial Office and colleagues in Alliance hospitals and other important institutions abroad. The European Medicines Agency also contributed to the solution. Following the BIH QUEST Center workshop, the agency removed a few impediments in the registry, thereby facilitating reporting for study leaders. Naturally, Strech is pleased with these developments, and even a little proud: »I think we have made a significant contribution to ensuring that the results of important clinical trials are disclosed. Without the cooperation of the Charité Clinical Trial Office, this would not have been possible. In the end, the process helps everyone involved: doctors, scientists and, last but not least, patients.« •

→ **BIH QUEST Center**
www.bihealth.org/en/translation/innovation-enabler/quest-center

Precise Diagnostics with AI

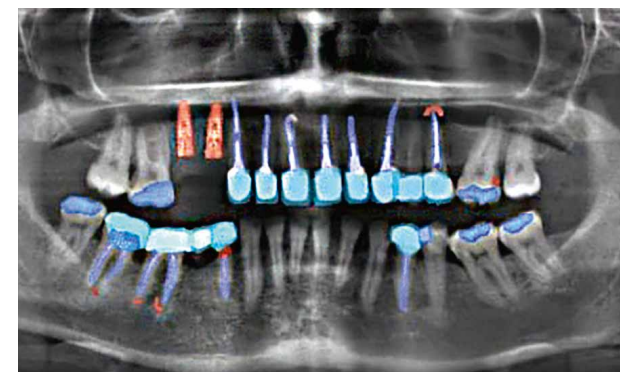
Evaluating X-rays or microscopy images takes a tremendous amount of time. Two research teams at Charité have each developed software that can reliably and quickly detect abnormal findings with the help of artificial intelligence.



Left: Histological preparation of a lung tumor.
Right: AI-based »heat map« highlights tumor cells (yellow) and normal tissue (bluish green).

Professor Frederick Klauschen studied physics and medicine, »a good combination for pushing forward the digitalization of healthcare,« says the Deputy Director of Charité's Institute of Pathology on Campus Charité Mitte. »With ever more samples from ever more patients, digital assistant systems can help to avoid mistakes,« Klauschen explains. »And humans are not as good at determining what percentage of tissue is affected by cancer or what percentage of tumor cells contain a certain therapeutically relevant receptor. Here our »digital colleague« can provide valuable help, because it is both faster and more precise when it comes to quantitative analysis.«

In order to train the »digital colleagues« in diagnostic pathology, the team led by Klauschen collaborated with lots of human colleagues from various university hospitals. They mapped the pathological changes on thousands of digital microscopic images of tissue sections. The pathologists »fed« the software with these findings, so that it could »learn« to distinguish, for example, tumor tissue from healthy tissue. »We performed these so-called annotations for different diseases,« Klauschen says. The scientists have so far trained the software to reliably identify lung, breast and colon cancer as well as immune cells in tumor tissue and various tumor markers. And the technique



With the help of AI-based diagnostics, fillings and restorations are immediately visible on X-ray images of the oral cavity.

is not limited to cancer detection: It can also be used to analyze infections as well as degenerative, connective tissue and autoimmune diseases, »anything that causes visible changes in tissue.«

In routine diagnostics the AI system promises not only to save time and help avoid mistakes, but also to pave the way for personalized medicine. Therapeutic decisions increasingly require the precise detection and quantification of certain characteristics in tissue samples. The software developed by the scientists is already being used in diagnostics at Charité's Institute of Pathology. Other institutes and clinics plan to follow suit; the software is currently in the process of being certified for broad use.

Detecting caries and infections in the oral cavity

Together with data scientists and programmers, dentists at Charité developed the software dentalXrai Pro. Since 2017, the team has been working with a clear goal in mind: to help dentists identify pathologies and restorations more accurately and in less time on jaw X-rays, enabling optimal treatment and improved patient communication. The Digital Health Accelerator of the Berlin Institute of Health (BIH) assisted and financed the project from prototype and product development all the way to the spin-off of the start-up dentalXrai GmbH.

