Creating Measurable Impact for Patients and Communities

Strategic Research Program 2023 – 2027
Preface and Acknowledgments

Creating measurable impact for patients and communities – this is the mission that the Berlin Institute of Health at Charité (BIH) is committed to with its strategic research program for the years 2023 to 2027.

After the integration of the BIH into the Charité in 2021, we presented the institute’s research program to an international panel of experts on the occasion of an external evaluation of BIH, in June 2023. The reviewers were convinced of the quality of the research and impressed by the motivation and enthusiasm of the BIH faculty, especially the young scientists, who deeply anchor the concept of translation in their work to fulfill the mission of BIH. The valuable suggestions and recommendations of the review panel during the evaluation process have been incorporated into the final version of the strategic program, which was approved by BIH’s Governing Board on May 7th, 2024.

We are very proud to be able to present to you today a document that combines the scientific excellence of our researchers and their teams with the translation-supporting platforms and programs of the BIH.

At this point, we would like to thank all those involved, above all the scientists, for their invaluable work and extraordinary commitment in the development process. The joint strategy development was a significant milestone in BIH’s still young history.

Together with our colleagues at Charité – Universitätsmedizin Berlin and the Max Delbrück Center for Molecular Medicine, the BIH is dedicated to strengthening and promoting the translational ecosystem in Berlin, as well as in the national and international context. Therefore, our thanks also go to our diverse partners from science, business, and society for their trustful cooperation and support.

We look forward to the implementation and insights from this research program – for the benefit of patients and for those who engage in biomedical translation.

Turning research into health.

We wish you an enjoyable and inspiring read.

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The Berlin Institute of Health (BIH) has an ambitious and important mission: biomedical translation. We define biomedical translation as a process that converts scientific discoveries into products and services to benefit patients. Patient care tends to follow standardized processes that are evidence-based but do not address all individual drivers of disease. The BIH tackles unmet medical needs in the field of precision medicine by contributing scientific concepts and practical solutions to directly benefit individual needs of patients and support translational communities.

The BIH is guided by the principle of responsible research. Scientific results must be highly reproducible, transparently evaluated, carefully validated, and able to meet patient needs. We respect the patient’s perspective throughout their patient journey, which includes: first awareness of symptoms; personalized prevention; deep genetic and phenotypic diagnostics; improved treatments; and innovative aftercare including real-world data. To benefit patients, the BIH is dedicated to advancing the concepts of open access and open innovation, sharing state-of-the-art research infrastructure and innovative data spaces for collaboration. To develop products, solutions and services, we invest significant effort into prototyping and refinement programs, and into support structures for entrepreneurship, spin-off formation, and public-private partnerships. We are thus building an agile translational ecosystem to foster individual skills and collaborations between researchers, clinicians, private-sector partners, patients, and other stakeholders. Our efforts facilitate the interdisciplinarity that is critical for an accelerated and efficient translation to patient care.

As a networking institute for excellent science, we provide infrastructures, resources, and concepts in partnership with regional, national, and international actors. Our researchers are globally recognized experts in developing computational methods, refined molecular diagnostics, and targeted advanced therapies. With the Strategic Research Program we pursue three interconnected and collaborative Research Objectives: (1) responsible translational methodologies, (2) computational and functional precision medicine, and (3) advanced regenerative therapies. In the resulting institutional agenda, defined scientific activities have been designed in close interaction between the BIH’s Research Groups and additional partners. The Research Objectives are driven by the BIH’s Research Groups and rely on support from the BIH’s translational Platforms and Programs. Translational platforms comprise our Core Units that offer specialized expertise and innovative technologies, as well as data and sample platforms and platforms for stakeholder networking. Translational programs provide milestone-dependent project support, career development, and counseling for entrepreneurial efforts.

Synopsis of the Strategic Research Program
The BIH thus presents a unique combination of scientific objectives, platforms, and programs, acting in concert to advance translation and offering numerous contact points for internal and external collaborations.

The BIH is integrated into the translational research landscape at all levels. We are part of Charité – Universitätsmedizin Berlin, one of Europe’s largest university medical centers with a strong research faculty. We appreciate a privileged partnership with the Max Delbrück Center for Molecular Medicine and have built additional alliances in academia and industry. Supporting nationally impactful initiatives and networks, implementing national mandates, and developing international partnerships are strategically important elements of our research program. Our interdisciplinary approach is based around the provision of infrastructural, financial, and conceptual support for translational researchers and their communities. Thanks to our unique constitution, mission and structure, the BIH is a pioneer in Germany’s scientific landscape, supported by federal funding yet integrated into a leading university medical center, thus contributing strongly to Germany’s national research strategy.

With our orchestrated scientific objectives, platforms and programs, we promote cutting-edge and responsible research in the field of translation. Our vision is to be Germany’s leading driver of a translational ecosystem for precision medicine and a key player in regional, national, and international networks, serving both patients and translational communities.

Figure 1: BIH at a Glance. Researchers from BIH Platforms, Programs and Scientific Sections form dedicated, interconnected teams to tackle unmet medical needs with biomedical translation as the focus of all activities. Our science is focused on Responsible Translational Methodologies, Computational and Functional Precision Medicine and Advanced Regenerative Therapies. Platforms (Technologies & Tools, Data & Samples, Networking) and Programs (Mindset, Skillset & Product Development) are essential enablers for translational science.
The BIH Mission and Vision

Our mission is biomedical translation, which is the conversion of scientific discoveries into products and services to benefit patients.

Patient care tends to follow standardized processes that are evidence-based but do not address all individual drivers of a disease. The BIH operates in the rapidly growing field of precision medicine, tackling unmet medical needs to turn research into health.

Our research is based on two principles:

**Patient orientation:** Patient-oriented research seeks to deliver tangible benefits to patients by centering their perspective, including: first awareness of symptoms, personalized prevention, deep phenotyping and diagnostics, improved treatments, and innovative aftercare.

**Community orientation:** Community-oriented research seeks to serve scientific communities and beyond by creating useful tools and services for innovation with direct or indirect benefit for patients. This includes developing novel approaches, useful analysis tools, and new products, solutions, services, and platforms for the scientific community, as well as contributing to guidelines, standards, protocols, and best practices.

Figure 2: Our mission is to benefit patients as well as scientific communities and beyond by creating measurable translational impact (see Figure 3).
Both approaches require iterative feedback mechanisms for constant improvement and a commitment to responsible translation, promoting and teaching practices that produce robust, transparent, and ethical results with efficient use of resources. As a networking institute, the BIH is developing an agile translational ecosystem that empowers scientists from Berlin and beyond to work together to address medical challenges. This includes support platforms, the development of translational personnel, validation programs, and strategic collaborations. The ecosystem leverages the interdisciplinary potential within the institute and beyond as part of Charité – Universitätsmedizin Berlin (Charité), in a privileged partnership with the Max Delbrück Center for Molecular Medicine (MDC), and in collaboration with other key players.

The BIH’s translational mission is shared with other medical faculties, universities, research institutes, and private-sector companies. The BIH is, however, unique in its choice of specific goals that address medical and scientific needs. Our institutional strategy comprises three interconnected Research Objectives whose unique combination within one institution creates opportunities to explore boundaries and exploit synergies:

- Research Objective 1: Validate and refine responsible translational methodologies
- Research Objective 2: Boost computational and functional precision medicine
- Research Objective 3: Develop advanced regenerative therapies

The Research Objectives are embedded in a rapidly changing health sector. On the one hand, societal and environmental stressors are accumulating in a globalized economy with unstable political conditions. On the other hand, novel opportunities are emerging from scientific and technological breakthroughs such as computational sciences with artificial intelligence, genomic medicine, synthetic biology, and medical devices. Between these challenges and opportunities, innovative solutions for unmet medical needs are required in areas such as communicable diseases, complex manifestations of frequent diseases, multimorbidity, and rare diseases.

Medical research in Germany is highly competitive in terms of scientific discovery, but much less efficient when it comes to developing and implementing comprehensive practical solutions, services, and products to help patients. Within this context, our research program seeks to bridge the gap between proof-of-concept discoveries in model systems and real-world applications. Our endpoints for successful translation reflect innovative impact in four areas:

- **Accelerated Translation to Patient Care**: directly impacting patient care via responsible research in situations where lengthy product development is not required e.g. some forms of computational approaches, or patient-centered design of clinical trials
- **Open Access and Use**: providing scientists within the BIH and beyond with access to data and analytical tools to improve patient outcomes and to support evidence-based practices, while addressing challenges related to data privacy, security, and intellectual property rights
- **Open Innovation**: fostering collaboration and transparency beyond the BIH and the Charité in order to develop novel solutions to benefit patients, while increasing efficiency in the healthcare, pharmaceutical, and biotech sectors
- **Entrepreneurship**: creating intellectual property, products, and spin-offs to transfer knowledge into innovative solutions for the market, while ethically balancing economic goals and patient welfare.
We are building on our experience in each of these areas by conducting the work described in the following pages. When executing this program in fruitful internal and external interactions, translational success will be monitored using suitable performance indicators.

Providing a perfect context for the BIH, the Charité sees translation as its key strategic task. As a university medical center, the Charité invests in a science-based culture of theory and practice, exploring boundaries in order to serve humans in all dimensions of health. The BIH complements this strategy with our three Research Objectives, while maintaining operational independence when making decisions about specific goals, methods, personnel, collaborations, and infrastructure.

Our agenda perfectly fits into Germany’s national research strategy and is well-aligned with the Charité’s mission, strategy, and structures. Our independent research remains connected to the Charité while fulfilling a national mandate alongside other national players such as the German Centers for Health Research.

Figure 3: Mission driven creation of measurable translational impact via accelerated translation to patient care, open access and use, open innovation, and entrepreneurship.

Our vision is to be Germany’s leading driver of a translational ecosystem for precision medicine and a key player in regional, national, and international networks, serving both patients and translational communities.
Our History – the Development of a Translational Ecosystem

When the BIH was conceptualized in 2011, the aim was to foster systems medicine and translation by bringing together the MDC, a successful life science research institute, and the Charité, one of Europe’s largest university medical centers.

In 2013, the BIH became a legally independent non-university research institution, a public corporation of the State of Berlin, formed by a partnership between the State of Berlin and the Federal Republic of Germany, with the Charité and the MDC as members of the BIH corporation.

Initially, we focused on building connections between our partners and fostering a translational systems medicine community in Berlin. The strategy involved providing intramural project funding and establishing translational infrastructure. Collaborative Research Grants (CRG) supported large translational research projects over a four-year period, while Twinning Research Grants (TRG) funded smaller projects for two plus one years. Both formats emphasized a balanced representation of Charité and MDC expertise. Four CRGs and seven TRGs were funded in total with 3 million an 8 million euros, respectively.

To support these research projects, a translational ecosystem of support structures was created from 2014 onwards, including the Omics Core Units (Genomics, Proteomics, Metabolomics, Bioinformatics), a Stem Cell Core Unit, a Research IT Core Unit, and investments in biobanking. A clinical research unit facilitated clinical studies and observational cohorts across four Charité campuses.

We also launched a project funding scheme for validation efforts. This initiative later entered into collaboration with SPARK Global (initiated at Stanford University) and became SPARK BIH, a central pillar of technology transfer activities at the BIH today.

Since 2017, the Digital Health Accelerator (DHA) has complemented SPARK BIH by implementing ideas for digital innovations in practice, including start-up formation.

We achieved the goals set for this first phase, resulting in fruitful collaborations between Charité and MDC, and a flourishing Clinician-Scientist Program, creating a community of young translational enthusiasts.

By 2016, we had entered a second phase, transforming project funding into long-term institutional funding. The BIH Strategy 2026 emphasized strategic recruitment, leading to the hiring of 35 professors, seven junior Research Group leaders, and five Core Unit leaders by 2019. Established in 2017, the QUEST Center for Quality, Ethics, Open Science, and Translation focuses on meta research and provided tools for translational research. At the same time, the BIH started a large cohort project, the Berlin Longterm Observation of Vascular Events (BeLOVE) cohort study, which aims to provide a rich resource for collaborations and the development of infrastructures for clinical research across sites and clinical disciplines.

To combine the best of the first two phases, the next phase aimed to identify common research interests of the BIH, the Charité, and the MDC, and to embed BIH recruitment in a network of collaboration partners. Research platforms evolved into translational hubs, focusing on digital medicine, clinical-translational sciences, multi-omics, organoids, and cell engineering. Intramural project funding kickstarted further collaborations, and key areas received strengthened support and new recruitment. As a result of these efforts, we strengthened our connection with the Charité and the MDC, fostering collaborations and serving a broad community. Most of our faculty had been anchored in the Charité for a number of years and several strong collaborations with Charité clinics had been established.

It was thus a natural step to embed the BIH into the Charité in order to make translational processes even more efficient and to sharpen our mission even more strongly towards responding to medical needs and developing new approaches to benefit patients. By 2020, preparations were underway to integrate the BIH into the Charité. BIH maintains a privileged partnership with the MDC, emphasizing cooperation in omics technologies, single-cell approaches, and cardiovascular research. Collaborating with the Charité, the BIH operates joint programs, including technology transfer, clinician scientist programs, and infrastructures for clinical research. Dual employment of BIH Research Group leaders in Charité clinics ensures the seamless translation of research findings into clinical practice.
Organization and Governance: the BIH being the Third Pillar of Charité

On January 1, 2021, the BIH became the third pillar within Charité, alongside patient care and the medical faculty. Accounting for 4% of the Charité’s personnel and 10% of its researchers, the BIH plays a crucial role in achieving the Charité’s translational goals. This integration was established through an Administrative Agreement signed on July 10, 2019, between the State of Berlin and the Federal Republic of Germany. The Berlin House of Representatives passed the BIH Integration Law on October 1, 2020, using Article 91b of the German Constitution, which allows structural federal support of state-owned scientific institutions. Within the Charité, we maintain economic and strategic independence, receiving 90% of our funding from the German Federal Government and 10% from the State of Berlin. The BIH retains separate assets, partial legal capacity, and decision-making autonomy.

Complying with the Berlin University Medicine Act, the BIH organizational structure includes governing bodies such as the Governing Board, Board of Directors, Extended Board of Directors, and the Scientific Advisory Board. The Board of Directors oversees strategic planning, and the Extended Board ensures the inclusion of full-time scientific staff in decision-making processes. The Governing Board monitors management effectiveness and provides guidance.

The Scientific Advisory Board, comprising up to 14 external experts, advises on scientific matters related to our research focuses, projects, and collaborations. Interfaces between the BIH and Charité are established through common governance, shared infrastructures, and administrative processes. The chair of our Board of Directors is a member of the Charité’s board of directors, and of our Governing Board chair holds a seat on the Charité’s supervisory board.

The BIH is structured into six sections. The two Administrative Sections are Central Management and Administration (CMA) and Competence and Project Development (CPD). The four Scientific Sections are: Translational Sciences and Applications (TSA), Exploratory Diagnostic Sciences (EDS), Advanced and Personalized Therapies (APT), and Medical and Health Data Sciences (MHDS). These sections are each led collegially by two section heads, fostering scientific-integrative cooperations.
Organizational and Personnel Development

We seek to strategically enhance our translational research capabilities and organizational effectiveness across key areas of organizational and personnel development. We commit to establishing a system for managing and identifying the skills and expertise that are essential for translational research. This includes dedicated curricula for doctoral students, postdocs, and faculty.

Team development and agile governance emphasize effective communication and transparent participatory decision-making to foster a positive organizational culture and the adaptive allocation of resources in milestone-dependent project development.

To account for the needs of personnel and career development, we promote transparent career paths and structured feedback processes linked with reliable financial support for basic equipment. We build capacity via targeted continuing education programs, a central landing page for accessible training programs, and translational leadership development with mandatory modules and coaching.

Our conceptual framework for translational research careers and the development of evaluation procedures is based on the European Framework for Research Careers and the Coalition for Advancing Research Assessment (CoARA).