X-ray analysis usually takes up a good deal of time in dental practices, yet rarely is it completely accurate. If the examining dentist is pressed for time or inexperienced, this will negatively affect the quality of the

Innovation Enablers: BIH Innovations

Since 2017, the BIH's Digital Health Accelerator (DHA) has been supporting scientists in translating their digital research projects into clinical practice. The DHA is a support and development program of BIH Innovations, the joint technology transfer office of the BIH and Charité. The first two companies were spun off in 2020.

diagnosis and the treatment derived from it. To solve this problem, the dentist Dr. Falk Schwendicke and co-founder Dr. Joachim Krois rely on artificial intelligence. Three years ago they started developing dentalXrai Pro; today they oversee a team of ten. The software enables the automated analysis of dental X-ray images using AI algorithms; it reliably detects caries, infections and restorations such as crowns, implants and root canal fillings and highlights the findings in color. The automated analysis of findings saves dentists a considerable amount of time.

»AI is not responsible for the dental examination and does not reach decisions on the treatment,« emphasizes Schwendicke, Head of the Department of Oral Diagnosis, Digital Health, and Health Services Research at Charité. »But it raises dentistry to a standardized, high-quality level and immensely speeds up the analysis of X-rays, so that dentists can use the time more effectively for talking to patients.« •

→ Learn more at:
dentalxr.ai
www.aiagnostics.com
www.bihealth.org/en/translation/innovation-enabler/innovations

Encounters

At the heart of every innovation are the people who work together to realize ideas. But where do those ideas come from? From working daily with patients and learning about their medical needs, and from discussions with colleagues, which uncover new possibilities for interdisciplinary collaboration. Those ideas grow within modern facilities that provide the right spaces for novel approaches.

Through its funding programs, events, and new buildings, the BIH creates forums for fruitful encounters that give rise to exciting new ideas.



»The Pandemic Caught Us Off Guard«

As an Associate Professor at the School of Public Health at the National University of Singapore (NUS), Professor Falk Müller-Riemenschneider specializes in broad-based population health studies. He is particularly focused on the prevention of common diseases. Since 2019 he has regularly traveled to Berlin as a BIH Visiting Professor, where his host is Professor Roland Eils, the BIH Chair for Digital Health. Müller-Riemenschneider is currently in Berlin for longer than planned as the COVID-19 pandemic has made it difficult for him to return to Singapore. Marie Hoffmann from Stiftung Charité spoke with the two in August 2020 via videoconference.



Falk Müller-Riemenschneider (left) and Roland Eils investigate the role of life style factors on common diseases.

Professor Müller-Riemenschneider, Professor Eils, how has the pandemic affected your joint project?

MÜLLER-RIEMENSCHNEIDER Our partnership had already come relatively far prior to the lockdown. Dr. Eils and I are both very interested in the application of mobile technologies for personalized medical care. The preliminary talks and work meetings we held in Berlin and Singapore were extremely promising and we had already identified other cooperation partners from Berlin and Singapore. The fact that the NUS recently became an official strategic partner of the Berlin

University Alliance made things even more interesting. Then the pandemic hit. Unfortunately, further organization has been on hold since then.

EILS My trip to Singapore to visit Dr. Müller-Riemenschneider in February was the last business trip I made abroad. Since then, I've been working primarily from home in Germany. We had already established some very promising approaches for the partnership, but the pandemic caught us off guard.

What challenges have you otherwise experienced in your work as a scientist?

MÜLLER-RIEMENSCHNEIDER With regards to scientific work, my team and I have been very limited. Our projects in Singapore are typically large-scale research projects with thousands of subjects who participate in our research. We then investigate risk factors or proactive factors for certain widespread diseases on the basis of the findings of our research. These findings enable us to develop programs to promote health. As a result of the pandemic, we were prevented from inviting subjects, the fundamental basis of our research. Only recently has this once again become a possibility under special hygiene requirements. This has set us back considerably.

EILS On a scientific level, the pandemic caused me to shift my research slightly towards SARS-CoV-2.

That's interesting. What precisely did you get involved with in current coronavirus research?

I'm actually a cancer researcher and specialize in the human lung. This has enabled me to gain extensive experience in the research of the pathophysiology of this organ, which has proven incredibly useful for COVID-19 research. We studied our COVID-19 patients at Charité and looked at which decisive factors may lead to a light or severe disease progression for the patient. We were able to establish how the immune system overreacts in patients who experience a severe course of disease.

I take it that this also significantly changed your daily research work?