Alumni outreach is something that BIH wants to start fostering, with plans to establish an alumni network integrated into the central Charité Alumni Platform, facilitating networking events and information sharing to maximize the benefits of our joint expertise.

Internationalization

The active knowledge exchange with international stakeholders increases the BIH’s impact and positions us as a global player in the field of biomedical translation. In addition to our researcher’s scientific networks, we collaborate with selected institutional partners in other countries on initiatives such as co-innovation programs (Singapore, Israel, SPARK global). We are also a popular point of contact for national and international organizations seeking knowledge exchange about specific translational measures (e.g. Clinician-Scientist Program, the BIH QUEST Center for Responsible Research).

Diversity and Equality

We are dedicated to cultivating a gender-sensitive and diverse organizational culture that seeks to eliminate discriminatory structures and promote equality and diversity, which we recognize as critical to producing innovative top-level science.

Our Equality and Diversity Strategy (2021-2025) aims to overcome prevalent discrimination in the scientific system by supporting women scientists and expanding efforts to include individuals with diverse backgrounds. This strategy addresses broader societal inequalities and integrates equality and diversity into our quality assessment and organizational development.

In alignment with the Charité’s evolving Equality-Diversity-Inclusion strategy, we adopt an intersectional approach, actively supporting the career development of women scientists, as well as trans*, intersex*, nonbinary, and queer individuals. Our initiatives include training, coaching, networking, and financial support for those with caregiving responsibilities.

To overcome structural barriers, we emphasize data collection and evaluation, covering aspects such as staff, funding, participation, resources, parental leave, international staff, and discriminatory experiences. Maintaining gender parity in elected leadership roles since 2021, we seek to address challenges predominantly faced by women. Supportive measures include childcare opportunities and contract extensions for scientists on parental leave, ensuring comprehensive support for people of all genders in order to minimize structural disadvantages and encourage the sharing of caregiving responsibilities. This also applies to individuals involved in translational projects with sharp milestones and performance-based allocation of resources.
Strategic Campus Development

We strategically develop our campus to align with our networking culture and translational mission. Currently the institute has around 25,000 m² lab and office space, located within the four Charité campuses, with 70% of the space being spread across Charité Campus Virchow-Klinikum (CVK) and Charité Campus Mitte (CCM). This facilitates close collaborations with our clinical and scientific partners at Charité and the MDC. We are also embedded in Berlin’s rich scientific, educational, and political landscape, surrounded by partners such as Humboldt Universität, Freie Universität and Technische Universität Berlin, various research institutes (Max Planck Institutes, Helmholtz Center, Fraunhofer Institutes, Leibniz Institutes), the Charité Foundation and Einstein Foundation, the European School of Management and Technology (Germany’s leading business school), and many others. Our infrastructure is distributed across the four campuses as follows:

– Our Advanced Therapeutics research activities are mostly located at CVK, fostering collaboration with exciting science and infrastructure projects such as the central biobank (ZeBanC), the Berlin Center for Advanced Therapies (BeCAT), theSimulated Human (Si-M), the Deutsches Herzzentrum der Charité (DHZC) and the National Center for Tumor Diseases (NCT).

– Our campus at CCM focuses on Medical and Data Science, Digital Health, and Genomic Sciences. Construction of the Rahel Hirsch Center was completed in 2023. Connected with the main hospital tower, this six-storey building brings together our translational research groups and the Charité’s clinical care. The Center is located within walking distance of two important partners: the German Center of Rheumatism Research (DRFZ) and the Berlin Institute of Medical Systems Biology (BIMSB), which is part of the MDC.

– In 2022, construction of the Käthe-Beutler-Haus was completed at Charité Campus Buch (CCB), the main MDC campus. Within this new laboratory building, Research Groups and omics Core Units from the BIH and the MDC are working in close collaboration.

– Our BeLOVE unit for realizing clinical and cohort studies is based at Charité Campus Benjamin Franklin (CBF).

Our long-term strategy prioritizes strengthening collaborations by sharing research infrastructure, enhancing modularity in lab and office spaces, and introducing flexible working concepts. This strategy thus also addresses sustainability and cost-efficiency. The BIH’s campus concept finely balances our interactive localization in Berlin’s rich and complex ecosystem, and the integration of expertise across multiple disciplines.

Figure 5: To promote collaboration and to accelerate translation, BIH researchers and employees conduct research and work in close proximity to clinical care and scientific partners on various campuses in the Berlin area.
Our three interconnected Research Objectives were developed in a participatory process involving all Principal Investigators (PIs) and their teams. They thus embody our institutional mission and the strengths, goals, and expertise of our people. Their interconnected nature adds value by pooling resources and fostering scientific interaction in order to address prominent medical and scientific needs. Connections emerge from thematic coherence, overarching projects, collaborations between PIs on different activities, and the joint use of BIH’s platforms and programs. Each Research Objective strives to advance its field while interacting with the other fields to address interdisciplinary topics or define common standards. The Research Objectives are mainly carried out by our Research Groups, supported by our Translational Ecosystem (Figure 6), which includes the BIA, the tech transfer team Charité BIH Innovations (CBI), and our Core Units. The BIA and CBI provide programs to develop translational mind-sets and skills. They also provide competitive milestone-dependent resources for personnel and project development. The Core Units provide admission to expert knowledge and state-of-the-art technologies and applications. Finally, our research profits from access to the excellent clinics and clinical dataspaces at the Charité.

The three Research Objectives bring together Research Groups and all units of the institute, scientific and administrative, while facilitating responsible translational research and nurturing a translational culture. We are thus open to new formats for co-creation, co-working, co-development, and co-education with partners from start-ups, industry, patient representatives, regulators, investors, and other translational stakeholders. Our unifying goal is to create measurable impact for patients and translational communities.

Figure 6: BIH and Charité form a comprehensive translational ecosystem, inviting additional players to create synergies.
The first Research Objective seeks to develop Responsible Translational Methodologies for biomedicine. Our goals include: robust reproducible research; transparent open access to research results and data; validated incentives and key performance indicators (KPIs); education; and a patient-centered translational culture at the BiH, with outreach to Charité, the translational ecosystem in Germany and beyond. Blending approaches from metascience and scientific standards, this Research Objective offers coordination and support for education and training, as well as project guidance for technology transfer. In particular, the various Core Units continuously develop infrastructures (technology, methodology, applications) to support preclinical and clinical research. Another key component is the development of FAIR (findable, accessible, interoperable, reusable) data platforms, which protect personal data while facilitating its use for healthcare and research. To unlock the full potential of data science in medicine, it is necessary to ensure data protection and interoperability while addressing federal structures which are particular challenging within the EU and Germany. By productively fusing responsible research, robust methodology, open science, and meta-research, this Research Objective embodies our view of translation as a science. It provides the foundation for our activities around technology transfer; clinical incubation; education programs promoting patient-centricity, inventions, and entrepreneurship; as well as additional valorization activities. The Computational and Functional Precision Medicine Research Objective takes...
an interdisciplinary approach to predictive and preventive personalized medicine, covering all aspects of data-driven and functional experimental research. This ranges from the use of artificial intelligence to the analysis of large health-related datasets using state-of-the-art biomolecular analytics in experimental studies to identify disease mechanisms. The goal is to match individuals with personalized prevention plans and interventions, addressing key steps of the patient journey. For example, we seek to deliver insights into diseases to facilitate decision support, as well as designing novel treatments and aftercare procedures. Our activities here also help shaping the field around medical informatics and bioinformatics Germany-wide.

We integrate computational analytics, experimental biology, and clinical medicine to advance the field of precision medicine. In addition to optimizing computational and experimental approaches, we seek to elucidate actionable mechanisms to improve the management of selected complex diseases, including single-gene disorders and rare diseases. Where appropriate, new discoveries are applied in translational projects to deliver new digital tools, diagnostic approaches, or therapeutic modalities.

Using different biological and mechano-biological approaches, the **Advanced Regenerative Therapies** Research Objective seeks to achieve homeostasis or restore the function of diseased or damaged tissue in patients with various progressive chronic diseases, acute illnesses, and injuries. Together with the Charité and MDC, we are developing the field of advanced therapies, including matrix-based approaches, cell therapy, and gene therapy. Our team includes experts in regulatory science, who collaborate with the responsible authorities to develop regulatory processes for novel therapies. Additionally, we seek internally and in collaboration with external manufacturers to optimize production processes for Advanced Therapy Medicinal Products (ATMPs) aiming to swiftly transfer these products to the clinic. This Research Objective profits from collaborations with academia and industry, and from the BIH’s role in moderating a National Strategy for Gene and Cell-Based Therapies.

In addition to the available BIH federal and state funds, the activities within the Research Objectives are driven by additional third-party funding raised by the scientific community. (Figure 8)
The BIH has established a unique ecosystem of support Platforms and Programs to enable effective translation through education, solutions and infrastructures.

Translational Support Platforms include the BIH Core Units, such as Technologies and Expertise for Integrative Multi-Omic Approaches; Tissues, Biospecimens, and Cellular Models for Research; and key tools and infrastructure for Data and Sample Platforms. The BIH Core Units continuously develop their service and technology portfolio, working with users to meet their needs and exploit the latest technological developments. In addition to analytical services, the Core Units offer project consulting, user training, and workshops to strengthen reproducible and valid research at the BIH and beyond. BIH, Charité, and MDC scientists can use the OpenIRIS portal to book services offered by these units. In addition to the Core Units, there are a number of Translational Support Platforms that are orchestrated by several Research Groups or centers (e.g. the Clinical Study Center, the QUEST Center). This includes a number of Data and Sample Platforms and the Responsible Research Toolbox. Independent Networking Platforms also foster connections between researchers and stakeholders within thematic communities.

Our Translational Support Programs provide funding and coaching programs to achieve innovation, researcher advocacy, and researcher empowerment within the BIH and the broader translational ecosystem. For example, Charité BIH Innovation (CBI) provides the Digital Health Accelerator, SPARK-BIH, and Match & Connect programs. The newly created Regulatory Support Unit, the Clinical Incubator for advanced therapies as well as the Clinician Scientist Program and its tailored variations provided by the Biomedical Innovation Academy (BIA) complement the portfolio. The Strategic Science Management supports the BIH research community and the Board of Directors in implementing our mission.

*Figure 9: Overview of topics and outcomes of BIH platforms and programs.*
The BIH Core Units offer multi-omics analysis such as genomics, transcriptomics, proteomics, and metabolomics for integrative and comprehensive molecular insights at the level of tissues or single cells. Great care is taken to offer high-fidelity services that approach diagnostic quality. We support procedures in molecular tumor boards and the Charité Berlin Center for Rare Diseases, directly impacting patient care.

The Flow and Mass Cytometry Core Unit offers expert service and state-of-the-art equipment for multiparameter flow and mass cytometry, high-speed cell sorting, and imaging mass cytometry to understand cellular relationships and mechanisms in the context of health and disease. Thanks to intensive user training and integrated quality management tools, we can generate high-quality data and reproducible results.

Jointly operated with the MDC, the Genomics Core Unit offers Illumina, Oxford Nanopore, and PacBio sequencing platforms with a focus on single-cell and spatial analyses to help clinical scientists gain insight into diseases like cancer and cardiovascular events. Also jointly operated with the MDC, the Proteomics Core Unit specializes in mass-spectrometry-based proteomics, offering global proteome and post-translational modification profiling, customized quantification techniques, and targeted assays. The Imaging Mass Spectrometry Core Unit offers mass-spectrometry-based imaging methods to analyze the spatial distribution of proteins, glycans, and metabolites in tissue sections. In addition to developing diagnostic or prognostic assays, this Core Unit helps scientists to discover novel biomarkers influencing tissue health. The Metabolomics Core Unit conducts mass spectrometry metabolomics research with translational medicine potential, emphasizing gut, heart, and brain health. Services include validated untargeted/targeted liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), metabolic imaging, and quantitative multiplexing. Together, these Core Units help advance the molecular characterization of complex biological and clinical samples.

The Bioinformatics Core Unit provides expertise in bioinformatics and data analysis in order to manage, analyze, and interpret the complex data generated by modern high-throughput methods. It serves biomedical and translational research by developing and combining standardized omics-data-processing workflows with project-specific solutions in bioinformatics, exploratory statistics, visualization, data mining, machine learning, and data integration. Training opportunities, including a Bioinformatics Training Module, focus on reproducible analyses and transparent quality-controlled research processes in close collaboration with the QUEST Center.

Cellular Models, Tissues, and Biospecimens for Research

The Pluripotent Stem Cells and Organoids Core Unit supports basic and translational research on human pluripotent stem cell (hPSC) and organoid technology. The services include the derivation, genetic manipulation, characterization, quality control, and distribution of human induced pluripotent stem (iPSC) cell lines, and the differentiation of hPSC into specific cell types in 2D culture conditions and 3D organoids. Importantly, this Core Unit provides scientists with state-of-the-art protocols for the proper handling and manipulation of hPSC, and pioneers virtual training formats with detailed videos. Jointly with the MDC’s Stem Cell Unit, this Core Unit offers Germany’s only training course on stem cells, focusing on standard operating procedures for reprogramming, gene-editing, and differentiation of stem cells.

Jointly operated by the BIH and the Charité, the Biobank collects, processes, stores, and distributes a wide range of biosamples for research projects, cohort studies, and clinical trials under safe and quality-controlled conditions. Internal and external researchers can use and access samples in line with transparent procedures. Services include tissue sectioning, histology, immunohistochemistry, and DNA/RNA extraction. BIH supports the German Biobank Node (GNB) and other developments that connect high-quality specimens with carefully documented clinical data, ideally in combination with other national and international actors from the German Network.
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Translational Support Platforms and Programs

of University Medicine (NUM) and the BBMRI European Research Infrastructure. For research activities that require fresh clinical samples, the BIH has established two pipelines that are independent of the biobank. The **Bioportal Single-Cells** supports single-cell research activities. It procures and transports fresh surgical tissue, and manages pseudonymized patient data, advising on ethical considerations, sequencing, and data storage in an integrated workflow. The **Cell and Tissue Harvesting Core Unit** supports musculoskeletal research activities by providing access to fully characterized human tissue from orthopedic or trauma surgery, including blood, bone marrow, and cartilage.

**Data and Sample Platforms**

The BIH orchestrates several initiatives towards developing high-power sample and data platforms for translational research. These are collaborative efforts between the Core Units and the Research Groups, drawing on their pooled expertise.

The **Research IT Core Unit** provides IT-services tailored to scientists’ needs and develops and operates the Health Data Platform (see below). The **eHealth & Interoperability Group** develops and implements international medical terminologies as well as IT standards for semantic interoperability in healthcare and medical research, enabling comparability, data exchange, and patient safety for global research and translational medicine. The **Clinical Study Center** focuses on patient data tools, molecular integration, a broad consent implementation, and a patient portal for additional health-related data. These tools include Study Matcher to optimize patient recruitment, DigiNet for patient networking, and trust-based solutions for data access. The **QUEST Center** fosters **patient and stakeholder engagement (PSE)** in the various research activities at the BIH.

The BIH’s Research Groups and Core Units also collaborate closely on the following tools and platforms that support translational research.

The **Health Data Platform (HDP)** is a comprehensive platform for integrated access to health data that aims at increasing the usefulness of medical data beyond its original purpose. In particular, this is intended to meet the needs of modern medical research by providing a scientific data platform that enables secure and data protection-compliant access to comprehensive, well-described, multimodal and quality-assured data from medical care and clinical research. In addition, by facilitating access to data, this platform also paves the way for innovation and collaboration with external partners through the possibility of data sharing.

**Human Phenotype Ontology (HPO)** serves as a computational resource for diagnosing rare hereditary diseases. Updated continuously, it matches clinical manifestations with gene mutations to facilitate clinical diagnostics. HPO is a pioneer in computational phenotype analysis, using artificial intelligence (AI) to help identify and track rare diseases. Algorithms bridge the gap between data science and applied medicine, emphasizing the integration of genomics into clinical practice.