EILS I typically work in a very international setting. Many of my cooperation partners are located abroad, particularly in Asia and in the United States. This has radically changed in recent months. All of a sudden, we have all been working together in Berlin. An unexpected number of very fruitful partnerships were forged, which would not have occurred without the pandemic. While I may have previously looked afar to find answers, now I have met some great colleagues in Berlin and released a number of exciting COVID-19-related publications with them.

Let's quickly return to your sponsorship as a Visiting Professor and the associated joint project: What do you hope to achieve in the future?

MÜLLER-RIEMENSCHNEIDER I hope that, once it's possible to travel again, all parties in Singapore and Berlin remain just as willing to participate as they were at the start of the year, and that we can seamlessly kick back off from where we left things. I really hope that the pandemic will not have too much of an impact on international cooperation and that our colleagues –

Stiftung Charité

With the Private Excellence Initiative Johanna Quandt, Stiftung Charité is supporting the establishment and development of the BIH. It concentrates in particular on sponsoring outstanding individuals in all phases of their academic career, from studying through to professorship. It supports individual projects generating a major added value for translational and systems medicine-oriented research.

A total of up to €40 million has been provided for the Private Excellence Initiative for the period of 2014–2022, making it one of the largest donations by a private person for science in Germany.

STIFTUNG CHARITÉ

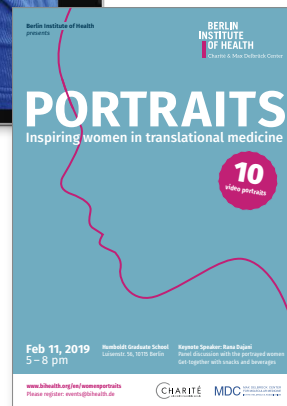
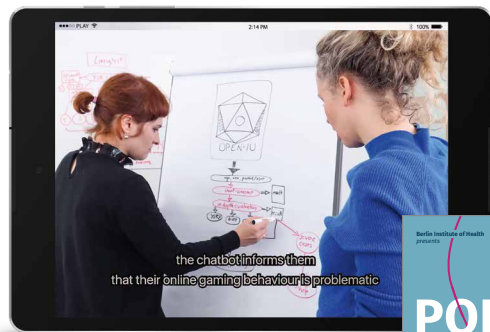
despite the fact that they will have a good amount of work to catch up on as a result of the pandemic – will find enough time for this.

EILS I can only agree. Hopefully, we will soon be able to release the organizational brakes and start planning for the joint Charité-NUS non-virtual workshop on digital health. •

→ The Private Excellence Initiative supports various projects at the BIH. Learn more at: www.bihealth.org/en/research/funding/excellence-initiative-johanna-quandt/professorships

Diversity in Science

To gain high-level innovative scientific insights we need input from a multitude of perspectives. It is therefore essential that more women be present at all hierarchical levels and on all scientific bodies. Improving equality of opportunity is a key component of the BIH's strategy. It aims to establish a gender-sensitive and diverse organizational culture with a more equal gender balance at every level.



With its structural measures, the BIH hopes to raise awareness of the disadvantages facing women and other underrepresented groups in the life sciences and to work towards eliminating those disadvantages in the longer term. One of the focuses of the BIH's work in this area has been to increase visibility of women scientists. There are numerous examples of remarkable women scientists who have not received the same attention as their male colleagues. In 2018–2019, the BIH produced a series of video portraits called Inspiring Women in Translational Medicine. In these 15 videos, women scientists at the BIH speak about their research and personal motivation.

The BIH has also organized several Diversithon meetings, where interested parties get together to edit existing Wikipedia biographies of women scientists and other underrepresented groups and to compose new ones, with the aim of making the world's biggest encyclopedia more diverse. •

→ **Inspiring Women in Translational Medicine**
www.bihealth.org/en/inspiring-women

Alongside ensuring family-friendly working conditions, the BIH's gender equality efforts focus on various structural and individual measures. The BIH offers career support to women scientists generally and is also working to compensate for existing disadvantages on the individual level. Concrete measures include the annual workshop and coaching program [femalecareer@BIH](mailto:femalecareer@bih) and the BIH Gender Equality Fund, which offers financial support to women postdoctoral scientists with family responsibilities.