The newly established **Case Analysis and Decision Support Platform (CADS)** aims to diagnose patients with rare diseases. It combines deep experimental genotyping and phenotyping techniques with expert panels for individual case analysis. CADS also evaluates novel technologies regarding their potential for conventional clinical care, bridging the gap between research and standard care to accelerate translational applications.

The **Berlin long-term Observation of Vascular Events (BeLOVE) cohort study** uses cross-organ phenotyping of cardiovascular patients for hypothesis-driven clinical research. In integrating various data sources, BeLOVE seeks to become a national resource. BeLOVE combines patient-centered interventions with a comprehensive findings management system. This harmonization accelerates translation and thus supports interdisciplinary expert panels for personalized patient care in close cooperation with the Charité and the MDC.

Focusing on regulatory and ethical aspects of AI in healthcare, the **Testing and Experimentation Facility for Health AI and Modelling (TEF Health)** aims to secure technology trustworthiness and facilitate market access. It addresses the knowledge discovery loop and innovation chain, contributing to a robust health research network. With its world-class reference testing facility, TEF-Health validates and certifies AI and
modeling in medical devices. It enables real or realistic environment testing, supporting market access for trustworthy intelligent technologies that adhere to new regulatory requirements. Testing and technical, administrative, medical, ethical, and legal aspects, fostering trust and acceptance in the user community. The BIH and the Charité play a crucial role by providing patient data, outcomes, and certified critical infrastructure, while ensuring information security.

**Responsible Research Toolbox**

Besides fostering, establishing and implementing a large range of responsible topics, the Center for Responsible Research (QUEST) has compiled a comprehensive toolbox for biomedical researchers to enhance reproducibility across the research project life cycle (literature research; experimental design; preregistration; target assessment; transparent execution and analysis; visualization of results; reducing the risk of reidentification; preprints, repositories, and publication). Literature tools (e.g. Unpaywall, Open Knowledge Maps, Lazy Scholar) help researchers find scientific content. Experimental design tools (e.g. Experimental Design Assistant, G*Power) help researchers plan reproducible studies. Preregistration tools (e.g. Preregistration on OSF and AsPredicted) ensure transparent analysis. For target assessment, there are tools to comply with GOT-IT (Guidelines on Target Assessment for Innovative Therapeutics), while the PREMIER Wiki platform supports documentation and knowledge sharing. For transparent analysis in the execution phase, there are tools for version control (Git), analysis notebooks (e.g. R, Rstudio, Jupyter Notebooks), and an electronic lab notebook (eLN). For non-programmers, there are several tools to help with the visualization of results (e.g. Interactive Dotplot, Interactive Line Graph). The risk of reidentification of people from data can also be managed by several tools (e.g. ARX Data Anonymisation), as well as the publication itself (e.g. Open Access Journal lists, the Publication Fund, FAQs on Open Data), data repositories (e.g. Zenodo), preprint servers for early visibility (e.g. bioRxiv, medRxiv). Tools for the publication of nonstandard results (e.g. FIDDLE) address publication bias.

Within a developed dashboard an up-to-date overview of the status quo (as well as the progress) of various metrics of trustworthy and useful research at Charité and the BIH was developed. Open Science (OS) and Responsible Research and Innovation (RRI) represent key concepts of the European research funding program Horizon Europe. QUEST fosters OS & RRI transformation at Charité and BIH through designing and implementing OS & RRI programs to ensure trustworthiness, usefulness, and ethics of biomedical research. To continuously evaluate its program activities, QUEST aims to establish the Monitoring & Evaluation System COMPASS.

Together with the Einstein Foundation the QUEST Center honors outstanding initiatives and individuals who are committed to improving research quality globally with a newly established award for Promoting Quality in Research.

**Networking Platforms**

The BIH provides several platforms that researchers can use to get in touch and exchange with relevant stakeholders in their field. The Office for External Affairs initiates connections with a broad spectrum of external stakeholders from academia, industry, patient representatives, investors, policy makers, and other societal actors. The Dialogue Platform for Stem Cell Research, a national activity supporting the German Stem Cell Network (GSCN), aims to promote stem cell research and related research areas such as regenerative medicine, cell engineering, cancer therapies, biomaterials, gene therapy, single-cell technologies, data science, and clinical trials. The Network Office for Gene and Cell-Based Therapies has been established as part of the National Strategy for Gene and Cell-Based Therapies (GCT) in October 2023. Its core tasks include networking, information, education and supporting all GCT stakeholders in science, business, politics, and society, as well as authorities, foundations, and patient organizations.
Translational Support Programs

Supporting Innovative Projects Towards Effective Translation

Charité BIH Innovation (CBI) is pivotal to the BIH’s translational mission, fostering the transformation of innovative ideas into commercially viable medical solutions. To help Charité and BIH researchers valorize their research, CBI evaluates and protects intellectual property, and offers translational project funding and coaching programs (e.g. Digital Health Accelerator (DHA), SPARK-BIH). Both DHA and SPARK-BIH offer mentoring, educational support, and financial support, and are unique in Germany. The DHA provides an interdisciplinary coworking environment, in which project teams can build innovative digital health technologies and MedTech products. The SPARK-BIH programs offer professional project management, milestone-dependent funding, and an international network of experts in support to develop the support of novel therapies (e.g. ATMPs, small molecules, biologicals, repurposing), medical devices, and diagnostics. The Match & Connect program connects startups to foster translational projects, co-development, and clinical validation. In 2023, an Idea Office and a Scouting Team were established to increase awareness and offer information and contacts for researchers. Over the years, CBI has significantly expanded its portfolio, supporting numerous projects, filing patents, and facilitating the establishment of start-ups. Looking ahead, CBI aims to expand its successful programs nationally as well as internationally, and plans to implement measures such as simplified negotiation processes, fixed start-up conditions, and long-term funding commitments, ultimately striving for a 50% increase in candidate projects in the innovation pipeline within the next five years.

CBI’s activities are complemented by the Regulatory Support Unit, which was recently established within the framework of the National Strategy for Gene and Cell-Based Therapies (GCT). The Regulatory Support Unit will provide nationwide regulatory advice and support to academic groups in the field of biological medicinal products with a focus on GCT. The team will further provide counselling in the early product development phase and assistance with initial interactions with regulatory authorities. To close the remaining gap on wet lab incubation, the Clinical Incubator supports research groups in the early stages of spin-off formation for advanced therapies.

Educating and Developing Translational Personnel

The BIH Innovation Academy (BIA) offers strategic personnel development for young biomedical researchers in academia. By recruiting around 75 researchers per year in any translational topic, BIA programs help build an interdisciplinary translational research community. Following the BIH’s evidence-based approach, the BIA analyzes the needs of young scientists at various career stages in order to develop targeted funding programs. The team emphasizes tailored training and the extending of opportunities to under-represented groups. To enhance translational skills and scientific entrepreneurship, the BIA disseminates career analyses and collaborates with external partners.

The BIH Charité Clinician-Scientist Program (CSP) offers a structured career path for clinician-scientists, setting national standards. For example, the (Junior) CSP and Advanced Clinician-Scientist pilot program promotes research-intensive clinical careers. The Medical Scientist pilot program supports translational career trajectories and research quality. All BIA programs undergo regular evaluation based on objective data describing entry criteria, selection mechanisms, qualification goals, and subsequent career paths of BIA alumni. Given the rich expertise gained from offering the various BIA programs, we plan to design and offer national CSPs on specific topics (e.g. gene therapy, cell therapy) with nationwide enrolment and intense extramural networking.

Future directions also include supporting early-career researchers not involved in patient care. For example, a BIH translational PhD Program was launched in 2023, a mandatory Translational Training Module is in development, building on established graduate school systems in regenerative medicine (BSRT) and oncology (BSIO).
Strategic Science Management

The Strategic Science Management team is central to the BIH mission because it assesses effectiveness, ensures resource efficiency, and shapes the BIH’s strategic profile. It evaluates the achievement of the BIH’s goals, considering research outputs, funding, collaborations, and societal impact. The team supports the board of directors with strategy development, fostering interdisciplinary collaboration. Further tasks include designing processes to align research efforts with the BIH’s objectives, focusing on metrics, translational potential, research portfolio management, innovation promotion, resource optimization, network development, and academic career paths. Additionally, the team manages the Core Units, supports project development, and fosters national activities. Ultimately, Strategic Science Management aims to strengthen BIH’s profile and position the institute as a precision medicine innovation leader regionally, nationally, and internationally.
Research Objective 1
Activity 1.1
Translational Metrology

Activity 1.2
Preclinical Evidence

Activity 1.3
FAIR Health Data

Activity 1.4
Clinical Translation

Responsible Translational Methodologies
Research Objective – Responsible Translational Methodologies

Overall Challenge, Vision and Goal

Transforming clinical and laboratory observations into interventions that lead to health benefits is challenging. While failures are to be expected, effectiveness can be increased by a streamlined translational pipeline that accounts for known and foreseeable threats.

Translational effectiveness is notoriously difficult to measure because it often takes years or even decades to move from initial discovery to clinical application in patients. Several BIH initiatives are therefore studying translational research in order to identify meaningful early markers of translational effectiveness.

The BIH has established a unique environment to support translational research and development aiming to mitigate the risks of failure. Core Units form a central pillar that provides cutting edge methods, technology, and infrastructure. Together with additional methodological developments (e.g. improved models within Research Objective 2), the Core Units interact with the Responsible PrecliniX project and the Clinical Study Center (CSC) to generate robust evidence for patient information. This is complemented by the various translational support measures, e.g.: Regulatory Support Unit; and strategies from Charité BIH Innovation (CBI) to promote the awareness and management of intellectual property and specific validation funds. For researchers and scientific entrepreneurs, the BIH Biomedical Innovation Academy (BIA) centralizes professional development opportunities pertaining to translational research and development (Figure 10).

These structures consider translational effectiveness and its proximate facilitators, typically requiring multidisciplinary expertise. Targeted activities will further strengthen translational effectiveness via researchers’ discoveries, patient involvement, and contributions from additional stakeholders (Figure 10) [1, 2]. All approaches will be accompanied and refined by the development and implementation of FAIR (findable, accessible, interoperable, reusable) data platforms and state-of-the-art techniques in modeling and data science.

Figure 10: Transdisciplinary interactions between BIH structures make translation more effective and beneficial for patients. This Research Objective seeks to improve communication between translational structures, guide product development, and develop translational personnel.
**Expected Impact**

The Responsible Translational Methodologies Research Objective will develop strong support structures to benefit the community at the BIH, the Charité, and beyond. By identifying promising research projects to embed in an efficient translational framework, our goal is to increase translational success. Beyond the BIH research projects, the translational framework should serve as a blueprint for national and international partners, including public-private partnerships. To strengthen preclinical robustness and foster close connections with the Computational and Functional Precision Medicine Research Objective, this Research Objective will make patient data available to a large research community, thus enabling the development and application of tools that directly benefit patients. We will create added value for patients and researchers by creating FAIR health data spaces and developing advancing modeling and artificial intelligence (AI) for clinical use.
Challenges and Goals

Translational research and development faces many challenges, such as: reproducibility; clinical irrelevance; lack of support; and delayed or omitted consideration of regulatory issues or economic aspects. A proactive strategy to address these challenges must consider all aspects of translational research and development across scientific and nonscientific areas, anticipating exactly how products must be designed to deliver patient benefit. Importantly, this must start early on because early suboptimal choices can prolong or hinder the translational process. Here, meta-research approaches could identify strategies and factors that are crucial for translational success.

This activity aims to create integrated translational support to assess and develop discoveries and researchers. We have identified five domains that are key to translational potential: robustness; patient-centricity; innovation; regulatory compliance; translational mindset. Specific expert groups at the BIH assess and consult for each domain, using and developing metrics to evaluate respective projects. These assessments will be collectively reviewed by a Translation Support Module involving expert members from each domain. The process provides timely feedback, addressing deficits and challenges, and devising strategies for development. This approach enhances translational effectiveness, fostering a culture of high-quality reproducible research. It ensures evidence-based entry into the translational pipeline and builds a robust portfolio of research projects. Additional goals include developing tools to assess innovation potential and establishing a shared language for project assessment, streamlining collaborations with academic and business partners to support the research community [3, 4].

Robustness (Responsible PreclinIX, Core Units). Innovations in biomedical research are usually tested in diverse and complementary experimental settings, where experiments test hypotheses about the mechanism or efficacy of a proposed innovation. Here, robustness refers to two quantitative research concepts: reliability (measurements are consistent) and validity (measurements measure what they are intended to measure). The robustness of research projects is assessed via a modified catalogue of questions developed for confirmatory preclinical multicenter studies. The Core Units will contribute to this metric by developing and expanding their quality management systems and creating a system to score the experimental design and execution of individual projects in their Core Units.

Patient-centricity (Clinical Study Center, Patient Engagement). From a patient-centric vantage point, clinical trials must be of highest quality and provide trustworthy information being the foundation for shared decisions that benefit the healthcare system. For researchers, the quality and efficiency of trial initiation and execution are essential. Innovation and expertise in trial design, operations, and evaluation can
improve trial performance, including quicker starting, reliable accrual rates, faster completion, and greater protocol compliance. The metric makes patient-reported measures actionable and helps stakeholders to identify critical research questions and disseminate useful results. This is complemented by ongoing patient engagement processes, which will be further explored in earlier research phases via potential participation in the Translation Support Module.

Innovation (Charité BIH Innovation, BIH Clinical Incubator, Regulatory Support Unit). Successful translation integrates innovations into patient care. This often requires collaboration with industry partners who provide financial investment and relevant expertise. However, such partnerships hinge on convincing data, secured IP, and an expected return on investment. It is therefore crucial to secure IP including patents, copyright, and know-how. Early IP evaluation considers factors such as patentability, relevance to medical needs, and market potential. Here, we raise awareness and educate researchers, working with the new Idea Office and Match & Connect initiatives.

Translation succeeds via early de-risking, when technology, product development, and an understanding of medical needs converge. This requires entrepreneurial spirit, close monitoring through metrics and tracking), and strategic partnerships with regulatory and business experts. We will therefore build a Clinical Incubator to foster creativity and collaboration, and to facilitate the translation and commercialization of innovative ideas into clinical practice.

The highly regulated market approval process considers efficacy, safety, and toxicity issues. Especially in the field of gene and cell therapy there is a need for support to academic groups. The BIH has recently established a Regulatory Support Unit that will provide counselling in the early product development phase and assistance with initial interactions with regulatory authorities.

Translational mindset (BIH Biomedical Innovation Academy). To train and educate translational personnel and projects, we will refine metrics for the translational skillsets of individual researchers. We will use these metrics to advise the BIH researchers on how to build their personal or team skills and improve their networking opportunities beyond academic circles. We will offer programs for all levels of career development and the early stages of company development. The new Translational Scientist Program (TSP) will bridge clinical practice and research, and foster collaborations between research and industry.

The Translational Support Module and metaresearch on translational support frameworks and metrics. The Translational Support Module will integrate and operationalize the five key domains in concrete measurable items to form metrics or measurable criteria and guidelines. The Translational Support Module will also create a central communication hub, where experts in the domains can develop actionable plans for Research Groups in close collaboration with Research Group members. The Translational Support Module will foster communication between different partners, leveraging the BIH structures and skills (e.g. Core Units, coordination of the CBI programs SPARK and DHA as well as the BIA's clinician scientist programs). It is challenging to measure translational potential due to the amount of time between an innovation's discovery and its application in the clinic. We will therefore also monitor proximal or surrogate parameters that mark important milestones. Based on these parameters, we will evaluate and refine the metrics. The Translational Support Module will also develop and implement a customer-oriented quality support system for entrepreneurs, scientists, clinicians, patients, and the community, to highlight the benefits of translational support.
Activity 1.2
Strengthen Preclinical Evidence Generation and Link to Clinical Contexts

The robustness of evidence from preclinical studies is pivotal for the successful translation of novel treatments and interventions.