Science for Your Ears

In the BIH monthly podcast »Turning Research into Health,« BIH scientists speak about their research, while also providing health information and advice. They talk about blood pressure, report on new cancer therapies for children, reveal the link between stressed mothers and overweight children, and explain what broccoli has to do with colon cancer. They provide insight into the development of innovative new therapies – for example, how bacteria can reduce blood pressure and how stem cells might be able to cure muscular disorders. While the first episode of the podcast had just 100 listeners, in the meantime the series has more than 18,000 enthusiastic subscribers. It has also been awarded a prize for health communication. The most listened to episode so far is No. 14 on the topic of novel viruses, posted on January 21, 2020 – with BIH Professor Christian Drosten!



Aus Forschung wird Gesundheit

BIH

→ You can subscribe to the podcast on all major podcasting platforms – or listen to it directly on the BIH website:
www.bihealth.org/en/news/media-center

Meet and Greet

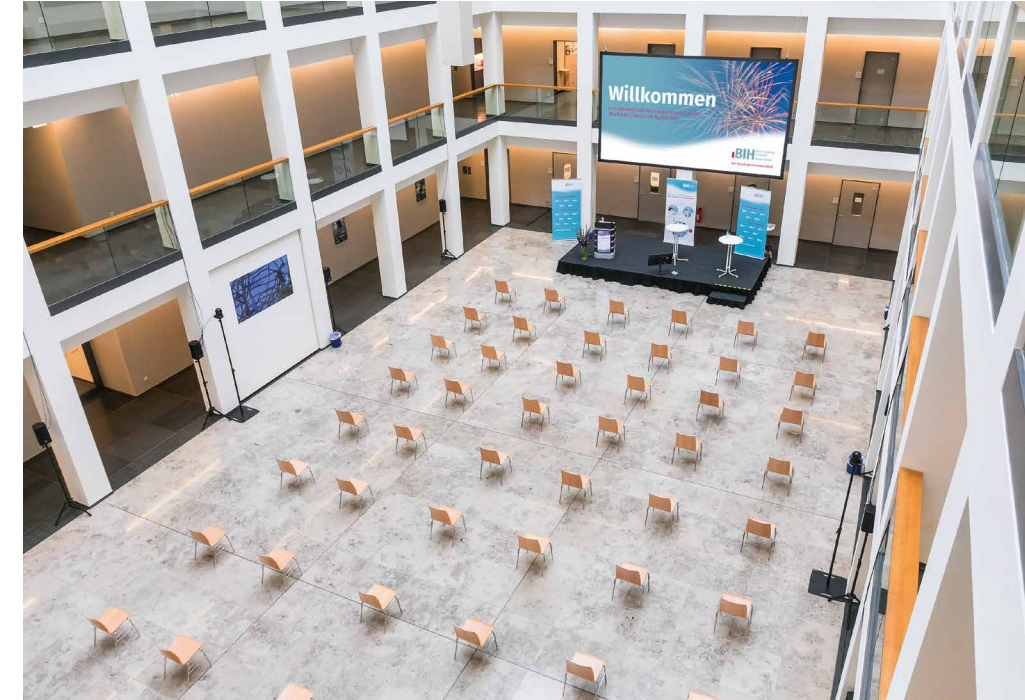
Conversations, presentations, meetings: without scientific exchange there can be no scientific progress. That's why the BIH organizes many opportunities for members of its community to meet up.



Governing Mayor of Berlin Michael Müller visits the biobank at the BIH and Charité during the Long Night of the Sciences.

Personal encounters are at the heart of every innovation; they are the spice of scientific life, and the seed from which new ideas grow. With that in mind, the BIH organizes many different events for its community each year – including the Clinician Scientists Retreat at Schloss Genshagen, the big Future Medicine Science Match with 1,000 participants at Kosmos Berlin, and the new BIH lecture series Frontiers in Translational

Medicine in the Virchow auditorium. Of course, scientists also have valuable meetings over coffee in the office kitchen. The coronavirus pandemic has taken all of that away from us. Some meetings have taken place virtually, but that has been a poor substitute for the personal encounters that the BIH needs in order to flourish. Hopefully we'll be able to meet again in person before too long! •



→ **Keep up to date on BIH events by visiting the BIH website or by subscribing to the Events Newsletter:**
www.bihealth.org/en/news/events

New Buildings for the BIH

Berlin-Buch and Berlin-Mitte will soon be home to new BIH research facilities.



Architectural rendering of the Käthe Beutler Building in Berlin-Buch.

In October 2018, BIH and MDC board members laid the cornerstone for the Käthe Beutler Building (KBB) on Campus Berlin Buch. Parts of the former Robert Rössle Clinic are being renovated and supplemented by a new building. Starting in 2021, researchers working mainly on vascular biomedicine will move into the KBB. The building, which is named after the German pediatrician Käthe Beutler, will contain around 2,500 square meters of floor space and provide space for some 135 researchers in laboratories, offices and communication zones. Construction costs total €24.3 million – 90 percent of which comes from the Federal Ministry of Education and Research (BMBF) and 10 percent from the Berlin Senate Chancellery – Higher Education and Research.

The border between Berlin and Brandenburg runs through the middle of the building. It is fitting, of course, that bridging the border between basic research and clinical practice is an everyday occurrence at the BIH.

The namesake is also well chosen, said Axel Radlach Pries, Dean of Charité and interim Chief Executive Officer of the BIH: »Käthe Beutler was in 1917 one of the first women to study medicine at Charité and then actually practice the profession. She unfortunately had to flee to the United States during the Nazi era, but she passed down her inquiring spirit. Her grandson, Bruce Beutler, won the Nobel Prize for Medicine for developing an immunotherapy to treat cancer. This is an important field and one that a BIH research team is also focusing on.«

World-class research and the best in patient care under one roof

On Campus Charité Mitte, the Outpatient, Translation and Innovation Center (Ambulanz-, Translations- und Innovationszentrum – ATIZ) is currently taking shape adjacent to the hospital's main patient care facility. The existing building, which formerly housed surgical, intensive care and emergency units, was gutted for reconstruction and will be used jointly by the BIH and Charité starting in 2022, after renovations are completed. Federal Research Minister Anja Karliczek and Governing Mayor of Berlin and Senator for Science and Research Michael Müller paid tribute to the successful progress of the construction work at a topping-out ceremony held in July 2020.

The modern six-story research building, which contains 14,875 square meters of floor space, will unite the BIH's innovative patient-centric translational research and Charité's medical care under one roof. It plans to house a joint translation center for international research groups, complete with state-of-the-art spaces for labs, offices and technology facilities; an innovation center



Michael Müller

» Berlin is the right place to create the medicine of tomorrow.«



Governing Mayor of Berlin Michael Müller and Federal Research Minister Anja Karliczek attended the topping-out ceremony for the ATIZ building.



with dedicated space for biomedical technology transfer; and a patient center of the BIH Clinical Research Unit equipped with examination and treatment rooms for clinical trials. Charité will have complementary research spaces in ATIZ, which will be used for over-arching studies. Patients will also receive care there outside of studies, such as in the Oncological Outpatient Department and Day Case Unit as well as in the

Skin Cancer Center of the Department of Dermatology and its surgical and functional units. In addition, the Simulation and Training Center will provide training to physicians within and outside Charité on how to use next-generation technologies and methods. •

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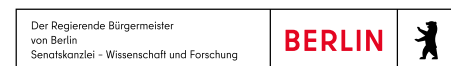


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What Is Translation?



Professor
Ulrich Dirnagl



Successful translation is based on **high-quality** and **reproducible research**.



Professor
Sylvia Thun



Translation in medicine means using innovative digital methods to **transfer research findings** into patient care and disease prevention.



Professor
Hans-Dieter Volk



Innovation with a defined clinical practicality and active engagement towards ultimately **achieving the critical goal of reduction to practice**.



Professor
Marcus Mall



Translation is a **complex process** that makes knowledge (from biomedical research) usable in medicine (to **improve disease prevention, diagnostics and therapeutics**).



Professor
Holger Gerhardt



Translation **bridges gaps** between disciplines, between their different languages, cultures and ways of thinking; it creates new understanding; provides meaning and utility; turns theory into practice; and **permanently changes** how we view and treat disease.



Professor
Petra Ritter



If we can plan **surgery** on a **virtual brain** and that leads to a **better outcome for patients**, then that is translation.



Professor
Thomas Sommer



Translation is an unfortunately ambiguous term that describes the **process** of how science can help **improve people's health**.

Turning Research into Health.