Challenges and Goals
The activity aims to optimize the thriving ecosystem of preclinical research at the BIH by strengthening connectivity between structures [5-10]. The Responsible Preclinix project will advise research and development projects on how to improve the robustness of preclinical evidence. The Core Units will develop new technologies and define organization-wide standards and state-of-the-art methodology to generate robust evidence.

Optimize the BIH ecosystem of preclinical research.
The Responsible Preclinix project will blend insights from psychology, target validation, quality management [11], and research methods in order to connect and advise different stakeholders on how to generate robust preclinical evidence for clinical translation. Responsible Preclinix will also work with Research Groups to develop a metric for the robustness of planned research. In collaboration with Core Units and expert networks for key technologies, this metric will be used to guide strategies to improve preclinical validity and reliability.

Establish a unified web portal for all Core Units. The Core Units are critical to the robustness of preclinical data because they are responsible for selecting technologies, model systems, and biosamples, and for implementing controls and quality management. The Core Units will establish a unified web portal that will offer comprehensive information on all phases of translational projects, including the available technologies, methods, sample handling, processing times, and contacts of experts. By enhancing knowledge transfer and communication, the web portal will improve the efficiency and quality of scientific endeavors.

Develop and implement new technologies for Research Groups. The Core Units provide high-quality scientific services and develop technology, applications, and methods with and for the Research Groups. Together with QUEST, the Core Units will establish a system to assess the Research Group’s needs in order to continuously update their services and transfer new technologies into practice. This will include seminars on new technologies and opportunities to test the proof of concept of new methods in experiments or studies.

Develop and implement quality assurance and control procedures and metadata annotation (BIH Best Practices) for each Core Unit and technology. In collaboration with QUEST, the Core Units will develop standards and best practices for their technologies and services to foster high-quality reproducible data. These will be disseminated to individual labs, with frequent training offered to Research Groups and external research partners. Preparation procedures, (bio) sample handling, and documentation standards will thus be harmonized across the Core Units. We will also increase the level of automation in Core Units in order to improve quality, reproducibility, capacity, and turnaround.

Contributing PIs and their teams
Activity 1.3

FAIR Health Data: Making Health Data Findable, Accessible, Interoperable, and Reusable

An alternative approach to leverage health data to improve health is to apply artificial intelligence (AI) for precision medicine. This requires the tailoring of modeling and data science algorithms to clinical use, and the consideration of ethical, legal, and societal issues. The following processes must be optimized: the acquisition of clinical data; the interfaces of workflows to extract knowledge; and structured phased pathways to validate and translate computational diagnostics and interventions.

Challenges and Goals

Various determinants of health and resilience are often studied by different disciplines, necessitating an interconnected and cross-disciplinary research community. Exchange and accessibility of health data needs to be enhanced through transparent FAIR (findable, accessible, interoperable, reusable) platforms that protect personal data while facilitating their use for healthcare and research. Improved FAIR data and technology is essential to convert singular data research activities into useful measures for prevention, diagnostics, and healthcare.

Our goal is to develop innovative technologies for acquiring, sharing, managing, and analyzing data to directly impact patients and researchers. We will also conduct basic research in digital medicine, health, and medical informatics, developing new methods to address the challenges that arise (Figure 12). This activity will draw on our extensive experience in research data infrastructure and FAIR data management including standards for sharing computational models and data, interoperability, privacy protection, and security [12-31]. We will also develop and adapt modeling and data science algorithms to address the challenges of precision medicine. Moreover, we will draw on our extensive experience in order to develop and implement state-of-the art techniques to ensure sufficient input data and optimized workflows for clinical applications [17, 32-41]. To make AI and computational methods routine in the clinic, we will optimize: i) the acquisition, annotation, accessibility, and protection of data; ii) the processing of incomplete clinical records; iii) the integration of high-dimensional multimodal patient data across a range of spatial and temporal scales; and iv) the use of knowledge for high-stakes medical decision-making.

Design innovative interoperable infrastructures. We will connect infrastructures for coordinated activity via documentation, communication, and collaboration in the BIH, Germany, and beyond. This includes: stakeholder engagement; project progress dissemination; a common development roadmap; technical documentation; integrated systems development; and needs assessment.

Define and monitor key performance indicators. We will define and monitor key performance indicators, such as: number of users; publication citing data and infrastructure; number of data points, data types, and data sets made FAIR; number of tools made FAIR; and number of quality control mechanisms.

Contributing PIs and their teams

Develop methods to increase the availability of structured and harmonized data. We will develop innovative and secure methods for FAIR data integration platforms for data-driven personalized medicine. We are working on systems for intelligent structured documentation and for standardized data collection in research and healthcare. Our recent achievements include: establishing a scalable repository for structured clinical data; introducing structured reporting in various contexts; and introducing ways to use standardized terminology and ontology at source and in subsequent integration processes. Several of our digitalization projects aim to provide informatics support for epidemiology, health services research, quality assurance, diagnosis, and therapy selection. We are also developing and establishing robust workflows to track data provenance as well as quality assurance approaches based on quality indicators and feedback loops to source systems (e.g. in the Medical Data Integration Center (MeDIC), Health Data Platform (HDP) and the associated data warehousing platform based on OMOP/OHDSI and i2b2).

Develop novel techniques to improve the FAIRness of data. A lack of standardization and harmonization often prevents the reuse of data. We are therefore working on national and international consensus datasets, common data models, and semi-automated annotation and harmonization pipelines following pay-as-you-go approaches. We are also working on user-friendly tools to provide access to interoperable and reusable data nationally. Our work on the modular core dataset of the German Medical Informatics Initiative (MII) is an important contribution to the implementation of standards. We are helping to develop national and international data models and standards. We are implementing data models to connect local infrastructures to international real-world evidence networks. We are also developing scalable and agile methods to retrospectively transform and harmonize data using innovative processing mechanisms, architectures, and declarative transformation processes. To increase findability and accessibility, we are working on graphical processing pipelines, visual tools for data and knowledge management, and innovative methods of data visualization.
Navigate the legal and regulatory frameworks. Making data findable and accessible requires governance structures and technical solutions that support tiered access. We develop innovative approaches to provide safe data and safe outputs in safe settings to safe people in safe projects (Five Safes Framework). We also develop structures and concepts for local, national, and international platforms that link organizational measures with technical protection mechanisms. We conduct activities related to legal and regulatory frameworks by developing and translating methods for local structures. Locally, we developed comprehensive data protection concepts for the HDP. In terms of governance, we set up a Data Use & Access Committee according to the MII’s guidelines and launched a project to introduce broad consent under the MII as a robust legal basis for the secondary use of health data at the BIH and the Charité. In terms of methodological research, we are working on innovative ‘privacy by design and default’ approaches for secure data access in national and international data infrastructures (e.g. pseudonymization, anonymization, federated analysis and learning). We are also developing internationally successful privacy-enhancing technologies.

Study modern platform architectures and data integration methodologies. Technical and organizational elements must be combined into coherent well-architected FAIR platforms to unlock their full potential. We implement and develop innovative architectural approaches to data management, working with domain experts. For example, pay-as-you-go integration systems can support agile harmonization processes. Moreover, polystore approaches allow the use of multiple diverse data storage systems within a single application. These approaches will help establish local, national, and international FAIR data platforms and reference structures.

Create international IT standards and healthcare terminology. Standardization of IT and medical terminology is critical for interoperability and AI for digital healthcare. We serve on several standardization committees (e.g. InteropCouncil, DIN, IHE), including as chair of HL7 Germany, thus contributing to the development of SNOMED CT and LOINC standards in Germany. Our goal is to help develop national and international standards for an interoperable digitalized healthcare system environment (e.g. Joint Initiative Council: iSO, CEN, DIN, HL7, DICOM, WHO, CDISC, OMOP, FHIR, SNOMED, LOINC, GA4GH Phenopackets). We research healthcare data standardization, focusing on medication, lab analyses, oncology, pathology, genomics, and microbiology. Our work includes developing interoperable solutions for clinical research, PROMs, and epidemiology, enhancing data accessibility for infection control, COVID-19, and rare diseases, following FAIR principles. Especially during the COVID-19 pandemic, our experts led research like the GECCO dataset and contributed to the National University Medicine Research Network (NUM) initiative. We are also lead of multiple modules to develop the MII’s Core Dataset. We aim to address global digital health challenges, leveraging the Berlin University Alliance’s expertise in interoperability, standards, and ethical considerations in data usage and storage.

Harmonize and standardize data for pan-European cohorts and Patient Summaries. We facilitate the cross-border exchange of health data and empower people to control and grant access to their health data for secondary use in line with international healthcare standards. Within the European project ORCHESTRA, we have enabled the joint analysis of health data across countries, establishing a pan-European COVID-19 patient cohort to study long-term effects. Standard terminology ensures consistent data identification and association with international codes, published on ART DECOR for reusability and interoperability. Since January 2024, we have used xShare to engage with interoperability players in Europe. The goal is to involve citizens in the European Health Data Space (EHDS). xShare leverages projects like International Patient Summary (ISO standard EN17269/ISO 27269) and XpanDH to develop the X-bundle, enhancing health system connections based on EEHRxF specifications. A central Hub will develop format specifications across the prioritized health information domains and apply them in three traditional verticals in the health sector: continuity of care, public health and cross-border threats, and citizen participation in clinical research.
**Increase the quality and usability of real-world clinical data.** In real-world contexts, nonstandardized and incomplete information makes it challenging to bring modeling and AI to the clinic. To address this, we plan to:

1. Collect standardized data to make datasets complete and machine-readable.
2. Develop methods to track provenance and data quality, combined with dashboards and feedback loops.
3. Identify case-relevant information for personalized data gathering.
4. Develop algorithms that are robust to missing data.

**Protect privacy in data science, modeling, and machine learning.** This activity aims to increase data protection by preventing the extraction of patients’ personal data during data sharing, from learned models, or from the results of data science analyses. We will develop and implement:

- Anonymization tools.
- Privacy assessment methodologies for machine learning models.
- Privacy-enhancing technologies (e.g., federated learning, synthetic data generation).

We are also developing and evaluating innovative approaches for privacy-preserving machine learning and risk assessment using real-world datasets and medical use cases. Our recent work has focused on anonymization and synthetization in trusted research environments, whole slide images, registry data, and risk assessment for synthetization mechanisms. We also seek to increase patient acceptance and trust in data usage by creating innovative patient-centric solutions that enhance health data management, privacy, and transparency.

**Address data heterogeneity via multimodal learning.** Traditionally, machine-learning models were applied to data of the same scale. Given the complexity of the human body, this is not ideal for a medical context. Both predictive and explanatory models need to account for multiscale, multimodal data. Within this activity, we will develop multiscale models for bone regeneration, and combined radiomic/genomic models for brain tumor prognosis, with neurodegenerative disorder and stroke data serving as demonstration cases. Spiking neural networks offer a promising way to integrate data across diverse temporal scales (e.g., detecting fast diagnostic markers within continuous data streams). We will therefore develop and apply learning algorithms for spiking neural networks. We will develop multimodal time series data models for real-time prognostication, risk assessment, and timely intervention in epilepsy, stroke medicine, and intensive care. These models will be based on data from high-density, time-continuous real-time in-hospital monitoring (data warehouse connect) and ambulatory monitoring (wearables).
Challenges and Goals

We join forces to optimize the standardization, harmonization, provision, linkage, and usage of patient data for continuously optimized diagnostics and treatment based on the latest research insights. The challenges we address are organizational (e.g. heterogeneity of different research areas and structures), regulatory (e.g. data protection and ethics), and technical.

Various initiatives at the BIH are involved in this activity. The Clinical Study Center (CSC) develops tools to curate patient data and integrate molecular data. The CSC is also designing and implementing a broad consent procedure for all Charité patients. BeLOVE is a long-term prospective observational cohort of patients with acute cardiovascular events or a comparably high chronic risk for cardiovascular events. BeLOVE's scientific value is that it is based on deep identical cross-organ phenotyping in patients with different patterns of cardiovascular disease, which can be used for hypothesis-driven clinical research. BeLOVE's structural value is that its structures and processes are reusable and transferable to other topics such as the study of the mechanisms of multimorbidity. QUEST is developing, supporting, and evaluating patient and stakeholder engagement throughout the research process. In collaboration with the German PROMIS National Center at the Charité, the BIH supports the integration of patient-reported outcome measures (PROMs) as a standard tool for clinical research.

Activity 1.4
Concepts and Tools to Support Translation into Clinical Action

We develop frameworks, tools, and pipelines to fully exploit the comprehensive, robust, and FAIR (see 1.3) patient data generated by molecular, clinical, and digital phenotyping. We thus accelerate the translation of biomedical advances to the clinic.

Broad consent. Patient consent is a legal prerequisite for research access to comprehensive patient data. The CSC plans to conceptualize and implement broad consent in line with Charité-wide activities within the MII. Broad consent enables the follow-up contact and tracking of patients, and the shared use of data and tissue. In addition to a planned consent and contact app, we will also establish a patient portal to collect patient data outside of the clinic.

Comprehensive platform for data and samples. BeLOVE has integrated harmonized data about the clinical, molecular, and digital phenotypes of cardiovascular patients via the HDP (see Act. 1.3). This includes: clinical data from the hospital information system; research data from various sources (e.g. electronic Case Report Forms, device-related data, laboratory data, OMICs data, wearables); complemented with the collection of a wide range of biospecimens. In addition, we are working with the Core Units to integrate analytical data from various research projects into the HDP. We are also developing data access concepts in accordance with the FAIR principles. By establishing and populating a comprehensive and unique platform of data and biomaterials for cardiovascular and metabolic research, BeLOVE is already a key regional resource for scientists, and will become an international resource in the future.

The CSC aims to provide patients and researchers with a health data space that can be fed with clinical data from different systems. For example, the DigiNet project (funded by the Federal Joint Committee, Gemeinsamer Bundesausschuss) allows networking between different sites and patients. In addition, the Data Trust Center of the Charité and the BIH are developing trust-based solutions (e.g. patient consent app) for patients to grant researchers access to their medical

Contributing PIs and their teams
Peter Brunecker, Thomas Gazlig, Fabian Prasser, Stefan Mundlos, Alexandra Stege, Sylvia Thun, Christof von Kalle, Joachim Weber, Sarah Weschke
data in compliance with data protection and consent requirements. We will develop data pipelines to link real-world data from wearables to existing clinical and research datasets (e.g. within the HDP), integrating clinical with digital phenotyping.

**Feasibility check and study matching.** The CSC will implement a Study Matcher that can use routine clinical data, study registries, patient registries, or similar resources to systematically search the entire patient pool for potential study participants. This will improve: i) the prediction of the available patient population for a given study; ii) the prediction of recruitment rates; iii) recruitment; and iv) the number of potential studies offered to patients. The Study Matcher will allow researchers to evaluate trial feasibility, improve recruitment, and minimize the likelihood of low performers.

**Patient and stakeholder engagement.** Patient and stakeholder engagement (PSE) is the active involvement of patients and other individuals or groups affected by research. QUEST is implementing a toolbox to manage PSE and is working with the Clinician-Scientist Program (CSP), among others, to train and advise researchers. The goal is to foster patient empowerment and responsibility by integrating PSE into the research process. We will conduct networking and public relations, and provide services and support for researchers, including promotions and incentives for PSE and research around PSE. Patient representation will also be further strengthened at the BiH’s Scientific Advisory Board. PSE activities of the BiH are aligned with the patient-centric measures of Charité’s medicine strategy and will create substantial additional synergy with related activities of the German Centers of Health Research (DZGs).

Along this path, the early involvement of patients or their representatives is important for the development of the National Strategy for Gene and Cell-Based Therapies, which operates in national networks, uses mechanisms of participatory health research, and creates resonance with federal entities (e.g. the Federal Ministry of Education and Research) and national research platforms (e.g. DZGs).

These initiatives will be pursued while integrating PSE into internal and national BiH funding lines, proactively identifying ways to raise researchers’ awareness about PSE.

**Accelerating translation to the clinic.** As noted above, BeLOVE has established a unique cohort of cardiovascular patients by harmonizing cardiovascular phenotyping across structures and projects. This can generate synergies with other structures and thus accelerate the translation process. For example, we will collaborate with the Friede-Springer Prevention Centre and implement a joint data and sample platform with the German Heart Centre at the Charité (DHZC). In addition, BeLOVE is a core cohort of the INTERACT excellence cluster application. INTERACT aims to increase our understanding of multimorbidity, and to translate the mechanistic findings and resulting models into concrete risk stratification, prevention, treatment, and education measures for patients. We will seek to answer patient-centered questions for more targeted patient care. For example, which factors should we use to phenotypically assign patients to particular risk classes for clinical events? By continuously recruiting, phenotyping, and analyzing patients and their data, we can provide customized trial-ready subgroups for a variety of projects.
Research Objective 2
Computational & Functional Precision Medicine

Activity 2.1
Population Health Data Research

Activity 2.2
Approaches and Models

Activity 2.3
Disease Mechanisms

Activity 2.4
Decision Support for Patients
Research Objective – Computational and Functional Precision Medicine

Overall Challenge, Vision and Goal

Precision medicine seeks to tailor healthcare to each individual’s unique condition for superior prevention, diagnosis, and treatment. This requires the integration of insights from disciplines including experimental biology, clinical medicine, and data science. The Computational and Functional Precision Medicine Research Objective therefore brings together 45 Principal Investigators (PIs), their teams, and collaborators to advance the field of precision medicine. Their interconnected efforts include: i) computational analytics of massive population data; ii) elucidating disease mechanisms using patient samples and model systems; iii) and demonstrating clinical utility for individual patients and diseases.

This Research Objective is based on the large-scale analysis of expansive health datasets, including genetics, multi-omics, biomarkers, functional and imaging analyses, comorbidities, medical interventions, and environmental factors from cohort studies and electronic health records. Advanced artificial intelligence (AI) and multiscale modeling techniques will integrate these heterogeneous data modalities to reveal multivariate patterns that stratify subgroups and predict individual disease trajectories. The computational models will help match individuals to tailored prevention plans, diagnoses, and treatments. They will also identify putative targets for future innovations.

In parallel, experimental studies in cells, model systems, organisms, and patient-derived samples will investigate the intricate biomolecular pathways underlying health and disease. By elucidating the mechanisms contributing to pathology in a given individual, as influenced by their genomic and environmental background, we will create new opportunities for more precise diagnoses, prevention, and therapy.

Ultimately, the utility of precision medicine will be to improve patient care and our understanding of disease. This Research Objective is therefore developing next-generation rapid diagnostics assays, sensors, and decision support tools to assist practitioners in matching interventions to individual patient profiles for optimal outcomes. Our carefully designed preclinical models, clinical trials, and real-world data will form feedback loops that allow us to refine our approaches. Furthermore, by identifying novel actionable targets, we will trigger research on advanced personalized therapies.

The combination of computational and functional approaches will allow us to unlock precision medicine’s full potential: measurable and meaningful improvements in healthcare on an individualized basis.

Expected Impact

This Research Objective adopts a co-design approach, engaging interdisciplinary research communities to address complex challenges. We will achieve impact by creating tools for research, innovation, clinical decision-making, and patient support, and making these tools available via open-access or open-innovation platforms or via transfer to commercial applications. In several cases, we will also directly impact patient care (see Activity 2.4).

One promising approach is to generate cohorts of multiscale digital twins of patients and healthy controls. We will develop a robust framework to ensure security, quality, and reliability, enabling researchers to exploit data from national and European platforms. Our goal is the improved translation of multidisciplinary data into predictors for medical outcomes and
personalized decision-making. Anticipated impacts are improved disease progression models, improved mechanistic understanding of disease, improved mapping of pathophysiological pathways, and contribution to a national and European data infrastructure for personalized medicine. By providing reusable data and computer models, we will also contribute to the Digital Single Market and European Health Data Space (EHDS).

Our individual projects will offer insights into disease mechanisms, thus improving diagnostics and therapeutics for cancer, immune-mediated diseases, and many others. At national level, we aim to advance medical informatics by promoting data integration for several diseases, contributing to the broader field of personalized medicine. Overall, we expect improved patient care, insights into disease mechanisms, and impactful advances in medical informatics.

**Figure 13:** Impact created by the Computational and Functional Precision Medicine Research Objective
Activity 2.1
Patient Cohort and Population Health Data Research

Identifying patient-specific and disease-specific treatment options requires a detailed mechanistic understanding of the underlying disease endotype. This activity is based on patient and population health data from human studies with detailed molecular and clinical phenotyping and long-term disease follow-up. By analyzing and interpreting such large-scale data sources, we will elucidate disease mechanisms to enable advanced target identification and disease prediction and prognosis.

Challenges and Goals

We will use data-driven approaches to elucidate the mechanisms of newly emerging and poorly characterized diseases, thus helping to identify disease-specific and patient-specific treatment options and improve treatment protocols. One goal is to identify key molecular targets in cross-organ diseases with unclear systemic pathomechanisms. We also seek to harness the potential of new and emerging technologies for disease prediction and prognosis. To prevent and manage diseases in a personalized or targeted cost-effective manner, individuals with the greatest risk of disease development, rapid disease progression, or poor treatment response need to be identified. We will draw on our extensive experience in identifying mechanisms of organ-specific diseases as well as multimorbidity [42-54] and applying new technologies for disease prediction and prognosis [50-52, 54-63]. Our goal is to develop digital health applications, elucidate disease mechanisms, improve diagnosis and define targets for therapeutic interventions.

Data-driven discovery of disease mechanisms and targeted interventions. For newly emerging diseases (e.g. COVID-19), enormous efforts are necessary to elucidate disease mechanisms in order to identify therapeutic targets and develop therapeutic strategies. We will use hypothesis-free analyses, based on large-scale multi-omics data, to discover unknown disease mechanisms and thus novel potential targets. We will also analyze the poorly characterized disease mechanisms of acute respiratory infections, lung diseases, chronic inflammatory and metabolic diseases, and the causes of multimorbidity.

During the COVID-19 pandemic, we used single-cell transcriptomics to identify chemokines as promising therapeutic targets, and launched a phase II clinical trial [42, 46]. We will use our established protocols and analytical pipelines to investigate the molecular mechanisms of dyspnea and impaired lung function associated with Long COVID in order to identify therapeutic opportunities. In particular, we will describe the immune-epithelial crosstalk and perturbed molecular pathways in COVID-associated impaired lung function and identify potential treatment strategies for respiratory lung disorders. By integrating genomic, epigenetic, proteomic, and metabolomic data, we have generated important insights into the mechanisms underlying and connecting many different diseases [50-52]. This has been possible because it is now feasible to assess an individual's chemical individuality (i.e. their genomic, proteomic, or metabolomic profile) at the population scale with unprecedented depth (population proteomics) and under open access. These advances may create further treatment opportunities. In integrating genomic, plasma proteomic, and metabolomic data, we will vastly expand our genetic/omic studies via collaborative international mesoscopic approaches and metaanalyses. As we successfully demonstrated for COVID-19 prognosis [49], we will apply the results to different diseases and...
expression data to achieve the genetically anchored identification of disease mechanisms and relevant tissues and cells. Working closely with health informatics partners in the UK (Health Data Research UK) and at Charité, we will integrate our genomic data with clinical phenomics expertise, using our computational approaches to study the mechanisms of undercharacterized yet common diseases. We will thus enhance the phenomic resolution of previously mapped proteo-genomic disease links (www.omicscience.org). For example, we seek to identify the genes and molecular mechanisms associated with the risk of Type 2 diabetes (T2D) and similar disorders. We also seek to elucidate the genetic architecture of refined metabolic phenotypes and to identify lean subtypes that would benefit from alternative therapies, and postchallenge (muscle) insulin resistance. We hope to identify the effects of these genes across the human phenome in order to establish causal connections between metabolic and other diseases and to uncover novel therapeutic strategies to target the shared etiology. One approach would be to integrate genomic and other blood-based omics data across different large-scale population and T2D patient studies.

Similarly, we have combined high-dimensional cytometry with single-cell transcriptional profiling of immune cells for the hypothesis-free identification of the mechanisms driving transplant rejection or severe COVID-19 [64-66]. We will apply this strategy to patients in investigator-initiated observational and interventional trials (e.g. regulatory T cell therapy in kidney transplant patients, immunoadsorption in post-COVID patients) [67-69]. Importantly, our results will form the basis of the hypothesis-driven investigations in Activity 2.3.

New technologies for disease prediction and prognosis. Our early application of new omics technologies at scale has generated insights [44, 50, 51, 70, 71] that we have shared with the scientific community. Blood-based omics could dramatically improve our ability to predict the onset and course of diseases. There have only been modest successes in genetic and polygenic prediction and its translation to the clinic, despite extensive international efforts. In contrast to the inherited genome, the dynamic and easily accessible markers of cellular stress and response (e.g. circulating proteins and cell-free DNA (cfDNA) [59] are attractive for the prediction, diagnosis, and prognosis of different diseases, with many examples in clinical use. While novel proteomic technologies show great potential [57, 62], larger-scale prospective studies with robust clinical outcomes data are needed to fully define and translate the potential utility of these emerging platforms, and to ascertain the viability of applying these techniques in the clinic. We will expand our blood-based proteomic efforts in new and existing collaborative studies, and will integrate data from large-scale industry-funded international efforts. Here, we will profit from our network to industry partners and the internationally recognized proteomic expertise at the BIH, Charité, and their Core Units. The BIH-led prospective cohort BeLOVE, with its in-depth phenotyping of patients with a recent acute event, will enable immediate testing and implementation in a near-clinical setting. While plasma proteomics is now possible at the population scale, blood proteins are often unspecific disease surrogates and we will systematically explore the use of cell-free DNA (cfDNA) as a highly cell-type-specific readout that enables a liquid biopsies of diseases-relevant tissues [55].

Metabolomics, other omics, and chemical analyses of large scale cohorts for biomarker discovery opens up new avenues of exploration for cause and treatments of diseases. Large scale datasets enable conclusions to be drawn based on robust data with good statistical power and improve the reproducibility and therefore the translation of results into the clinic. Such population-size cohorts (including the NAKO and BeLOVE cohorts), necessitate new developments in the field of quality management tools and bioinformatic structures designed for big data [72-74].
Activity 2.2
Advancing Approaches and Models to Identify and Validate Targets and Develop Diagnostics and Prognostics

We develop and refine bioinformatics and technological approaches to identify targets and thus improve diagnostics and prognostics for unmet clinical needs. In particular, we use artificial intelligence (AI) tools (e.g., large language models) and mathematical models, which require systematically generated and comprehensive patient data.

Challenges and Goals

We develop and refine cutting-edge strategies and tools to identify and validate targets in order to elucidate disease mechanisms and improve diagnostics and prognostics. Here, our focus includes bioinformatic and modeling approaches, AI tools, and novel technologies.

It is challenging to detect and interpret structural variants and non-coding DNA variants. We seek to more accurately predict the effects of these variants in a joint effort between bioinformaticians, clinical researchers, and geneticists. Specifically, we will develop bioinformatics approaches to predict the effects of DNA variants in monogenic and multifactorial diseases, then validate these predictions experimentally. We will also develop AI tools to model complex and heterogeneous datasets. Crucially, these tools will be able to synthesize evidence from multiple heterogenous data entities. The Testing and Experimentation Facility for Health AI and Modeling (TEF-Health) focuses on closing the knowledge discovery loop and the innovation chain for health AI and modelling, involves many international partners in the EU, and thus contributes to international harmonization while accelerating translation based on the principles of robust research.

Bioinformatics approaches. Accurate diagnoses and prognoses require the identification of the genomic variants that drive disease risk and alter treatment response and also a thorough mechanistic understanding. Researchers worldwide already use two of our computational tools to predict the effects of coding and non-coding DNA variants: Combined Annotation Dependent Depletion (CADD) [75] and MutationTaster [76]. We have also developed various computational tools to investigate genetic disease and cancer [30, 75, 77-87] and we are developing the VarFish software for integrated genotype analysis and variant assessment [88]. In this activity, we will combine deep phenotyping prediction tools (e.g., SAMS [89]) in a fully-fledged multi-omics analysis pipeline for both monogenic and multifactorial diseases, with options to share data with external collaborators.

For non-coding sequence effects, we support the analysis of massively parallel reporter assays (MPRAs) and other functional data. We do this by quantifying
the cell-type-specific effects of regulatory variants and by developing sequence-based computational models to derive mechanistic insights from regulatory sequences. We are developing machine learning (ML)-based models to better recognize transcription factor sites and the effects of variants in transcription factor binding. We recently demonstrated that ML-based approaches can outperform traditional motif-based analyses and identify new transcription factor binding sites [90]. As part of the NIH Impact of Genomic Variation on Function Consortium, we measure the effects of thousands of regulatory sequence variants and develop computational models to understand disease biology and single-variant resolution. We also seek to better predict variant effects on splicing, since correct splicing is a key requisite for functional proteins. In addition to software aimed at small variants, we are also working to better detect and assess structural variants (SV), particularly copy number variants (CNV) [85]. We will construct a pipeline that can fully detect SVs/CNVs even in whole-exome sequencing (WES) data and identify pathogenic SVs. We will take existing variant prediction applications for WES and whole-genome sequencing (WGS) data and tools for deep phenotyping [89] and integrate them into our VarFish software [88], making them compatible with the new GA4GH Phenopackets standard [30]. We will also develop VarFish to include other types of omics data and tools to better assess noncoding variants. Our aim is for VarFish to be used on open-access and open-innovation platforms. Ongoing applications in the Charité’s Molecular Tumor Board and CADS (case analysis and decision support for patients with rare genetic disorders) reveal the utility of our bioinformatic tools.

In addition to developing novel tools for the in silico interpretation of variants, we will experimentally validate the predictions e.g. by using targeted genome engineering and high-throughput screening approaches. These assays are applied in disease-relevant cell types or animal models to discover causal genotype-phenotype relationships and to provide an experimental platform for potential preclinical testing of therapeutic strategies [77]. We also aim to identify tissue/cell-specific regulators and develop technologies to test variants in these regions. New technologies have created opportunities to study the effects of the noncoding genome on gene regulation and to discover new disease mechanisms [91-93].

Cancer is driven by a set of somatic alterations during clonal expansion. This activity aims to systematically profile genomic changes throughout the course of the disease to enable a better understanding of the transition from normal to premalignant and malignant clones. We plan to expand our existing computational tools, leveraging additional genomic and epigenetic data types and developing new methods that more accurately determine the cancer type and subtype for an individual patient’s tumor. We further aim to detect and classify malignancies based on cfDNA in cerebrospinal fluid or blood plasma using nanopore sequencing (liquid biopsy methylation), and to design train-once classifiers that are robust to variable input features while retaining sensitivity.

**AI tools, mathematical modeling, and TEF-Health.** We will develop and apply AI-based tools, working closely with clinical partners for the early validation of AI-driven discoveries in the context of individual patient cases, including individualized treatment planning. For example, we will analyze large datasets of antibody sequences to identify biomarkers of in vivo DNA repair. We will thus seek to define the donor-specific ability to maintain genome integrity for DNA-repair-associated disease susceptibility, treatment, and prevention. We will also use AI tools to integrate imaging [47] with (epi)genomic classifiers for improved tumor detection and classification across data modalities, defining macroscopic correlates of molecular perturbations and vice versa. We also aim to resolve the spatial composition of cell types in healthy and diseased tissue biopsies using hybridization-based in situ sequencing to deliver novel diagnostic information in digital pathology [58, 94]. AI tools will also be used to harness time-resolved data from smart wearables in the BeLOVE cohort to develop prognostic models with direct feedback to patients.

We will mathematically model physiological and pathological processes to generate insights into disease mechanisms and simulate interventions in silico. As with other data-driven approaches, these models require high-quality data and will thus benefit from interactions between the modeling Research Groups and those generating, preparing, and providing the datasets. Bidirectional information exchange during these interactions will improve model performance and transfer model-based insights to clinical and scientific collaborators (Activity 2.3).
AI tools and approaches will be developed and validated within TEF-Health, a pan-European academic and industrial consortium to accelerate the value chain for health AI and simulation. This digital innovation cluster supports innovators in validating and certifying AI and modeling in medical devices. TEF-Health is developing a world-class reference testing and experimentation facility to validate AI solutions in real or realistic environments. It is also developing evaluations to facilitate market access for trustworthy intelligent technologies, with a focus on new regulatory requirements and easy access to evaluations.

**Novel technologies and pipelines for precision medicine and application in trials/studies.** We integrate single-cell and spatial assays into clinical trial procedures in order to pave the way for their routine use in the clinic. We are developing technology to study diseased cell populations and tissues to identify targetable disease mechanisms and biomarkers. For example, we are developing single-cell multi-omics technologies, screening platforms, and novel high-throughput analysis procedures to measure molecular alterations and functional avidities and interpret these in the context of disease. These technologies allow us to study disease at unprecedented resolution in large cohorts of patients (e.g. with hematologic cancers). We also aim to systematically register omics and metadata in dynamic repositories for national and international dissemination, while using database models for the advanced analysis of these resources (e.g. deep neural network approaches).

As a complement to applying modern single-cell technologies, we aim to develop multi-omic approaches to co-capture distinct data modalities (e.g. RNA, chromatin, protein, DNA genotypes) [95]. We will optimize existing approaches for scale and cost-effectiveness to expand the range of sample characteristics that can be measured and analyzed in a clinical context. For example, we will integrate advanced high-dimensional single-cell cytometry-based and imaging-based approaches, facilitating the rapid immunomics of immune cells for precision diagnosis of immune-mediated diseases [96]. We will combine these with ex vivo high-throughput gene editing or small molecule screens to generate data to mathematically model age-mediated and disease-mediated deviations of signal transduction pathways in order to identify therapeutic targets. Collectively, these efforts aim to comprehensively characterize disease phenotypes, generating different molecular layers of information at single-cell resolution (e.g. nuclear genetics, mitochondrial genetics, transcriptomics, proteogenomics). These efforts include: innovative technologies and experimental designs to investigate the contribution of somatic mutations to disease [97]; the use of somatic mitochondrial DNA variants to trace human cell lineages and cellular population dynamics in health and disease [95] and assessments of the epigenetic and transcriptional heterogeneity of benign and malignant tumors using single-cell/single-nuclear transcriptomics and chromatin profiling. We use these technologies to study mitochondrial genetics at the single-cell level in the context of congenital mitochondrial disorders and somatically evolving phenotypes. Here, we aim to innovatively integrate metabolic readouts with high-dimensional genomic technologies. In addition to generating deeper data and capturing more molecular layers per cell, we will gather and leverage spatial information [61, 98].

While omics technologies hold great promise for improved diagnostics and prognostics, their translation to clinical practice can be challenging. One solution for proteomics is to integrate results from exploratory studies with targeted biomarker panels that are quantified on routine instruments and technologies like mass spectrometry [99]. This approach, which we used during the COVID-19 pandemic [57, 100, 101], forms the basis of ongoing translation to routine laboratory use.

We will also design studies and data analysis strategies to investigate disease heterogeneity and pathophysiological mechanisms, and to identify novel diagnostic markers and therapeutic targets. For example, we use longitudinal and spatially resolved measurements to decode complex genetic and nongenetic alterations, their interplay, and their heterogeneity in order to understand the transition from healthy to premalignant to malignant cells. In the context of acute myeloid leukemias, we aim to identify, characterize, and target rare leukemic stem cells responsible for relapse. We will use functional interrogation approaches to characterize somatic variants in the nuclear and mitochondrial genome as a function of age, and assess their contribution to cellular mosaicism, heterogeneity, clonal population structures, and, more broadly, complex human disease phenotypes.
Activity 2.3
Hypothesis-driven Characterisation of Disease Mechanisms

An interplay of genetic and environmental factors influences the development of diseases. However, most rare diseases can be traced back to changes in a single gene. Additionally, there is poor understanding and characterization of disease interactions and trajectories in patients suffering from multimorbidity. We seek to comprehensively understand disease mechanisms, including cross-organ and systemic pathophysiology, in order to develop patient-specific and disease-specific therapeutic approaches.

Challenges and Goals

In a multidisciplinary approach, we seek to: discover disease-causing genes; characterize the complex molecular pathways underlying pathology; identify novel biomarkers; and use our findings to develop new therapeutic approaches and improve patient management. We use high-throughput technologies to capture different omic levels (genome, epigenome, transcriptome, proteome, cellular phenotype, functional state). To address multifactorial interactions, we develop innovative experimental tools, analytical tools, and model systems. Our hypothesis-driven approaches complement Activities 2.1 and 2.2 in seeking to discover and understand disease mechanisms and develop new treatment approaches.

Discovery of Disease Mechanisms and Actionable Targets for Diagnosis, Therapy, or Prevention. We analyze the complex etiologies and disease courses of immune-mediated pathologies. This includes the investigation of aberrant immune responses directed against autoantigens or solid organ grafts, triggered by infections, and contributing to tumor progression. We aim to discover novel pathomechanisms, identify novel targets, and test FDA-approved drugs for repurposing in a hypothesis-driven manner. Here, we draw on results from Activity 2.1. We have used our findings on the balance of coreceptors to launch a project investigating checkpoint-receptor-mediated B-T-cell communication as a novel target for autoimmune diseases. Similarly, we are using our knowledge on age-induced type 1 interferon signaling deviation to investigate other age-associated inflammatory diseases such as anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV).

We aim to elucidate the role of functional T-cell receptor (TCR) avidities in immune-mediated diseases. We also investigate monogenic inborn errors of immunity to improve the detection rate, speed, and management options. Upon identifying affected genes with unknown or poorly defined function, we will perform mechanistic studies to elucidate the functional consequences. For affected genes with known or partially defined function, we will use and develop multiplex screening assays to identify in detail the signaling downstream defects of receptors that are involved in immune cell activation and communication. To improve patient management and develop therapeutic approaches, we will conduct gene editing of patient-derived hematopoietic stem cells.

Contributing PIs and their teams
To improve survival and outcome in cancer patients, a major challenge is the unique pattern of genomic and nongenomic alterations in an individual’s malignancy, and the complex interactions with the microenvironment. We therefore seek to broaden our understanding of tumorigenesis throughout the course of the disease [102]. We also seek to systematically profile lesions in time (longitudinally) and space (spatially) using genomic [103], epigenomic, proteomic, transcriptomic, and metabolic approaches. In particular, we aim to improve computational tools and experimental methods to dissect the heterogeneity of tumorigenesis in human samples throughout the course of the disease. Overall, we aim to: i) increase understanding of the underlying pathophysiology of tumor evolution; ii) identify new potential targets for immunotherapy; and iii) provide innovative biomarkers to improve patient stratification, diagnosis, and disease monitoring. For example, we were involved in the Personalized and Digital Oncology (PeDiOn) program, a clinical sequencing program at the BIH and Charité. PeDiOn used molecular information to guide patient stratification and to individualize therapy, moving closer to the promise of personalized oncology.

Genetic alterations of mitochondrial DNA (mtDNA) are associated with a variety of human phenotypes. Given the central role of mtDNA in the functionality of the respiratory chain and the ubiquitous nature of mitochondria, these diseases often present as multisystemic disorders. However, given their clinical heterogeneity and the unique features of mtDNA (e.g. heteroplasmy), diagnosis is often delayed. We have developed multi-omics sequencing technologies that enable mtDNA genotyping in individual cells along with measures of cellular state to further characterize the genomic consequences of variable burdens of pathogenic mtDNA [104, 105]. We seek to apply these technologies to facilitate diagnosis, advance our understanding of mitochondrial genetics, and elucidate cell-type specific pathophysiological and adaptive responses to pathogenic mtDNA.

Primary aldosteronism, the excessive production of the adrenal steroid hormone aldosterone, is the most common cause of secondary hypertension. Frequent subtypes include aldosterone-producing adenomas (benign tumors of the adrenal gland) and bilateral hyperaldosteronism, whereas familial hyperaldosteronism, a monogenic disorder, is rare. We have helped identify somatic mutations in aldosterone-producing adenomas and germline mutations in familial hyperaldosteronism [106-108], and we continue to search for novel disease genes. We use animal models [109, 110] and novel cellular models to investigate the underlying pathophysiology.

Vascular anomalies (VAs) comprise a heterogeneous group of rare disorders that require lifelong clinical management. Many standard treatments induce significant collateral tissue damage and nonperfused scars, and management is often incomplete. Thus, there is a need to develop new therapeutic modalities that target these disabling pathologies in a more specific, effective, and enduring manner. Building on our major contributions in the field of (cardio)vascular diseases [111-113], we aim to identify novel genetic causes of human VAs, particularly VAs characterized by endothelial overgrowth. We also seek to: i) elucidate the molecular and cellular mechanisms disturbed by the mutations using in vitro organoid models; ii) validate and further explore the pathophysiological mechanisms using in vivo zebrafish and mouse models; and iii) identify and test potential molecular therapies for VAs in model systems. Another goal is to identify potential VA drug targets and novel ways to target previously undruggable targets via targeted protein degradation (TPD) and preclinical testing (repurposing) of known drugs. To facilitate diagnostic-related therapies (theranostics) for cardiomyopathies, we investigate the genetic background of cardiomyopathies and their links to a dysregulated immune system.

Infectious diseases are characterized by an interaction of the host with the pathogen. Pathogenic microbes vary in both their ability to cause infections and their drug susceptibility. Both properties are influenced by an interplay of genetic and environmental factors, with metabolism playing a central role. Using experimental molecular biology and functional omics approaches [114-116], we study host and microbial metabolism to better understand their interactions, to inform strategies to change the host microenvironment, and to ultimately improve treatments [117].

Disease interaction in multimorbid patients is important for treatment and prognosis, but the underlying cross-organ and systemic pathomechanisms are poorly understood. To tackle these challenges, we combine approaches from network science, ML, and computational phenotyping to shed light on the interactions between comorbidities and to identify the
underlying pathomechanisms via data integration. Our goal is to develop a comprehensive generic disease network that maps clinical and molecular phenotypes, and links them to multidimensional datasets from electronic health records, biomedical imaging, and registries, real-life and environmental data, and omics data and pathways.

**Design and analysis of disease models.** Complex preclinical systems are powerful research tools. These model systems can be used for disease modeling, disease phenotyping, target identification, and target validation. They can thus feed into translational pipelines for drug discovery or drug screening, or proof-of-concept experiments in cell-based therapy approaches. We are developing preclinical model systems, challenging them against medical pathophysiology, and using them to gain mechanistic understanding or evaluate proof of principles. These model systems include organoid models [118-120], organ-on-a-chip [121-123], 3D imaging [124-126], in vivo systems [124, 127, 128] and in silico approaches [129].

In disease modeling, for example, we have applied and developed genome engineering techniques in pluripotent stem cells (human induced pluripotent stem cell (iPSCs) and mouse embryonic stem cells (mESCs)) to create models of genetic disease that elucidate previously unknown disease mechanisms (CRISPR-Cas9, CRISVar [91], synthetic-biology-based methods) [130]. We are also methodologically improving and designing in vitro and in vivo models, including induced iPSC models, to study VAs and angiogenesis in general. This work is closely connected to the characterization of the role of environmental factors (e.g. metabolism, flow, 3D architecture) in normal and pathological angiogenesis. It is also connected to the structural and functional imaging of morphogenetic processes in VA development and response to therapies. Further applications are i) the adaptive imaging and perturbation of tumor organoids; ii) the profiling of cell interactions in tumor microenvironments; iii) the metabolic benchmarking of cell and organoid models; and iv) immune cell integration and testing in human gut organoids.
Challenges and Goals

Individual patients may not be diagnosed or treated satisfactorily in conventional care structures. These patients need access to exploratory analyses for detailed research-based phenotyping or genotyping. Suitable platforms can identify new diagnostic or therapeutic approaches, including new experimental or bioinformatics procedures, and help incorporate them into patient care. In acute medical care, it is important to suggest suitable therapies as quickly as possible. Speed is also important in pandemic situations or in critical care without standardized therapy options. We seek to optimize the identification and application of individualized treatment protocols by using rapid molecular, transcriptomic, genetic, and proteomic analyses and imaging modalities with a solid digital basis.

Case Analysis and Decision Support (CADS). The CADS platform aims to provide precision medicine to patients with rare diseases who have not received a timely diagnosis or optimal therapy [131]. Precision diagnostics are the key to innovative therapies tailored to the individual patient’s needs. CADS bridges the gap between research and conventional care. Patients suffering from an unknown disease will be able to use CADS to access novel experimental bioinformatical and technical procedures and so obtain a swift diagnosis. At the same time, we will use CADS to evaluate novel diagnostic procedures for the highest success rates and benefit to the public and prepare them for translation to conventional care. In addition, CADS provides support, if required, with referrals to specialists, including psychosocial counseling and support. We will provide a structured data space to integrate and store pseudonymized research data in a rare disease database, along with quality-assured biobanking of biosamples. The integration of CADS into the BIH/Charité ecosystem will provide new opportunities for developing novel diagnostic algorithms and procedures and therapies. This includes the establishment of a state-of-the-art pipeline for the standardized analysis of genotype and phenotype data.

Sign-based deep phenotyping for prognosis and the prediction of medication effects. Clinical signs and symptoms offer a readily available alternative to costly laboratory measurements and have been structured in the Human Phenotype Ontology (HPO). However, their predictive and prognostic applications have not been explored at scale. In collaboration with the Centre for Rare Kidney Diseases (CeRKid), we have developed the SAMS software and database for HPO-based deep phenotyping and guided differential diagnosis. By phenotyping the CeRKid (out)patients, we will trace patient trajectories at unprecedented depth in order to explore the predictive and prognostic value of these easily accessible patient characteristics.

Analyses for molecular tumor boards. We provide bioinformatics services and analytics platforms, and participate in collaborative research projects for precision oncology. Specifically, we analyze gene expression and DNA/RNA sequencing data in an integrative manner in order to identify critical genetic alterations (e.g., drivers, fusions, amplifications) to guide the selection of therapies. We also interpret somatic mutations in order to estimate tumor mutational burdens and inform about the utility of immunotherapy. Additionally, we mine sequencing data to shed light on the origins and progression of cancers. In collaborative projects between the Bioinformatics Core Unit (CUBI)

Contributing PIs and their teams
Janine Altmüller, Dieter Beule, Christian Conrad, Martin Kircher, Claudia Langenberg, Irina Lehmann, Sören Lukassen, Christian Meisel, Stefan Mundlos, Ute Scholl, Dominik Seelow
and the Comprehensive Cancer Center, we explore the potential of large language models to support decision-making by the Charité Molecular Tumor Board. To translate results from research to the clinic, we are part of the precision oncology certification (Platform for personalized cancer medicine) and participate in precision oncology ring trials for whole-exome sequencing.

**Fast-track diagnosis of individual patients for personalized therapy.** We support the diagnosis and treatment decisions for patients with unspecific symptoms and undiagnosed disease. We will focus on cardiovascular therapy, using ultra-rapid long-read sequencing and analysis to identify druggable targets for patients with unexplained chest pain. We aim to leverage the BeLOVE study, which has created a high-dimensional database using our FAIR data platforms from a prospective cohort study with a focus on cardiovascular diseases integrating a broad spectrum of data sources for the application of AI-based methods.

**Data-driven support of targeted intervention.** We will develop mathematical models to detect and segment brain tumors and detect and classify kidney tumors. To justify their predictions, these models will point to informative correlations and relationships of features across modalities. For example, molecular information about DNA methylation will be correlated with macroscopic information from magnetic resonance imaging (MRI) or computed tomography (CT). The models will thus not only predict but also improve our understanding of the disease. Furthermore, by incorporating uncertainty, the models will highlight weak predictions and allow for targeted improvements.

**Digital pathology – spatial transcriptomics.** In digital pathology, we use spatial transcriptomics to decipher the gene expression of individual cells within the tissue context. Our goal is to determine the role of immunological and intercellular communication in the onset and manifestation of disease. By accurately measuring malignant lesions in patient biopsies at diagnosis, we enable better treatment choices.

**Ambulatory long-term video-EEG for accessible diagnosis.** People with epileptic and nonepileptic seizures need a rapid correct diagnosis so they can begin the right treatment. The gold standard for diagnosis, long-term video-EEG, is only available in specialized centers, making it difficult to access. We will compare this gold standard against ambulatory long-term video-EEG monitoring (ALVEEG), which uses wearable sensors and AI. Our prospective, multicenter, randomized, controlled study will compare the clinical utility, validity, patient-reported outcomes, and economic costs of these two diagnostic procedures. Our long-term goal is to establish ALVEEG as a diagnostic procedure in Germany.

**Sensor-based and AI-based monitoring and intervention.** We investigate the potential of wearable sensors and AI for continuous long-term monitoring and risk assessment in the context of personalized, proactive, and time-critical outpatient therapies. In particular, we assess novel wearable sensors and AI for their ability to: i) robustly estimate seizure burden in epilepsy patients; ii) forecast seizures; and iii) provide continuous long-term monitoring in other neurological diseases.
Research Objective 3
Advanced Regenerative Therapies

Activity 3.1
Stem Cell Products

Activity 3.2
Immuno-modulation

Activity 3.3
Extracellular Matrix

Activity 3.4
Mechanobiology
Research Objective – Advanced Regenerative Therapies

Advanced regenerative therapies aim to fully regenerate affected tissues and restore physiological homeostasis. These curative therapies remove the need for repeated costly interventions, chronic medication, or other lifelong treatments, thus benefiting patients and society.

Overall Challenge, Vision and Goal

Our aim is to develop innovative strategies for regenerative therapies (Figure 14) and to revise current treatment guidelines, which have so far failed to restore physiological homeostasis locally or systemically. Our comprehensive approach will address the full translational pipeline. After characterizing insufficient regeneration in patients and improving patient stratification, we will analyze the underlying (patho)mechanisms and use the insights gained to develop novel therapeutic and diagnostic strategies, such as living drugs (Advanced Therapy Medicinal Products, ATMPs) and combinatorial therapies. To avoid late failure, we will test new approaches in suitable preclinical models before assessing safety and efficacy in clinical trials and real-world contexts. Eventually, cycles of improvements of the new approach may be completed iteratively, to achieve refined translation and ultimately a superior treatment option.

The need for regeneration after various medical insults and diseases is so ubiquitous that a holistic approach is required. In a comparative approach, we therefore aim to identify the basic mechanisms that hinder endogenous regeneration in a variety of organs and medical conditions. These basic mechanisms could be promising upstream targets for novel regenerative approaches.

In this Research Objective, we will analyze the following factors that impact regeneration across different organ systems and medical conditions: stem-cell-derived cellular differentiation (Activity 3.1); inflammation and immune imbalance (Activity 3.2); the extracellular matrix (Activity 3.3); and mechanical and mechanobiological conditions (Activity 3.4). Promising concepts that could result in therapeutic products or treatments will be validated in clinical trials. We will also conduct long-term follow-up by monitoring appropriate biomarkers and real-world data. In addition to achieving primary endpoints (safety first and efficacy later), we aim to gain insights into therapeutic mechanisms that can fully restore organ function. These insights will feed into iterative cycles of improvement (refined translation) to deliver true breakthroughs in regenerative medicine.

With its translational focus on developing novel therapeutic approaches, this Research Objective primarily contributes to the patient-oriented arm of the BiH mission. In doing so, a scientific reflection of translation as a refinement process is enabled and we contribute to the development of translation as a science in itself, thus strongly interacting with the Translational Methodologies Research Objective. In our iterative refinement of advanced regenerative therapies, we will
The need for regeneration is ubiquitous ...

... after chronic disease
(e.g. obesity, diabetes,...)

... after acute incidences
(e.g. injury, infection,...)

... after therapy
(e.g. chemotherapy, transplantation,...)

Even if the primary pathology can be successfully treated, full local and systemic regeneration cannot always be achieved.

Figure 14: This Research Objective’s vision is to develop advanced, often personalized, regenerative therapies to curatively restore local and systemic homeostasis in various different clinical indications.

also benefit from the expertise and insights gained in the Computational and Functional Precision Medicine Research Objective, to which we will contribute future use cases. Finally, in achieving our goals, we will develop scientific technologies and know-how (e.g. bioengineering solutions, innovative cell therapies, improved genetic and epigenetic modification technologies, novel cellular reprogramming approaches). We will thus help patients serve the scientific translational community and create valorization potential. To upscale and disseminate promising regenerative approaches, we will proactively seek out regulatory interactions, entrepreneurship, and co-development in public-private partnerships at an early stage of the translational project development.
Expected Impact

By developing new approaches to advanced regenerative therapies and improving specific diagnostics, we expect to directly impact disease management and prevention. By conducting clinical trials, designing monitoring tools for long-term follow-up, creating spin-off companies, and extending public-private partnerships, we expect to advance the field of ATMPs.
Activity 3.1
Human iPSC and Organoid-based Therapy to Support Tissue Regeneration

Pluripotent stem cells, specifically, human-induced pluripotent stem cells (hiPSCs) and organoids derived from primary tissues offer a unique opportunity for regenerative medicine. hiPSCs and organoids can be easily derived from almost any patient and could thus enable personalized cell-based therapies. Promising first steps have been taken to introduce hiPSCs to the clinic [132-134].

Challenges and Goals

Before hiPSCs and organoids can reach the clinic, the following challenges must be addressed: i) the insufficient functionality of cells grown in vitro; ii) the risk of immune rejection; and iii) the difficulty of transferring academic protocols to the clinic. In this activity, we will address these challenges by achieving the following goals: i) improve the functionality of cells generated in vitro from hiPSCs and organoids to match specific disease attributes for tissue regeneration; ii) address challenges caused by immune rejection during cell-based therapy; and iii) develop new methods for growing and differentiating cells at scale in culture conditions compatible with clinical needs.

Produce functional cells for cell-based therapy applications. To bypass current limitations in differentiating hiPSCs for disease modelling and cell-based therapy approaches [135-140], we are exploring two options: The first approach uses forward programming (FoP) methods to recreate the transcriptional networks of an adult cell type by overexpressing a cocktail of transcription factors in hiPSCs [141]. We have already applied FoPs successfully [142, 143], suggesting that this approach could be used for the large-scale production of cells for clinical applications. An additional goal here is to demonstrate the safety and efficacy of FoP cells for cell-based therapy. The second approach is to develop co-culture systems in 3D to recreate a physiological micro-environment that promotes functional maturation. Importantly, this co-culture system will have multiple applications, including disease modelling and cell-based therapy.

Avoid immunosuppressive treatment. We have begun to address the challenge of immune rejection in hiPSCs and cholangiocyte organoids [144, 145]. This will enable the production of immune-silent hiPSCs/organoids, which will decrease immune rejection in the context of long-term transplantation and also control inflammation associated with diseases such as liver failure.

Develop methodology for clinical compliance. Complying with the regulatory requirements and industrial standards of cell production at scale is a key barrier to the use of hiPSCs and organoids for cell-based therapy. The first open-source hiPSC lines compatible with cell-based therapy have been developed by deriving hiPSC lines in compliance with Good Manufacturing Practice (GMP). For organoids, we aim to derive the first GMP-grade cholangiocyte organoid line, which is essential for harnessing the potential of organoids for regenerative medicine. We will establish the necessary quality controls to develop genetically modified hiPSCs and organoids that meet all regulatory requirements for clinical applications.

Cell-based therapy for larger organs such as the liver will require large-scale production of cells. We are therefore developing closed bioreactor systems to produce FoP hepatocytes and cholangiocyte organoids.
Activity 3.2
Immuno-modulatory Therapeutics and Refined Translation of ATMPs

Inflammation and a persistent immune imbalance are major challenges for regeneration. A delicately balanced immune response is the key to fully restoring local and systemic homeostasis after disruptive events. Modulating inflammation is thus a promising approach to regenerative therapy. This can include the integrative improvement of established therapies (‘refined translation’).

Challenges and Goals

Our goal is to develop therapeutic strategies to re-store immune balance and so foster full regeneration and support therapeutic hiPSC-derived organoid transplants. We begin by discovering pro- and anti-inflammatory cells or molecular mediators that can influence either regenerative processes or the acceptance of hiPSC-derived therapeutic grafts. We can then identify specific promising targets for novel immunomodulatory treatments and test these treatments in preclinical models. Following optimization, the treatments will move to clinical trials to validate our approach. An associated goal is to accelerate and refine the clinical development of personalized regenerative therapies by: i) characterizing ATMPs to develop quality biomarkers; ii) accompanying clinical trials with next-generation staging to gain deeper longitudinal insights into treatment-induced changes at the molecular, cellular, tissue, and organismic levels; and iii) accurately capturing the pharmacokinetics/pharmacodynamics of ATMPs and their surrogate efficiency markers in order to develop advanced strategies for patient stratification in clinical trials.

Adjusting the immunological balance to foster regeneration of the musculoskeletal system. The musculoskeletal system is ideal for analyzing regenerative processes because it contains tissues with different endogenous repair capacities (e.g. bone, cartilage) [146-151]. By comparing the role of inflammation in healing these tissues, we can understand the processes that lead to successful vs. impaired regeneration and we can translate these principles across indications. Based on previous work [152-156], we are currently validating novel diagnostic/prognostic biomarkers for the early identification of patients at high risk for compromised fracture healing in a large multicenter clinical trial (BioBone). We are also exploring the clinical potential of immunomodulatory intervention strategies, such as the repurposing of ilomedin in the prospective randomized IloBone trial. Within this context, we are evaluating cell-based therapies, including the Phase I/IIa human trial OSTEOHEAL and the Phase III trial HIPGEN [157-162]. In addition to these ongoing clinical trials, we are developing a biomaterial platform technology for the local and time-controlled release of immunomodulators [161-164] and for the cellular trapping of pro-inflammatory cells that impair the regeneration process.

Adjusting the immunological balance to foster local and systemic regeneration during and after infection. Imbalanced immune responses lead to uncontrolled collateral tissue damage and impairment of the regenerative capacity of the affected tissue and the entire body. To gain a detailed understanding of the mechanisms involved in impeding full regeneration, we helped establish a large phenotyping platform for COVID19 (Pa-COVID-19 study) [43, 165], and are cur-
rently working on identifying the molecular switches for successful resolution of fibrosis and other biomarkers [42, 46]. We are also conducting clinical trials (CATCOVID study), developing vaccine candidates for better safety and efficacy profiles (Ratswohl et al. unpublished), and establishing cell therapy approaches using the adoptive transfer of virus-specific T cells [166-169]; (COVIM project ‘TReAT’).

Adjusting the immunological balance to maintain and restore cardiac function. Despite its low regenerative potential, the heart has the capacity to remodel. Inflammation and an imbalanced immune system are the main contributors to maladaptive cardiac remodeling. We investigate the interplay between cardiac fibrosis and inflammation, focusing on innate immunity, in order to identify tailored anti-inflammatory/anti-fibrotic therapies (e.g. repurposed drugs, extracellular vesicles, cells, devices) to address the broad spectrum of heart failure [170-172]. This includes clinical trials with promising therapeutic agents (OLdTIMer).

Facilitating immune regeneration after organ and hematopoietic stem cell transplantation (alloHSCT). Organ transplantation is the ultimate and sometimes only therapeutic option for end-stage organ failure. Similarly, alloHSCT is the only curative therapy for some forms of hematological diseases. However, transplantation carries the risk of detrimental adverse effects, which in many cases require lifelong medication. We therefore aim to establish new or improved therapies to achieve full regeneration of the transplanted organ and the immune system after alloHSCT.

Based on previous work [67, 167, 169, 173-176], we aim to improve the current adoptive T cell therapy approaches to solid organ transplantation (ReSHAPE consortium, CONAN Project, TReAT Project). For alloHSCT, we aim to define an optimal alloHSCT graft with improved reconstituting capacity and with minimal risks of initiating graft-versus-host disease (GVHD), which is associated with high morbidity and mortality [177-181]

Accelerating Clinical Developments and Trials of ATMPs. To identify lead ATMP candidates and derisk those in preclinical studies, we will apply molecular profiling with state-of-the-art omics technologies [182-185] to current and novel therapeutic products for regenerative medicine. We will also develop appropriate in vitro models for the functional characterization of ATMPs. In contrast to standardized clinical staging, we will accompany clinical trials with next-generation staging by longitudinally implementing a portfolio of immunoassays [67, 160, 176]. Our current focus is on expanding the immunobiomarker testing platform and integrating new technology platforms with high levels of standardization [186, 187]. We complement the current clinical gold standards with longitudinal patient-specific functional data and results from preclinical in situ and in vivo studies [180, 188-190]. We can thus investigate system-wide immunological changes in patients undergoing treatment with advanced therapies and so determine whether specific functional immune alterations reflect and/or predict response to therapy or the occurrence of (immune-related) adverse events (irAE) [122].

To further develop novel patient stratification strategies in established treatments and in ATMP clinical trials, our goal is to integrate testing platforms into the clinical decision-making process. One example is the development of a multiscale imaging approach that analyzes identical samples at several levels in order to provide multiple biomarkers. In doing so, we seek to gain insights into the individual diseased tissue, the pharmacological treatment, and thus the patient’s outcome and survival. We are also enhancing patient stratification by defining biomarkers for prognosis and therapy in bone healing [153, 155] and cardiology [118].
Activity 3.3
Extracellular Matrix as a Therapeutic Tool and Target in Regenerative Medicine: Conserving and Restoring Tissue Function

While life sciences have traditionally focused on understanding disease development and progression at cellular and molecular levels, there is growing interest in the extracellular matrix (ECM) as both a therapeutic target and a therapeutic product. By understanding the ECM’s pathophysiology, biophysics, and how its characteristics influence cellular behavior and function, we can elucidate the ECM’s current and potential roles in controlling cell behavior during disease progression or tissue healing. This knowledge will pave the way for the development of ECM-based and ECM-targeting therapies.

Challenges and Goals

Our goal is to reveal the therapeutic potential of engineered, biological, and bio-inspired matrices and to harness this potential in advanced medtech or combinatorial approaches (with cells as ATMPs). Conceptually, we will begin by characterizing native ECM in various pathophysiological settings to identify the relevant matrix alterations and matrix markers that cause or are associated with tissue malformation or disease development. We will verify the basic principles by engineering synthetic ECM with the corresponding pathophysiological or proregenerative properties [120, 191-193]. We will explore the immune system’s role in altering the ECM and impairing its function. Using our mechanistic understanding of matrix-driven pathophysiology, we will develop matrix-based therapeutic approaches to control or modulate regenerative processes. By involving a variety of disciplines and organ systems, we will identify principles common to the various systems. These principles will guide us in addressing the remaining challenges in the field of regenerative therapies.

Characterizing the role of the ECM in disease development and unsuccessful healing. The ECM influences and regulates many cellular functions of tissue cells. Studies in different organs and organ models have indicated that alterations in the amount, composition, chemical structure, and spatial network structure of the ECM are associated with disease progression or failing tissue regeneration, e.g. in atopic dermatitis and bone healing [191, 193-196]. Our own evidence points towards the inflammatory potential of fibroblasts [197-199] leading to tissue fibrosis in the heart and the skin [200]. Across these organ pathologies, fibroblasts and fibroblast-like cells play a central role. Because of their predominant role in ECM secretion, remodeling and local inflammation, we will focus on fibroblasts in this activity. We will use and further develop in vitro [199, 201] and in silico models [202], including vascularized systems, to study the principles of pathology-related ECM alterations and influencing factors across organs. We will also focus on the ECM’s role in progressive diseases and hindered regeneration [120]. Within the activity, we will use high-end approaches [126, 193, 203-207] to better understand the principles of ECM formation and remodeling that are common to the different organ systems (starting with skin, bone, and heart). We will also consider additional factors such as aging, metabolism, low-grade inflammation and mechanosensation in the heart and other organs like the liver and vasculature/angiogenesis.
Development of matrix therapies. We will use the resulting insights into the ECM’s role in disease progression and failed regeneration in order to develop advanced matrix therapies. Specifically, we will use ECM molecules and 3D ECM scaffolds/networks as therapeutic tools along with drugs or cells. This approach is promising due to its low costs, high safety level, and broad availability. We have already delivered examples of this approach [191, 208, 209]. A mechano-hybrid scaffold platform with optimized architectural and mechanical properties is being evaluated for its effectiveness in regenerating bone defects in the absence of additional therapeutic treatments. This pure biomaterial approach uses the body’s endogenous regeneration capacity, and we aim to progress it to the clinic. We are also exploring the possibility of tailoring scaffolds for bone tissue regeneration in patients with compromised healing potential (e.g. based on aging or Type 2 Diabetes). In addition, we aim to mimic the individual properties of natural ECM (e.g. stress relaxation behavior), using synthetic cell niches to create proregenerative environments [161, 162]. Little is known about how the ECM’s viscoelastic properties can alter the immune response during healing. In a joint effort, we will characterize the ECM in heart failure patients and experimental heart failure models in order to stratify patients and identify ECM-directed therapeutic targets. Further insights into the inflammatory potential of fibroblasts in the context of cardiac fibrosis will allow us to evaluate the efficacy and possible off-target effects of repurposing therapies and to develop fibroblast-subtype-directed therapeutic approaches.
Activity 3.4
Mechanics and Mechanobiology for Improving Regenerative Processes

Tissues and organs in the human body are designed to support different kinds of mechanical loads. Most importantly, cells within tissues are able to sense and respond to those mechanical signals, not only in physiological homeostasis and pathologic settings but also during regeneration. Successful tissue regeneration can only occur within given ranges of mechanical stimuli, with mechanical signals that are too high or too low leading to repair failure. Understanding the mechanical signals within tissues and the cellular response to these mechanical signals is therefore important for the treatment of many disorders.

Challenges and Goals

Within this activity, we will characterize the patient-specific functions of tissues and joints and the resulting biophysical cues in the human body during daily activities. We will thus identify groups that are at risk for the mechanical overloading or underloading that leads to repair failure. We also aim to understand how systemic biophysical cues impact regeneration and patient rehabilitation. Our goal here is to design patient-stratified treatment strategies that provide the right level and duration of mechanical stimulation or unloading to promote endogenous tissue regeneration (‘mechano-therapeutics’) [210].

To achieve mechano-therapeutics, we will quantify and understand the mechanical conditions within human bodies and how they impact homeostasis and tissue regeneration across multiple scales. Finally, we will use the resulting knowledge to engineer personalized treatment strategies that provide controlled mechanical environments to boost or actively guide regeneration or avoid degeneration.
**Biophysical cues in the human body.** Alongside biochemical cues, biophysical conditions can trigger cellular behavior. We aim to harness this potential and make it available in personalized therapies. We have used unique telemetric technologies to measure loads acting on joints in vivo [211-218]. Our technology has made internal mechanical load data available for public use [219, 220]. Along with control over adequate mechanical load magnitudes, patient kinematics or mobility is essential to health. We synchronously quantify post-op joint mobility and load [221] in order to improve implant designs or surgical strategies [222, 223]. We have used these in vivo patient measurements in various approaches in order to overturn the “one-solution-fits-all” strategy in favor of precise diagnoses, personalized treatments, and mechano-morphological/biological optimizations of the current clinical interventions [224, 225]. We recently introduced dynamic imaging technology in MRI [226] in order to better quantify the benefits of personalized or advanced therapies. We directly translate these fundamental biomechanical principles to patients [227, 228]. Wearable technologies allow us to incorporate dynamic field measurements into our biomechanical functional assessments of dedicated patient cohorts [229, 230]. We aim to elucidate how chronic lower back pain is affected by unfavorable patient alignment, functional abnormality, and improper long-term mechanical loading, and to demonstrate how personalized surgical and nonsurgical treatment could prevent disease progression.

**Mechanical optimization of treatment strategies.** Tissue regeneration requires a specific range of mechanical stimulation. Mechanobiologically optimized treatments can promote regeneration across different tissues [171, 191, 209, 237]. The underlying mechanobiological regulation of these tissue regeneration processes has already been identified [39, 129]. These models can now be used to develop mechanobiologically optimized technologies for personalized implants that foster endogenous tissue regeneration even in cases where healing would otherwise be impaired.

**Impact of mechanical signals on endogenous regeneration.** Mechanical conditions drive regeneration and adaptation in several tissues, including those of the musculoskeletal and cardiovascular systems. Surgical treatment influences healing, with unfavorable mechanical conditions potentially resulting in organ or tissue failure [231]. Moreover, the mechanical regulation of tissue adaptation and repair is altered in aged or otherwise compromised settings. Reduced cellular mechano-response is known to play a major role in impaired healing [231]. Functional microvasculature, a key to regeneration, is also influenced by the local mechanical setting. Mechanical stimuli critically impact the self-organization of fibroblast and endothelial networks in early callus formation [232-234] and endothelial cell-cell interactions in reaction to the blood flow driving vascular network formation [235]. One of our aims is to understand how mechanical loading influences functional vascular network formation and tissue organization in physiological and compromised conditions. Moreover, we will investigate how intrinsic and extrinsic mechanical signals synergistically control healing cascades in compromised and noncompromised conditions. Finally, using bone as a model system, we will compare scar-free healing with scarring in other organs [197, 236] to understand how mechanical stimuli influence pathological ECM remodeling [120, 201].
Strategic Collaborations

Our overall goal is to develop an interactive, flourishing, and sustainable ecosystem for precision medicine, fostering the role of the BIH and our partners in regional, national, and international networks.

The BIH’s Local Network

We pursue our mission by building strong ties with Berlin’s scientific and translational ecosystem. According to the terms of our constitution, the BIH is institutionally embedded into Charité – Universitätsmedizin Berlin and maintains a privileged partnership with the Max Delbrück Center for Molecular Medicine. Based on this setup, we build a solid network of local partnerships and participate in numerous network initiatives. For example, bilateral cooperation exists with the Max Planck Institute for Molecular Genetics and with the German Rheumatism Research Centre Berlin (DRFZ). We are also involved in most of the Berlin Einstein Centers – a funding line of the Einstein Foundation Berlin, which is designed to enable interinstitutional and interdisciplinary collaboration in Berlin and strengthen innovative research areas and internationally visible hubs. In terms of academic networks, we contribute to the Berlin University Alliance (BUA), an Alliance of Excellence funded by the German Excellence Strategy. The BUA facilitates the implementation of joint projects and structural improvement of its members. In terms of non-university networks in Berlin, we are a founding member of Berlin Research 50 (BR50), which brings together almost all non-university research institutes and centers in the Berlin metropolitan area. Further strong interactions exist with Stiftung Charité; this foundation supports BIH, MDC and Charité through many important mechanisms (among others, visiting professors, fellows and scientists; recruitment packages; promotion of women scientists; conferencing; open science activities). Collaborating with the European School of Management and Technology (ESMT), Germany’s leading business school, we offer and develop formats of entrepreneurship training for life scientists and clinicians as well as individual coaching for early and advanced stages of spin-off formation. Additional advanced training activities are planned jointly with the Academy of the Helmholtz Association.
Selection of Key Regional Partners
Selection of Key National Partners
The BIH’s National Mandate

Along with developing strategies to advance biomedical translation, we are involved in national initiatives and policy advice to give patients access to scientific achievements. Our Principle Investigators contribute to: i) national initiatives from the Federal Ministry of Education and Research to form a joint data space connecting all German university medical centers (Medical Informatics Initiative under the umbrella of the NUM); ii) an initiative from the Federal Ministry of Health for healthcare data interoperability; iii) the German Council of Experts for the Assessment of Healthcare Developments; iv) advising national and international funders and policy makers in various formats; v) fostering local, national, and international standards in Digital Medicine. Furthermore, we seek to: act as a reference point for responsible research (e.g. MERIT App, CoARA); set standards for preclinical models (e.g. QUEST Center); develop broadly applicable methods to make data FAIR; and contribute to the SNOMED CT standard, the HL7 FHIR standard, and Human Phenotype Ontology (HPO) in the field of computational and functional precision medicine. We also interact with the following German Centers for Health Research (DZG): i) the German Cancer Consortium (DKTK); ii) the German Center for Child and Adolescent Health (DZKi) in the context of CADS; and iii) the German Center for Cardiovascular Research (DZHK) and the German Center for Mental Health (DZPG) in the context of the long-term observational cohort study BeLOVE. Last but not least, we offer national support and services for the German Stem Cell Network (GSCN), the German Biobank Node (GBN), and the German Society of Gene Therapy.

National Activities of the BIH

Platforms and Networks
- Dialog Platform for Stem Cell Research
- National Network Office GCT
- Academic GMP Network

Education and Advice
- QUEST Center for Responsible Research
- National Entrepreneurship Education Curriculum in GCT
- National Regulatory Support Unit for GCT

BIH contributions to national Networks
- NUM, NCT, DZGs, NFDI, Mi-I, genom.de, GHGA, Interop-Council, ...

Figure 18: Overview of our national involvement (GMP Network – Good Manufacturing Practice Network, QUEST – BIH Center for Responsible Research, NUM – German Network University Medicine, NCT – National Center for Tumour Diseases, DZG – German Center for Health Research, NFDI – National Research Data Infrastructure, Mi-I – Medical Informatics Initiative Germany, GHGA - German Human Genome-Phenome Archive)
National Strategy for Gene and Cell-Based Therapies

On behalf of the Federal Ministry for Education and Research, the BIH coordinates a multistakeholder process for the development of the National Strategy for Gene and Cell-Based Therapies (GCT). This strategy aims to accelerate research and development of Advanced Therapy Medicinal Products (ATMPs) and their sustainable translation into patient care. The goal is to develop safe, efficient therapies for patients with congenital or acquired diseases, and to make Germany an internationally competitive location and strong contributor to international development partnerships for this key technology.

Core Elements in Implementing this National Strategy are:

The development of a strategy document in a multi-stakeholder process
The science-based and patient-centered National Strategy for GCT proposes concrete measures to optimize the conditions for developing and accelerating the transition of GCT to patient care. The National Strategy was designed in a collaborative, open, and transparent process involving public and private stakeholders throughout the translational value chain, with more than 150 experts in eight working groups to assess the current status and define future measures. Cooperation between politics, society, the public sector, and the private sector is essential to implementing these measures in order to strengthen research and innovation in Germany for the sustainable long term. The BIH is coordinating this strategy.

The establishment of a national network office at the BIH
The GCT network office has been launched at BIH to become the point of contact and exchange hub for regional and national stakeholders and public authorities. It offers project management services and centrally bundles and disseminates information. Its GCT dialogue platform involves stakeholders (e.g. patient representatives, interested investors, political decision-makers) in a proactive dialogue. The GCT dialogue platform supports the German Society for Gene Therapy (DG-GT) in implementing and organizing a joint mission. This is similar to the established model of the German Stem Cell Network (GSCN) with its dialogue platform for stem cell research at the BIH.

A national facilitator program for academic research groups and start-ups
The newly designed GeneNovate facilitator program serves GCT research groups and start-ups by offering stage-specific, continuous, and individually tailored mentoring, coaching, training, and further education in entrepreneurship. GeneNovate is a collaborative format designed by the BIH, UnternehmerTUM Munich, and the University Medical Center of the University Mainz. It is designed for national roll-out and thus brings together leading German life science hubs in a joint environment for researchers, future entrepreneurs, and mentors. This program offers starting points for super-regional networking, expert think tanks, and the formation of spin-off companies that integrate knowledge and actors on a national and international scale.

National career development programs for clinical and nonclinical scientists in the field of GCT
In interaction with the national community, BIH plans to launch new funding lines that support clinician scientists and life scientists with a deep interest in GCT. In the design of new funding lines, we take care to promote interactions between academia, industry, and start-ups by supporting co-development and open innovation activities.

National funding for GCT research and development projects
Funding will be made available for projects to support the development of novel therapies in the field of GCT,
with a focus on translational activities in the preclinical phase. This funding will be accessible across sectors and will take into account existing infrastructures and research activities, emphasizing the importance of patient-centric research design and principles of robust research.

**Establishment of a Regulatory Support Unit**
The novelty and complexity of ATMPs often creates uncertainties about regulatory requirements. The Regulatory Support Unit at the BIH has been launched to reflect the latest regulatory developments and offer regulatory advice based on a detailed assessment of the target product profile, supplementing related activities of the German Centers for Health Research (DZGs).

**Networking of GMP facilities**
Over the years, a substantial number of facilities has been opened in Germany, often associated with or run by University Medical centers, for the production of various forms of ATMPs. As part of the National Strategy, these centers will be connected to advance the exchange of expert knowledge in various fields: training of qualified personnel; protocol design; automation of complex procedures; choice and production of critical ingredients; quality control and release testing; and regulatory requirements and approval. Addressing major bottlenecks in the development of ATMPs, this initiative will also invite GMP facilities run by private companies to share expertise and knowledge. Eventually the German GMP4GCT network will also help forming international partnerships for the creation of safe, efficient, affordable, accessible and sustainable GCT products.

**A translation center for gene and cell therapies in Berlin**
The State of Berlin, Charité, and Bayer have joined forces to establish a translational center for GCT in Berlin. Here, start-ups and spin-offs will be supported in transferring novel therapies to the clinic. BIH helps developing framework conditions for this center as part of the National Strategy for GCT.
23,479 Employees
Average Annual Number of Employees across Charité Group of Companies

5,671 Researchers and Physicians

321 Professors

125 Nations

>100 Departments and Institutes

4 Campuses with BIH Infrastructure

25,000 m² Overall BIH Space

3,293 Beds as per the State of Berlin’s Health Care Plan 2020 (of September 14, 2021)

787,757 Outpatients

137,825 Inpatients and Day Care patients

>567 Funded Clinician Scientists

95% Publication Rate of Clinical Trials

Accelerated Translation Patient Care

>43% are Women since Start of the Clinician Scientist Program

Open Access & Use

based on annual data for 2023
799 Employees
Staff financed by the Budget and Third-Party Funds

501 Researchers and Physicians
38% Third-Party Funded

66 Professors and Non-Professorial Working Group Heads
39% are Women

> 65 Research Groups
incl. Core Units Organized in 4 Scientific Sections

35 Mio €
External funding
Third-Party Income in 2023

10 ERC grants
5 Starting
3 Advanced
1 Consolidator
1 Synergy

18 + 2 Research Consortia
Third-party Funded National and International Research Grants and Consortia with Lead of BIH Scientists

7 Ongoing External Funded Professorships and Research Groups

5.685 Publications
Considered are all publications by scientists with BIH affiliation and publications made possible by BIH funding.

~200 Translational Projects since 2017
Co-development, IP Generation and Licensing, Clinical Trials

Portfolio of 547 Patents of Charité BIH Innovation

41 Spin-offs since 2017
Entrepreneurship

Open Innovation

International
References

47. Jabareen, N. and S. Lukassen. Segmenting Brain Tumors in Multi-modal MRI Scans Using a 3D SegNet Architecture. 2022: Cham: Springer International Publishing.
71. Stricker, S., et al., RECAST: Study protocol for an observational study for the understanding of the increased Rsiilence of Children compared to Adults in SARS-CoV-2 infection. BM Open, 2022. 3(4): p. e005221.
References

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